CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-036 /S-001

CLINICAL PHARMACOLOGY and BIOPHARMACEUTICS REVIEW(S)

TABLE OF CONTENTS

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 21-036 S-001
Type of Application: Supplemental New Drug Application
Drug: Relenza® (Zanamivir for Inhalation).
Indication: Treatment of Influenza A & B in Pediatric Patients.
Dosage Form: Inhalation Powder Packaged in Blisters of 25 mg each (Rotadisk®).
Strength: 5 milligrams of Zanamivir per Blister
Route of Administration: Oral Inhalation
Inhalation device: Diskhaler®
Applicant: Glaxo Wellcome, Inc.
Submission Dates: October 25, 1999; March 3, 2000; March 9, 2000
Draft Review: February 9, 2000, March 2, 2000, March 21, 2000
Reviewer: Sandra Suarez, Ph.D.

1. BACKGROUND

1.1 INTRODUCTION

Zanamivir is a member of a novel class of compounds with antiviral activity against Influenza A and B viruses through inhibition of viral neuraminidase. The amino acid residues which define the active site of this enzyme, and with which zanamivir interacts, are highly conserved from strain to strain. This makes the active site of influenza viral neuraminidase an ideal target for anti-viral action. Zanamivir is a highly specific inhibitor of influenza virus neuraminidases, having low affinities for both mammalian and bacterial neuraminidases. Zanamivir has the chemical name 5-(acetylamino)-4- [(aminoiminomethyl)-amino]-2,6-anhydro-3,4,5-trideoxy-D-glycero-D-galacto-non-2-enonic acid (Figure 1). Zanamivir exists as a single enantiomer, with five chiral centers and is derived from naturally occurring N-acetylneuraminic acid.

Influenza infection is spread primarily by droplets produced by cough and sneezes. Virus replication probably occurs throughout the entire respiratory tract and the principal site may be in the ciliated columnar epithelial cells. Infection begins in the tracheobronchial epithelium and then spreads to the rest of the respiratory tract. The sponsor states that because the respiratory tract is the primary site of viral infection and replication, the optimal route of zanamivir administration is by inhalation using the ROTADISK®/DISKHALER®.

The initial IND for zanamivir was submitted [redacted] Zanamivir received FDA approval on July 26, 1999 for use in the United States for treatment of uncomplicated acute illness due to influenza virus in adults and adolescents 12 years and older who have been symptomatic for no more than 2 days. It is administered to the respiratory tract by oral inhalation only. The recommended dose of RELENZA in this population is two inhalations (10mg) twice daily for 5 days.

The absorption, distribution, metabolism, and elimination of zanamivir have been evaluated in healthy adult and adolescent subjects. These findings were presented comprehensively in NDA 21-036 (refer to Brad Gillspie's review, dated 6/8/99) and are summarized below.

1.2 PHARMACOKINETICS

The pharmacokinetics of zanamivir have been previously evaluated in adults and adolescents; a summary of these findings is presented below.

1.2.1 Absorption. Pharmacokinetic studies in humans have shown that the absolute oral bioavailability of zanamivir is low (mean [min, max] is 2% [1%, 5%]). The effect of food on the oral bioavailability of zanamivir has not been studied. Studies of orally inhaled zanamivir indicate that approximately 10% to 20% of the dose is systemically absorbed, with serum concentrations generally peaking within 1 to 2 hours. There is not significant systemic exposure to zanamivir after oral inhalation. The pulmonary bioavailability of zanamivir has not been determined. There is no evidence of modification in the pharmacokinetics after repeated dosing via oral inhalation.

1.2.2 Distribution. After oral inhalation, zanamivir is widely deposited throughout the respiratory tract. The major immediate site of deposition is the oropharynx (mean 78%) from which zanamivir is rapidly eliminated to the gastrointestinal tract. The total lung deposition ——— Zanamivir has limited protein binding (<10%).

1.2.3 Metabolism. Zanamivir is excreted entirely as unchanged drug and does not undergo metabolism. *In vitro* studies demonstrated that zanamivir does not affect the activity of a range of probe substrates for cytochrome P450 enzymes ——— in human hepatic microsomes, suggesting that metabolic interactions between zanamivir and other drugs are unlikely *in vivo*. The administration of zanamivir did not interfere with the immunity provided by influenza vaccine.

1.2.4 Elimination. The serum half-life of zanamivir following administration by oral inhalation ranges from 2.5 to 5.1 hours. Zanamivir is entirely excreted unchanged in the urine. Total clearance ranges from 2.5 to 10.9 L/h, as approximated by urinary clearance. Renal elimination is completed within 24 hours.

1.2.5 Special Populations

- **Impaired Hepatic Function:** The pharmacokinetics of zanamivir have not been studied in patients with impaired hepatic function.

- **Impaired Renal Function.** The clearance of zanamivir is substantially decreased in renally impaired patients compared to patients with normal renal function. In mild to moderately impaired patients AUC nearly doubled, while in severely impaired patients AUC increased by nearly 7-fold. The elimination half-life was prolonged ——— in mild to moderately impaired patients and ——— severely impaired patients. Safety and efficacy have not been evaluated in the presence of severe renal insufficiency. No dose adjustment is recommended for patients with impaired renal function.

- **Population Pharmacokinetics.** A NONMEM analysis was conducted using data from two Phase 1/2 trials. The analysis found no significant covariate interaction due

to study type, demographic factors, formulation, and infection status or concurrent medication usage.

- **Pharmacokinetic/Pharmacodynamic Correlation.** No studies have been conducted.

1.3 EFFICACY

Zanamivir has demonstrated potent anti-influenza activity against both influenza A and B viruses, *in vitro* and in animal and human challenge models. The sponsor evaluated the efficacy and safety of zanamivir in adults and adolescent in three pivotal trials: NAIA3002 (North America), NAIB3001 (Australia, New Zealand, and South Africa), and NAIB3002 (Europe). The sponsor showed a significant treatment effect in NAIB3002, an intermediate effect in NAIB3001 and no significant effect in NAIA3002. A reasonable explanation for these treatment differences was not apparent. These trials were reviewed under the original Relenza NDA

The zanamivir pediatric treatment clinical program was designed to assess the efficacy and safety of zanamivir in the symptomatic treatment of influenza A and B infections in children. Three studies, NAIA1009, NAI30009, and NAI30010, included pediatric subjects aged 5 to 12 years. The pharmacokinetics of zanamivir have been evaluated in a single study (NAIA1009). Safety and efficacy information is provided by NAI30009. In addition, supporting safety and efficacy information was provided from pediatric subjects aged 5 to 12 years enrolled in the prophylaxis study NAI30010 (the proposed prophylaxis regimen, to be addressed in a future submission).

Four hundred seventy-one (471) subjects with influenza-like illness were enrolled in NAI30009; 224 subjects were randomized to zanamivir 10mg inhaled twice daily for 5 days and 247 subjects were randomized to placebo. The results showed that zanamivir was significantly more effective than placebo in the treatment of influenza in children. The primary endpoint of time to alleviation of influenza symptoms occurred significantly earlier (1.25 days) in the zanamivir treated subjects compared with the placebo treated subjects (refer to Dr. Baylor's review for more details on this matter). According to the sponsor, zanamivir is an effective and well-tolerated treatment for the management of symptomatic, laboratory confirmed influenza A and B in children 5-12 years of age.

2. RATIONALE

At present, there is no standard approved treatment for children with demonstrated efficacy for symptomatic influenza A and B viral infections. The rationale for studying this patient population was based on the fact that the morbidity associated with influenza is most pronounced in children and young adults. In addition, serious complications, including primary viral and secondary bacterial pneumonia, can occur in this population if left untreated.

3. SYNOPSIS

The pharmacokinetics of zanamivir have been evaluated in a single study (NAIA1009) in the pediatric population. The subjects ranged in age from 3 months to 2 years and from 6 to 12 years of age. Although zanamivir is expected to exert its effect locally in the respiratory tract, serum concentrations are of interest for safety and to

confirm delivery. The question based review approach has been used in writing the synopsis section. A detailed review begins on page 12.

1. How was the zanamivir dosing regimen for children selected?

The dosing regimen of zanamivir proposed for use in children, 10mg twice daily for five days, is the same as that approved for use among individuals >12 years of age. The sponsor claims that this dose was selected for adults to minimize the potential for development of resistance and to maximize efficacy. Studies of orally inhaled zanamivir indicate that approximately 10% to 20% of the dose is systemically absorbed, indicating no significant systemic exposure. Because zanamivir was well tolerated in the adult population following intravenous doses of 1200mg/day and inhaled (nebulized) doses of 64mg/day, any increased exposure, either systemic or local, noted in pediatrics from a surface area point of view might not be considered problematic. Thus, the sponsor believes that due to the good safety and tolerability of zanamivir shown in adults and adolescents, there was no obvious need for dose reduction in the pediatric population. According to the sponsor, a 5-day duration of dosing corresponds not only to the time period during which the intensity of acute influenza symptoms is greatest, but also to the time necessary to reduce culture positivity below the limits of detection, as demonstrated in the adult/adolescent Phase II/III studies submitted in NDA 21-036.

2. Is zanamivir 10mg twice daily well tolerated in pediatric patients?

Yes, the data submitted with this NDA supplement indicate that zanamivir is well tolerated in pediatric patients. No serious adverse events or deaths occurred in study NAIA1009. The subjects' baseline physical examinations, vital signs, and laboratory findings were consistent with acute respiratory illness. Of the seven adverse events reported in six subjects (2 subjects per age group), just one, an episode of headache (in a 12 year old child), was considered to be possibly drug-related. Except for 3 incomplete resolution date/time, the adverse events were resolved before discharge.

Adverse events in the placebo and zanamivir groups were similar and infrequent in studies NAI30009 and NAI30010. Medication was discontinued prematurely due to an adverse event in only one subject receiving zanamivir among those enrolled in NAI30009 and index cases in NAI30010. This subject was a 7 year old male who developed pneumonitis, gastroenteritis, and dehydration. Among subjects receiving study medication for influenza prophylaxis in NAI30010, one patient in the zanamivir group (gastrointestinal pain) and one in the placebo group (nausea, vomiting and rash) had their medication discontinued prematurely due to and adverse event. Refer to Dr. Baylor's review for more detail.

3. Are the rate and extent of absorption in pediatric patients similar to those in the adult population?

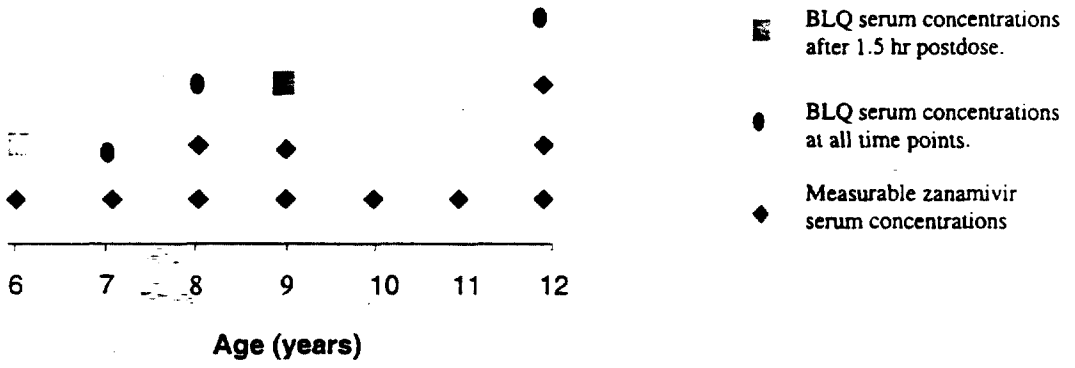
Yes, the data presented in this study showed that the rate and extent of absorption in pediatric patients receiving either single powder inhalation or single nebulization of 10mg zanamivir are similar to the those observed in the adult population who received a single dose of 10mg zanamivir via DISKHALER (Study NAIB1001).

Parameter	3m to 2y	6 to <9y	9 to 12 y	>20y
N	7	4	7	12
T_{max} (hrs)	0.8 (0.5,1.3)	1(0.4,1.5)	1(0.4,1.5)	1.5**
C_{max} (ng/mL)	47(16,65)	47(15,74)	40(34,54)	34(17,65)
AUC_{inf} (ng*hr/mL)	184(54,282)	192(58,272)	167(123,279)	186(111,328)*

*N=10; **mean value. Data represent median (min, max)

4. Is the delivery of zanamivir using the DISKHALER device consistent across patients in the pediatric population?

No, the delivery of zanamivir via DISKHALER in the pediatric population is not consistent. Although the data presented in the table above suggest that pharmacokinetic variability was similar in pediatric and adult subjects, five pediatric subjects were excluded. These subjects were excluded from pharmacokinetic analysis due to undetectable zanamivir serum concentrations or. low drug concentrations (8.32-10.38 ng/mL) that were not detectable after 1.5 hr. Therefore, this reviewer believes that there is not enough PK evidence that supports the consistency of delivery in children ages 6 to 9. The figure below shows the relationship between children's age and the detection of zanamivir in serum samples.



5. Is there any correlation between efficiency of drug delivery and serum zanamivir concentrations and between efficiency of delivery and efficacy of zanamivir ?

Pharmacokinetic measurements are not predictive of efficacy for orally inhaled products; therefore, efficacy studies for these products are necessary. Although zanamivir is expected to exert its effect locally in the respiratory tract, serum concentrations are of interest for safety and to confirm drug delivery from the device.

DISKHALER is a breath activated device; therefore, both the discharge from the dose system and the degree of powder disintegration depend on the generated inspiratory flow through the device. A flow rate (FR) of 60 L/min is considered optimal for dry powder inhalers [1-3]. It is important to maintain an optimum flow rate since low FR may fail to discharge the device and high FR may promote fine particle generation which is rather disadvantageous from a deposition point of view. High FR velocities increase the fraction of oropharynx deposition, resulting in a reduced fraction of deposition in the tracheobronchial and peripheral lung. Therefore, an optimum inspiratory condition must

be balanced between fine particle generation and the loss of these particles due to oropharyngeal deposition.

The present study shows that serum zanamivir concentrations are correlated to peak inspiratory flow rate (PIFR) values. Those children (one 6, one 7, one 8, one 9 and one 12 year old) who had either relatively low (lower than 60L/min) or relatively high (higher than 120 L/min) PIFR values failed to show quantifiable zanamivir serum concentrations. All those children who had PIFR in the range of 60 to 120 L/min show quantifiable serum zanamivir concentrations. A greater proportion of children >9 years old had PIFR values in the range of 60 to 120 L/min, as compared to children ≤ 9 years old. Efficacy results from trial NAI30009 revealed that in the 5 to 7 year olds, symptoms were alleviated one day sooner in the treatment group, as compared to the placebo group. In the 8 to 12 year old group, symptoms were alleviated 1.5 days sooner in the treatment group, as compared to the placebo group (refer to Dr. Baylor's review). The effect for younger children is even smaller if only 5 and 6 year old patients are considered. Therefore, this study showed that an optimal inhalation profile results in an adequate deposition of the drug along the respiratory tract which is reflected in efficacy and in this case, quantifiable serum zanamivir concentrations.

4. LABEL

The proposed label is attached to this review.

5. RECOMMENDATION

The pediatric pharmacokinetic data submitted in NDA 21-036 S-001 are similar, in terms of rate and extent of systemic zanamivir exposure, to the data submitted in NDA 21-036 for adults and adolescents older than 12 years of age. However, studies in the supplement demonstrate a lack of consistent delivery in children ages 6 to 9.

This is a 5-day medication and children must be treated within 2 days of initiation of symptoms, making it difficult to include a "training period" with the device. It is rather difficult to establish a cut-off age for the appropriateness of the use of the device based solely on the PK results, due to the small number of patients enrolled in this study. It is important to consider that the PK study is based on a single dose administration, while the efficacy study is based on a 5-day administration period. The PK study failed to demonstrate that children <10 years of age can use the device properly, which implies lack of efficacy in this population. The efficacy study showed that 5 and 6 year old children did not do as well as older children in terms of days to alleviation of symptoms. One can speculate that this inconsistency observed between PK and efficacy results may be due to a more rapid learning of the use of the device in the older children than the 5 and 6 year olds during the 5 days of the drug administration period

A mentioned earlier, the PK study failed to demonstrate that children <10 years of age can use the DISKHALER device properly. However, because in study NAI30009 the administration of zanamivir using the device showed efficacy in children 5 to 12 years of age, the approval decision for the use of the device for the administration of zanamir in this pediatric population will be subjected to the medical officer's decision.

7. CHEMISTRY OVERVIEW

7.1 Chemical name: 5 -(Acetylamino)-4- [(aminoiminomethyl)-amino]-2,6-arthydro-3,4,5 -trideoxy-D-glycero-D-galacto-non-2-enonic acid (Figure 1).

7.2 Structural formula:

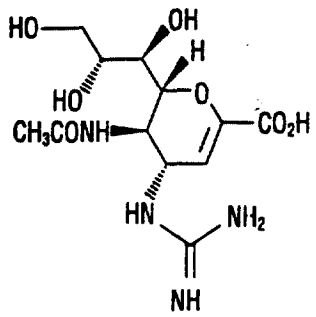


Figure 1. Structural formula of zanamivir.

7.3 Molecular formula: $C_{12}H_{20}N_4O_7$

7.4 Molecular weight: 332.3

7.5 Solubility: 18 mg/mL in water at 20 °C.

8. FORMULATION AND INHALATION DEVICE

8.1 Powder Formulation. The quantitative composition for inhaled zanamivir is summarized in Table 1.

Table 1. Quantitative composition for inhaled zanamivir

Ingredient	Unit amount	
	mg/blister	%w/w
Zanamivir (micronized)	5	
Lactose monohydrate NF		

Each RELENZA ROTADISK® contains 4 regularly spaced double-foil blisters. The contents of each blister are inhaled using the DISKHALER, a specially designed breath-activated plastic device for inhaling powder. After a RELENZA ROTADISK is loaded into the DISKHALER, a blister that contains medication is pierced and the zanamivir is dispersed into the air stream created when the patient inhales through the mouthpiece. Under standardized in vitro testing, RELENZA ROTADISK delivers 4 mg of zanamivir from the DISKHALER device when tested at a pressure drop of 3 kPa (corresponding to a flow rate of about 62 to 65 L/min) for 3 seconds. In a study of 5 adult and 5 adolescent patients with obstructive airway diseases, the combined peak inspiratory flow rates ranged from 66 to 140 L/min.

The mass median aerodynamic diameter (MMAD) and geometric standard deviation (GSD) determined by cascade impaction varied between 2.288μ and 2.741μ and from 1.515 and 1.727, respectively when tested at a flow rate of 28.3L/min

8.2 Solution Formulation: The zanamivir ampule is intended for oral inhalation via a nebulizer. The sterile solution contains 16mg/mL zanamivir, which is filled into 5mL glass ampules. It is isotonic with sodium chloride. This formulation is not available commercially.

9. INDICATION (as per proposed label)

Zanamivir is indicated in the treatment of uncomplicated acute illness due to influenza A and B virus in adults and pediatric patients 5 years and older who have been symptomatic for no more than 2 days.

10. DOSAGE AND ADMINISTRATION (as per propose label)

Relenza is for administration to the respiratory tract by oral inhalation only, using the DISKHALER device provided. The recommended dose of RELENZA for treatment of influenza in adults and pediatric patients 5 years and older is 2 inhalations (one 5-mg blister per inhalation for a total dose of 10 mg) twice daily (approximately 12 hours apart) for 5 days.

"Pharmacokinetics of Zanamivir (GG167) Following Inhaled Administration in Pediatric Subjects with Signs and Symptoms of Respiratory Illness"

Study Report No. RM1998/00266/00
Protocol No. NAIA1009
Volume: 2

OBJECTIVE

To evaluate the pharmacokinetics and to assess safety of zanamivir administered by DISKHALER™ with ROTADISK™ in subjects 5-12 years of age, or by solution with nebulizer in subjects 3 months up to 5 years of age.

SUBJECTS

Male and female children from 3 months to 12 years inclusive. Twenty-four subjects (24) with respiratory signs and symptoms were enrolled in this study.

STUDY DESIGN AND TREATMENT ADMINSTRATION

This was an open-label, single-dose, single-center, parallel study in 3 age groups:

1. 8 subjects ≥3 months to <5 years of age received 10mg of 16mg/mL zanamivir solution
   via nebulizer twice a day (10 mg).
2. 7 subjects ≥5 to <9 years of age received 10mg zanamivir ROTADISK via DISKHALER.
3. 9 subjects ≥9 to ≤12 years of age received 10mg zanamivir ROTADISK via DISKHALER.

Since this was an exploratory study to evaluate the PK and safety of inhaled zanamivir in children, no placebo control arm was deemed necessary.

For subjects at least 6 years of age, zanamivir was inhaled from two ROTADISK blisters and the inhalation profile was recorded. For younger children, 1 mL of zanamivir 16mg/mL was mixed with 2mL Normal Saline as nebulizing solution. The mixture was placed in the [redacted] nebulizer chamber, which was equipped with a facemask. The solution was nebulized for 10-15 minutes or until "apparent dryness". The airflow of the nebulizer was set to 5L/minute.

FORMULATION

The following formulations and batch numbers where used in this study.

Table 2. Zanamivir formulation used in this study

Study Drug/Strength	Batch Number	Expiration Date
Zanamivir solution 16mg/mL for nebulization or intranasal administration	U96/323A	31-Dec-98
Zanamivir ROTADISK 5mg	GFD30105	31-Mar-99
Placebo to match zanamivir ROTADISK 5mg for practice use	GFD30104	31-Mar-99

PHARMACOKINETIC MEASUREMENTS

Blood sampling. Venous blood samples (1.5mL to 5mL) were withdrawn from children at least 6 years of age via an intravenous cannula or by venipunture according to the following schedule:
Predose, 0.5, 1, 1.5, 2, 3, 4, 6 and 8 hours postdose.

Nasal wash sampling. For children at least 6 years of age, nasal washings were collected 4 hours (± 30 minutes) postdose (at least one-half hour after meal).

Urine sampling. Urine samples were collected predose and over 0-8 hours postdose if attainable, from children at least 6 years of age.

SAFETY MEASUREMENTS

Safety was evaluated in this study by monitoring of adverse events, laboratory safety data, physical examinations, and vital sign evaluations.

DATA ANALYSIS

Analytical Method

Concentrations of zanamivir in human serum and nasal wash were determined by LC-TIS/MS/MS and LC/UV, respectively. Urine samples were analyzed by HPLC with UV detection.

Table 3. Assay performance for zanamivir in serum and nasal wash

	Serum	Nasal Wash	Urine
Linearity		Unknown: Standard curve ranged from 5-1000ng/mL; statistics were not provided.	Unknown: Standard curve ranged from 0.3-50.8 µg/mL; statistics were not provided.
Accuracy		Unsatisfactory: not evaluable n=2	Unsatisfactory: not evaluable n=2
Precision		Unsatisfactory: not evaluable n=2	Unsatisfactory: not evaluable n=2
Sensitivity		unknown	unknown
Specificity		Satisfactory: chromatograms submitted	Satisfactory: chromatograms submitted

Pharmacokinetic Data Analysis

All pharmacokinetic parameters were calculated using a validated pharmacokinetic package, WinNonlin, version 1.5. Pharmacokinetic analysis consisted of standard non-compartmental analysis. Derived pharmacokinetic parameters: C_{max}, t_{max}, $AUC_{0\rightarrow8}$, AUC_{last}, AUC_{inf}, $t_{1/2}$, CL/F, V_z/F, A_e, CLr, and % recovered in urine.

Pharmacokinetic Results

Plasma and Urine PK Results

All enrolled patients completed the study. However, five subjects who received zanamivir via DISKHALER were excluded from pharmacokinetic analyses due to undetectable zanamivir serum concentrations or low drug concentrations (8.32-10.38 ng/mL) that were not detectable after 1.5 hrs. These children represent 43% of the 6 to <9 years, and 22% of the 9-12 year olds. Figure 2 shows the relationship between children's age and the detection of zanamivir is serum samples. No children between the ages of 3 and 5 years, inclusive were included in this study. Because no efficacy and safety information has been provided for children younger than 2 years following nebulization of zanamivir in solution, the PK data provided for children 3 months to 2 years of age are not relevant for this sNDA.

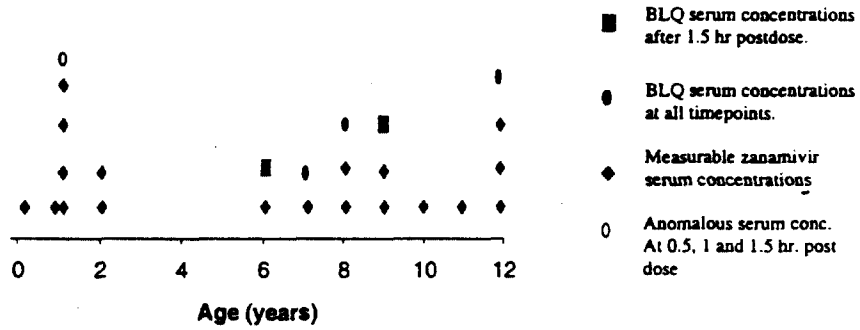
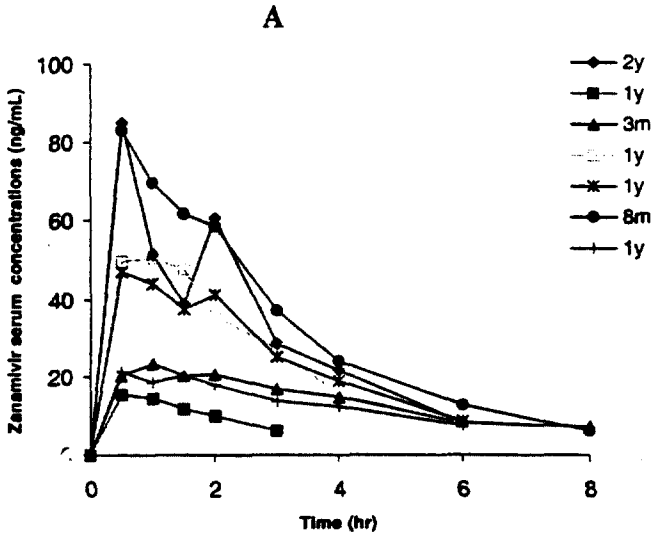


Figure 2. Detection of zanamivir in serum samples as a function of the patient's age.

Figure 3 shows the individual serum concentration-time profiles for patients in the 3 age groups. Subjects with BLQ serum concentrations at all timepoints, or after 1.5 hr, are not included. The mean serum concentrations versus time profiles for all subjects are presented in Figure 4. Average pharmacokinetic parameters are represented in Table 4.



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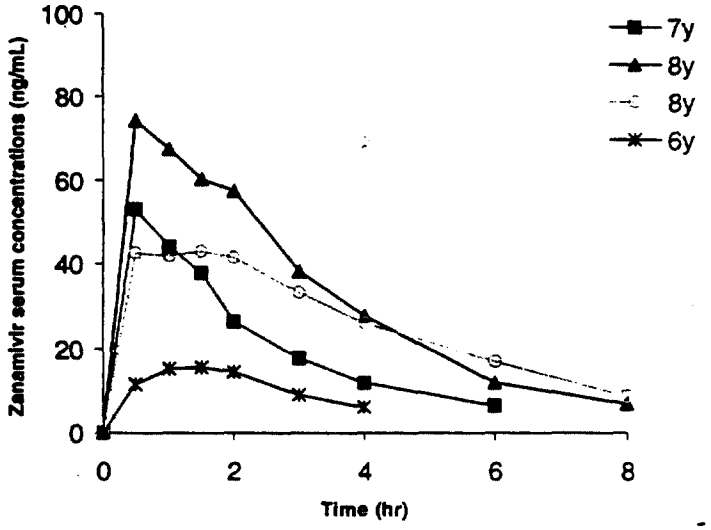

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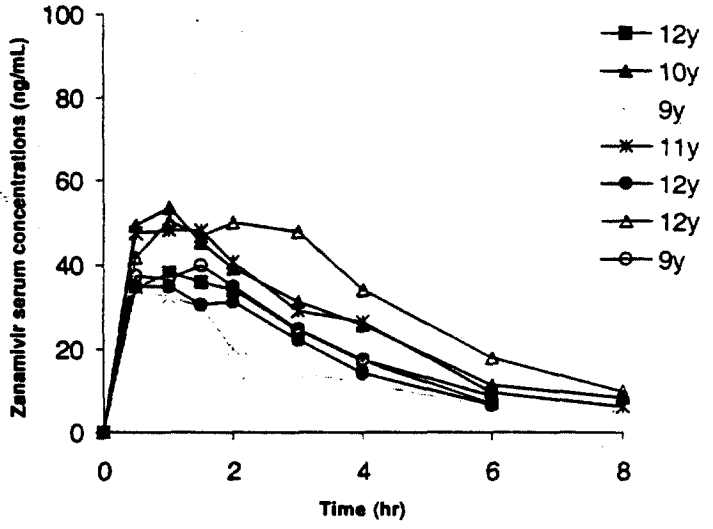

Figure 3. Individual zanamivir serum concentration-time profiles following single inhalation in: A) children 3 months to 2 years, B) 6 to <9 years old, and C) 9 to 12 years old.

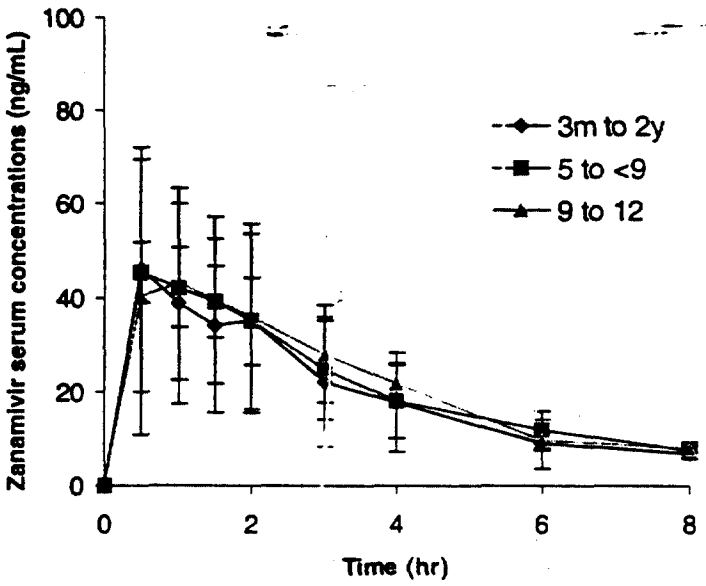

Figure 4. Mean zanamivir serum concentration-time profiles in children 3 months to 12 years of age following single inhalation of 10 mg zanamivir. Bars represent ± SD.

Table 4. Median (minimum, maximum) values of the pharmacokinetic parameters obtained following single 10 mg zanamivir inhalation in children.

Parameter	3m to 2y	6 to < 9 years old	9-12 years old
N	7	4	7
T_{max} (hours)	0.8 (0.5, 1.3)	1 (0.4, 1.5)	1 (0.4, 1.5)
C_{max} (ng/mL)	47 (16, 65)	47 (15,74)	40 (34, 54)
$T_{1/2}$ (hours)	1.9 (1.7, 4)	2 (1.7, 2.5)	2 (1.6, 2.3)
$AUC_{0\rightarrow\infty}$ (ng*hr/mL)	184 (54, 282)	192 (58, 272)	167 (123, 279)
$AUC_{0\rightarrow last}$ (ng*hr/mL)	161 (36, 265)	167 (43, 252)	147 (103, 248)
CL/F (L/hr)	54 (35, 192)	55 (37, 171)	60 (36, 81)
Vz/F	151 (96, 510)	174 (106, 413)	161 (115, 268)
A_e (mg)	NA	0.49 (0.14, 0.57)*	0.72 (0.38, 0.8)
% of Dose Recovered in Urine	NA	4.89 (1.42, 5.65)*	7.25 (3.75, 7.98)
CL_r (L/hr)	NA	2.42 (2.24, 2.56)*	3.95 (2.46, 5.51)

* N=3 patients.

Nasal Washings Results

Table 5 shows the zanamivir concentration determined in nasal washings 4 hours post inhalation. According to the sponsor, zanamivir concentrations in nasal washings were to have been adjusted by a factor equal to blood urea concentration divided by nasal urea concentration. However, the lab erroneously failed to use the high resolution BUN (blood urea nitrogen) test necessary to quantify the low level of urea present in the nasal washings. Therefore, pharmacokinetic analysis was not conducted in nasal washing samples. In addition, zanamivir concentrations in nasal washings were below the limit of

detection in the majority of children. Data for the four subjects with quantifiable concentrations are listed in Table 5.

Table 5. Zanamivir concentrations in nasal washing samples 4 hours post-inhalation

Age (years)	Concentration (ng/ml)
9	14.34
8	44748.35
11	34.16
12	95.71

Inhalation Profile Results

Figure 5 shows the distribution of peak inspiratory flow rates as a function of the patient's age. The peak inspiratory flow rate (PIFR) had a median value (minimum, maximum) of 84.3 L/min (30.5, 122.4). The lowest PIFR (30.5 L/min) corresponded to a twelve year old child whose zanamivir serum concentrations were BLQ. The highest PIFR (122.4 L/min) corresponds to an eight year old child whose zanamivir serum concentrations were also BLQ.

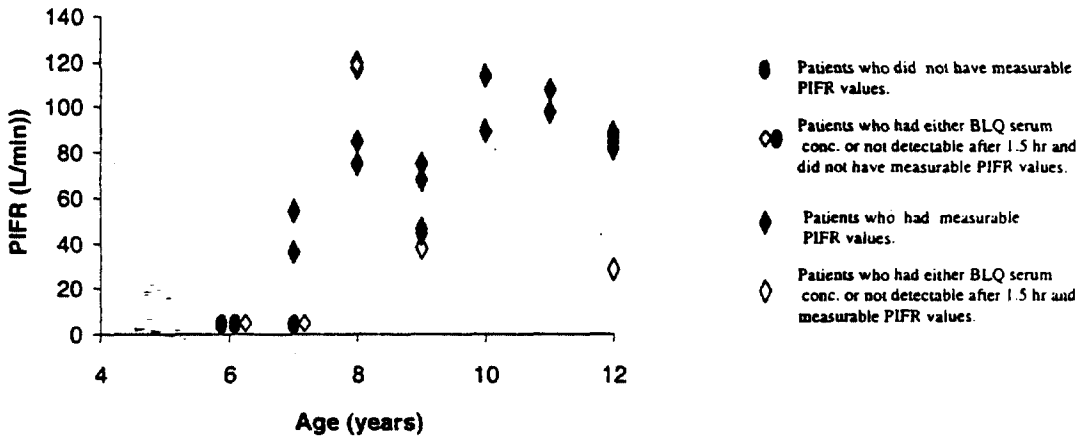

Figure 5. Peak inspiratory flow rates (PIFR) in pediatric patients measure through the DISKHALER. The majority of patients had two inhalations reported except one 8 year old, one 9 year old, and one 12 year old who had only one PIFR reported.

Safety Results

No serious adverse events or death occurred in the study. The subject's baseline physical examinations, vital signs, and laboratory findings were consistent with acute respiratory illness. Of the seven adverse events reported in six subjects (2 subjects per age group), just one, an episode of headache (in a 12 year old child), was considered to be possibly drug-related. Except for 3 incomplete resolution date/time, the rest were resolved before discharge. Nobody withdrew due to adverse events.

"Systemic Exposure Comparison to Healthy Adult Volunteer Data"

Objective

To compare the systemic exposure of 10mg inhaled zanamivir:

1. In children 3 months to 12 years of age with respiratory signs/symptoms and in healthy adults.
2. As solution through a nebulizer and as powder via DISKHALER.

Populations

Sixteen children in this study and twelve adults in Protocol NAIB1001 who had evaluable systemic exposure pharmacokinetic parameters C_{max} and AUC_{inf} after a single 10mg zanamivir inhalation are included in the analysis. Tables 6 and 7 and Figure 6 show the median pharmacokinetic parameters and individual C_{max} and AUC_{inf} values for these populations, respectively. Because the same analytical assay method (LC-TIS/MS/MS) was applied to quantify zanamivir serum concentrations in NAIB1001, it was chosen as the comparator study out of two adult pharmacokinetic studies.

Methods

The pharmacokinetic parameters of interest in this study were individual C_{max} and AUC_{inf}, which were used as independent variables in an ANOVA. Two models were run. In the first model, the age effect was estimated with protocol as a covariate. In the second model, the formulation effect was estimated with age as the covariate. A nonparametric test of medians (Brown-Mood from SAS NPARIWAY) was used to confirm the differences of age and formulation.

Results

Table 6 and 7 and Figure 6 show that no age, protocol or formulation effects were observed in zanamivir C_{max} or AUC_{inf} in the evaluable patients.

Table 6. Mean C_{max} and AUC_{inf} values following single 10-mg zanamivir inhalation for children age 3 month to 13 years and adults

Zanamivir Dose/Formulation	10mg in solution via nebulizer	10 mg Dry powder via DISKHALER		
Protocol	NAIA1009	NAIA1009	NAIB1001	
	N=7	N=11	N=12	N=10
Age (years)				
Mean (SD)	1(1)	9(2)	29(8)	31(8)
Median (min, max)	1(0,2)	9(6,12)	29(20,42)	31(20,42)
C_{max} (ng/mL)				
Mean (SD)	47(29)	44(15)	37(15)	
CV%	62%	34%	41%	
Median (min,max)	47(16,85)	43(15,74)	34(17,65)	
AUC_{inf} (ng.hr/mL)				
Mean (SD)	171(73)	183(68)		194(67)
CV%	43%	37%		35%
Median (min,max)	184(52,282)	167(58,279)		186(111,328)

Data reported by the sponsor

Table 7. Analysis of variance for the effect of formulation and age

	C_{max} (ng/mL)		AUC_{inf} (ng.hr/mL)	
	Median (min,max)	**P value**	**Median (min,max)**	**P value**
Formulation effect (age as a covariate)	F1: 40(17,75) F2: 47.03(15.54,85.14)	0.4759	F1: 161.8 (52,328.3) F2: 184.1(52.07,281.8)	0.5534
Age effect (protocol as a covariate)	G1:47.03(15.54,85.14)	0.4912	G1:184.1(52.7,281.8)	0.8154
	G2:42(17,75)		G2:160(52,280)	
	G3:34.4(17.4,65.3)		G3: 186.4(110.7(328.3)	

F1: Powder formulation; F2: Solution; G1: 3months to 5 years; G2: 5 to <9 years; G3:9 to 12 years. Data calculated by the reviewer.

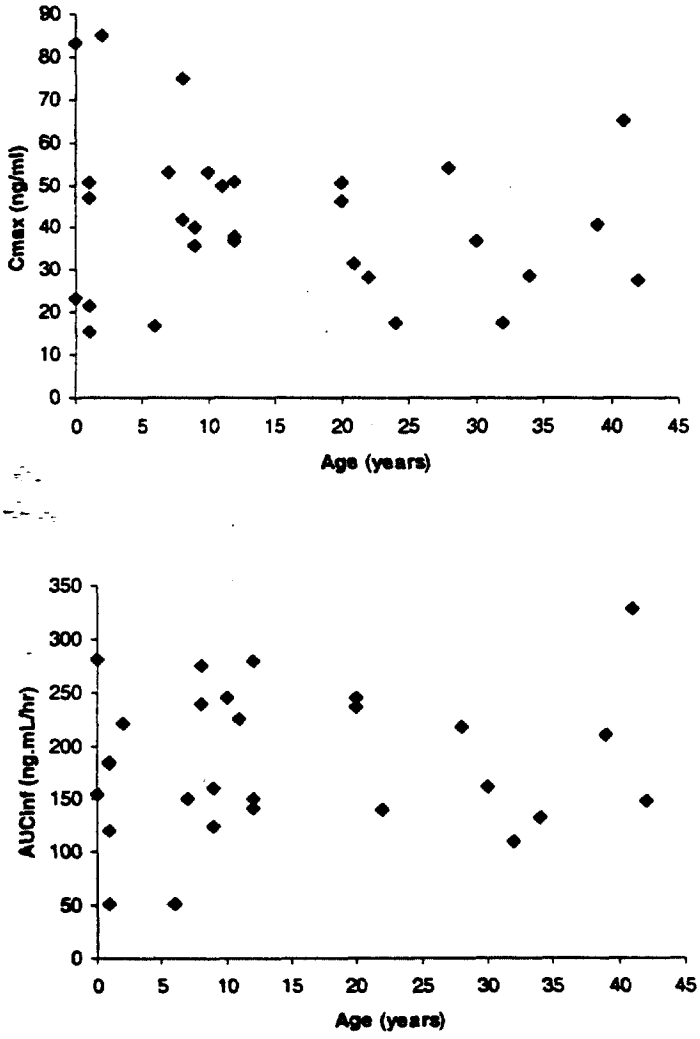

Figure 6. C_{max} and AUC_{inf} distribution as a function of age following zanamivir inhalation.

DISCUSSION

Although Figure 4 shows no pronounced difference in the concentration-time profiles between groups (age groups, solution vs. powder formulation groups), Figure 3 and Table 4 show that children younger than 10 years old had higher variability than the ≥10 to 12 year old group. This is reflected in AUC_{∞} values of 58 to 272 ng*hr/mL, C_{max} values of 15 to 74 ng/mL and % of dose recovered in urine of 1.42 to 5.65 for the 6 to <10 year old group compared to the 10 to 12 year old group who have AUC_{∞} values of 123 to 279 ng*hr/mL, C_{max} values of 34 to 54 ng/mL and % recovery in urine of 3.75 to 7.98. In addition, the 6 to <10 year old group had no detectable zanamivir in nasal washings 4 hours after dosing (Table 5), had the widest range in the peak inspiratory flow rate (Figure 5), and 43% of the children show either BLQ serum concentration at all times points or no detectable concentrations 1.5 hours postdosing. These results indicate inconsistency of drug delivery via DISKHALER in this age group, which is most likely due to an inappropriate use of the device.

In part 2 of this study, the sponsor showed no statistically significant differences in the AUC_{∞} and C_{max} values between the children who used the DISKHALER and the adult group (Tables 6 and 7). The sponsor claims that because both groups have the same zanamivir exposure, same variability in the PK data, and the drug was well tolerated in both populations, there is enough evidence to administer the same dose to children. This reviewer agrees with this statement.

CONCLUSION

The data presented in this study provided evidence to support the administration of zanamivir 10 mg twice daily via DISKHALER in children ages 10 to 12 years of age. There are not enough PK data to recommend the administration of this drug via DISKHALER in children younger than 10 years old. The present study also support the administration of zanamivir 16mg/mL twice daily in children from 3 months to 2 years of age via nebulization. However, further studies are needed in this population since efficacy data have not been provided.

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/S/ 3/20/00

Pharmacokinetics Reviewer, DPEIII, OCPB

Concurrence: /S/ 2/4/00

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cc:

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	/PKTL/KReynolds
HFD-340	/Viswanathan

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 21-036 S-001
Type of Application: Supplemental New Drug Application
Drug: Relenza® (Zanamivir for Inhalation).
Indication: Treatment of Influenza A & B in Pediatric Patients.
Dosage Form: Inhalation Powder Packaged in Blisters of 25 mg each (Rotadisk®).
Strength: 5 milligrams of Zanamivir per Blister
Route of Administration: Oral Inhalation
Inhalation device: Diskhaler®
Applicant: Glaxo Wellcome, Inc.
Submission Dates: October 25, 1999; March 3, 2000; March 9, 2000
Draft Review: February 9, 2000, March 2, 2000, March 21, 2000
Reviewer: Sandra Suarez, Ph.D.