CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 021036/S-008

Trade Name: **RELENZA**

Generic Name: **Zanamivir for Inhalation**

Sponsor: **GlaxoSmithKline**

Approval Date: 03/29/06

Indications: RELENZA is indicated in adults and pediatric patients 5 years of age and older for prophylaxis of influenza

CENTER FOR DRUG EVALUATION AND RESEARCH

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021036/S-008

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-036/S-008

GlaxoSmithKline
Attn: Sherman N. Alfors, US Regulatory Affairs
PO Box 13398
Five Moore Drive
Research Triangle Park, NC 27709

Dear Mr. Alfors:

Please refer to your supplemental new drug application dated November 4, 2005, received November 4, 2005, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for RELENZA® (zanamivir for inhalation).

We acknowledge receipt of your submissions dated:

November 21, 2005	February 7, 2006	March 7, 2006
December 2, 2005	February 22, 2006	March 14, 2006
January 18, 2006	March 1, 2006	March 21, 2006
January 26, 2006	March 2, 2006	March 26, 2006
		March 27, 2006

This supplemental new drug application provides for the use of RELENZA® (zanamivir for inhalation) for prophylaxis of influenza in adults and children five years of age and older.

We completed our review of this application, as amended. This application is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert and text for the patient package insert).

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved supplement NDA 21-036/S-008**." Approval of this submission by FDA is not required before the labeling is used.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric subjects unless this requirement is waived or deferred. We are waiving the pediatric study requirement for this application for subjects less than five years of age.

We remind you of your postmarketing study commitments in your submission dated March 26, 2006. These commitments are listed below.

1. Provide an annual update on emergence of resistance to zanamivir, as well as cross-resistance between zanamivir and other neuraminidase inhibitors, as an integrated review of information from NISN (Neuraminidase Inhibitor Surveillance Network), data collected by GlaxoSmithKline (GSK), and information in the published literature. Each annual update will include information on the methodologies (e.g., culture, PCR) used in studies during that reporting period. Timeline: GSK will provide this annual update as part of the NDA Annual Reports due within 60 days of the original approval anniversaries in July 2007, July 2008, and July 2009.

2. Submit a postmarketing adverse drug experience report to Division of Antiviral Products (DAVP) as a "15-Day Alert Report" for each of the following serious adverse events:
    a. anaphylaxis
    b. bronchospasm or other pulmonary adverse event
    c. cardiovascular adverse event
    d. any adverse event with a fatal outcome

    Consistent with 21 CFR 314.80, GSK will make diligent efforts to obtain as complete a set of information as possible, including information about antecedent and concomitant medical circumstances of the adverse experience or fatality, results of laboratory tests, a copy of any available medical records, and a copy of the autopsy report (if performed). A "15-Day Alert Report - Follow Up" will be submitted to DAVP if additional information is obtained after the deadline for submission of the initial report. The 15-Day Alert Reports due to DAVP each week will be collected and submitted as a batch, once a week, to DAVP. Each such submission will be sent to NDA 21-036 as "General Correspondence: Safety Reports per Postmarketing Commitment". Timeline: Such Alert Reports will be prepared and submitted by GSK for the specified events occurring through May 31, 2009.

3. Prepare a Wall Chart for medical practices and pharmacies on how to use the Relenza Diskhaler. This Wall Chart will be an illustration-intensive (not text intensive) aid to patient education. Versions will be prepared in English and Spanish. Timeline: GSK will submit the proposed Wall Chart and distribution plan/timeline to DAVP for review and comment no later than June 30, 2006.

4. Meet with investigators at NIAID to develop a Concept Protocol and seek funding to assess the effects of zanamivir 10mg inhaled once daily for 2 months on clinical laboratory measures of safety. Timeline: GSK will meet with NIAID by July 31, 2006 and provide DAVP with meeting minutes including the outcome of the meeting by August 31, 2006.

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled

"**Postmarketing Study Commitment Protocol**", "**Postmarketing Study Commitment Final Report**", or "**Postmarketing Study Commitment Correspondence**."

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH
Food and Drug Administration
WO 22, Room 4447
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call David Araojo, Pharm.D., Regulatory Project Manager, at (301) 796-0669.

Sincerely,

{See appended electronic signature page}

Debra Birnkrant, M.D.
Director
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure: approved draft labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Debra Birnkrant
3/29/2006 10:47:17 AM
NDA 21-036

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021036/S-008

LABELING

PRESCRIBING INFORMATION

RELENZA®

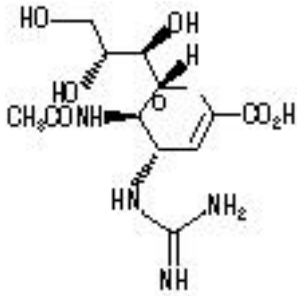
(zanamivir for inhalation)

For Oral Inhalation Only

For Use with the DISKHALER® Inhalation Device

DESCRIPTION

The active component of RELENZA is zanamivir. The chemical name of 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. It has the following structural formula:



Zanamivir is a white to off-white powder with a solubility of approximately 18 mg/mL in water at 20°C.

RELENZA is for administration to the respiratory tract by oral inhalation only. Each RELENZA ROTADISK® contains 4 regularly spaced double-foil blisters with each blister containing a powder mixture of 5 mg of zanamivir and 20 mg of lactose (which contains milk proteins). The contents of each blister are inhaled using a specially designed breath-activated plastic device for inhaling powder called the DISKHALER. 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. The amount of drug delivered to the respiratory tract will depend on patient factors such as inspiratory flow. 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 (PIFR) ranged from 66 to 140 L/min. In a separate study of 16 pediatric patients, PIFR results were more variable; 4 did not achieve measurable flow rates, and PIFR for measurable inhalations by 12 children ranged from 30.5 to 122.4 L/min. Only 1 of 4 children under age 8 had a measurable flow rate (see CLINICAL PHARMACOLOGY: Pediatric Patients, INDICATIONS AND USAGE: Description of Clinical Studies, and PRECAUTIONS: Pediatric Use).

MICROBIOLOGY

Mechanism of Action: The mechanism of action of zanamivir is via inhibition of influenza virus neuraminidase with the possibility of alteration of virus particle aggregation and release.

Antiviral Activity: The antiviral activity of zanamivir against laboratory and clinical isolates of influenza virus was determined in cell culture assays. The concentrations of zanamivir required for inhibition of influenza virus were highly variable depending on the assay method used and virus isolate tested. The 50% and 90% effective concentrations (EC_{50} and EC_{90}) of zanamivir were in the range of 0.005 to 16.0 μM and 0.05 to >100 μM, respectively (1 μM = 0.33 mcg/mL). The relationship between the in vitro inhibition of influenza virus by zanamivir and the inhibition of influenza virus replication in humans has not been established.

Resistance: Influenza viruses with reduced susceptibility to zanamivir have been recovered in vitro by multiple passages of the virus in the presence of increasing concentrations of the drug. Genetic analysis of these viruses showed that the reduced susceptibility in vitro to zanamivir is associated with mutations that result in amino acid changes in the viral neuraminidase or viral hemagglutinin or both. Resistance mutations selected in vitro which result in neuraminidase amino acid substitutions include E119G/A/D and R292K.Mutations selected in vitro in hemagglutinin include: K68R, G75E, E114K, N145S, S165N, S186F, N199S, and K222T.

In an immunocompromised patient infected with influenza B virus, a variant virus emerged after treatment with an investigational nebulized solution of zanamivir for 2 weeks. Analysis of this variant showed a hemagglutinin mutation (T198I) which resulted in a reduced affinity for human cell receptors, and a substitution in the neuraminidase active site (R152K) which reduced the enzyme's activity to zanamivir by 1,000-fold. Insufficient information is available to characterize the risk of emergence of zanamivir resistance in clinical use.

Cross-Resistance: Cross-resistance has been observed between some zanamivir-resistant and some oseltamivir-resistant influenza virus mutants generated in vitro. However, some of the in vitro zanamivir-induced resistance mutations, E119G/A/D and R292K, occurred at the same neuraminidase amino acid positions as in the clinical isolates resistant to oseltamivir, E119V and R292K. No studies have been performed to assess risk of emergence of cross-resistance during clinical use.

Influenza Vaccine Interaction Study: An interaction study (n = 138) was conducted to evaluate the effects of zanamivir (10 mg once daily) on the serological response to a single dose of trivalent inactivated influenza vaccine, as measured by hemagglutination inhibition titers. There was no clear difference in hemagglutination inhibition antibody titers at 2 weeks and 4 weeks after vaccine administration between zanamivir and placebo recipients.

Influenza Challenge Studies: Antiviral activity of zanamivir was supported for infection with influenza A virus, and to a more limited extent for infection with influenza B virus, by Phase 1 studies in volunteers who received intranasal inoculations of challenge strains of influenza virus, and received an intranasal formulation of zanamivir or placebo starting before or shortly after viral inoculation.

CLINICAL PHARMACOLOGY

Pharmacokinetics: ***Absorption and Bioavailability:*** Pharmacokinetic studies of orally inhaled zanamivir indicate that approximately 4% to 17% of the inhaled dose is systemically absorbed. The peak serum concentrations ranged from 17 to 142 ng/mL within 1 to 2 hours following a 10-mg dose. The area under the serum concentration versus time curve (AUC∞) ranged from 111 to 1,364 ng•hr/mL.

Distribution: Zanamivir has limited plasma protein binding (<10%).

Metabolism: Zanamivir is renally excreted as unchanged drug. No metabolites have been detected in humans.

Elimination: The serum half-life of zanamivir following administration by oral inhalation ranges from 2.5 to 5.1 hours. It is excreted unchanged in the urine with excretion of a single dose completed within 24 hours. Total clearance ranges from 2.5 to 10.9 L/hr. Unabsorbed drug is excreted in the feces.

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

Impaired Renal Function: Systemic exposure is limited after inhalation (see Absorption and Bioavailability). After a single intravenous dose of 4 mg or 2 mg of zanamivir in volunteers with mild/moderate or severe renal impairment, respectively, significant decreases in renal clearance (and hence total clearance: normals 5.3 L/hr, mild/moderate 2.7 L/hr, and severe 0.8 L/hr; median values) and significant increases in half-life (normals 3.1 hr, mild/moderate 4.7 hr, and severe 18.5 hr; median values) and systemic exposure were observed. Safety and efficacy have not been documented in the presence of severe renal insufficiency.

Pediatric Patients: The pharmacokinetics of zanamivir were evaluated in pediatric patients with signs and symptoms of respiratory illness. Sixteen patients, 6 to 12 years of age, received a single dose of 10-mg zanamivir dry powder via DISKHALER. Five patients had either undetectable zanamivir serum concentrations or had low drug concentrations (8.32 to 10.38 ng/mL) that were not detectable after 1.5 hours. Eleven patients had C_{max} median values of 43 ng/mL (range 15 to 74) and AUC_{∞} median values of 167 ng•hr/mL (range 58 to 279). Low or undetectable serum concentrations were related to lack of measurable PIFR in individual patients (see DESCRIPTION, INDICATIONS AND USAGE: Description of Clinical Studies, and PRECAUTIONS: Pediatric Use).

Geriatric Patients: The pharmacokinetics of zanamivir have not been studied in patients over 65 years of age (see PRECAUTIONS: Geriatric Use).

Gender, Race, and Weight: In a population pharmacokinetic analysis in patient studies, no clinically significant differences in serum concentrations and/or pharmacokinetic parameters (V/F, CL/F, ka, AUC_{0-3}, C_{max}, T_{max}, CLr, and % excreted in urine) were observed when demographic variables (gender, age, race, and weight) and indices of infection (laboratory evidence of infection, overall symptoms, symptoms of upper respiratory illness, and viral titers) were considered. There were no significant correlations between measures of systemic exposure and safety parameters.

Drug Interactions: No clinically significant pharmacokinetic drug interactions are predicted based on data from in vitro studies.

Zanamivir is not a substrate nor does it affect cytochrome P450 (CYP) isoenzymes (CYP1A1/2, 2A6, 2C9, 2C18, 2D6, 2E1, and 3A4) in human liver microsomes.

INDICATIONS AND USAGE

Treatment of Influenza: RELENZA is indicated for treatment of uncomplicated acute illness due to influenza A and B virus in adults and pediatric patients 7 years of age and older who have been symptomatic for no more than 2 days (see Description of Clinical Studies and PRECAUTIONS).

Prophylaxis of Influenza: RELENZA is indicated in adults and pediatric patients 5 years of age and older for prophylaxis of influenza.

Important Information on Use of RELENZA:

- RELENZA is not recommended for treatment or prophylaxis of influenza in individuals with underlying airways disease (such as asthma or chronic obstructive pulmonary disease [see WARNINGS]) due to risk of serious bronchospasm.
- RELENZA has not been proven effective for treatment of influenza in individuals with underlying airways disease.
- RELENZA has not been proven effective for prophylaxis of influenza in the nursing home setting.
- RELENZA is not a substitute for early vaccination on an annual basis as recommended by the Centers for Disease Control's Immunization Practices Advisory Committee.

Description of Clinical Studies: ***Treatment of Influenza: Adults and Adolescents:***

The efficacy of RELENZA 10 mg inhaled twice daily for 5 days in the treatment of influenza has been evaluated in placebo-controlled studies conducted in North America, the Southern Hemisphere, and Europe during their respective influenza seasons. The magnitude of treatment effect varied between studies, with possible relationships to population-related factors including amount of symptomatic relief medication used.

Populations Studied: The principal Phase 3 studies enrolled 1,588 patients ages 12 years and older (median age 34 years, 49% male, 91% Caucasian), with uncomplicated influenza-like illness within 2 days of symptom onset. Influenza was confirmed by culture, hemagglutination inhibition antibodies, or investigational direct tests. Of 1,164 patients with confirmed influenza, 89% had influenza A and 11% had influenza B. These studies served as the principal basis for efficacy evaluation, with more limited Phase 2 studies providing supporting information where necessary. Following randomization to either zanamivir or placebo (inhaled lactose vehicle), all patients received instruction and supervision by a healthcare professional for the initial dose.

Principal Results: The definition of time to improvement in major symptoms of influenza included no fever and self-assessment of “none” or “mild” for headache, myalgia, cough, and sore throat. A Phase 2 and a Phase 3 study conducted in North America (total of over

600 influenza-positive patients) suggested up to one day of shortening of median time to this defined improvement in symptoms in patients receiving zanamivir compared to placebo, although statistical significance was not reached in either of these studies. In a study conducted in the Southern Hemisphere (321 influenza-positive patients), a 1.5-day difference in median time to symptom improvement was observed. Additional evidence of efficacy was provided by the European study.

Other Findings: There was no consistent difference in treatment effect in patients with influenza A compared to influenza B; however, these trials enrolled smaller numbers of patients with influenza B and thus provided less evidence in support of efficacy in influenza B.

In general, patients with lower temperature (e.g., 38.2°C or less) or investigator-rated as having less severe symptoms at entry derived less benefit from therapy.

No consistent treatment effect was demonstrated in patients with underlying chronic medical conditions, including respiratory or cardiovascular disease (see WARNINGS and PRECAUTIONS).

No consistent differences in rate of development of complications were observed between treatment groups.

Some fluctuation of symptoms was observed after the primary study endpoint in both treatment groups.

Pediatric Patients: The efficacy of RELENZA 10 mg inhaled twice daily for 5 days in the treatment of influenza in pediatric patients has been evaluated in a placebo-controlled study conducted in North America and Europe, enrolling 471 patients, ages 5 to 12 years (55% male, 90% Caucasian), within 36 hours of symptom onset. Of 346 patients with confirmed influenza, 65% had influenza A and 35% had influenza B. The definition of time to improvement included no fever and parental assessment of no or mild cough and absent/minimal muscle and joint aches or pains, sore throat, chills/feverishness, and headache. Median time to symptom improvement was one day shorter in patients receiving zanamivir compared with placebo. No consistent differences in rate of development of complications were observed between treatment groups. Some fluctuation of symptoms was observed after the primary study endpoint in both treatment groups.

Although this study was designed to enroll children ages 5 to 12 years, the product is indicated only for children 7 years of age and older. This evaluation is based on the combination of lower estimates of treatment effect in 5- and 6-year-olds compared with the overall study population, and evidence of inadequate inhalation through the DISKHALER in a pharmacokinetic study (see DESCRIPTION, CLINICAL PHARMACOLOGY: Pediatric Patients, and PRECAUTIONS: Pediatric Use).

Prophylaxis of Influenza: The efficacy of RELENZA in preventing naturally occurring influenza illness has been demonstrated in 2 post-exposure prophylaxis studies in households and 2 seasonal prophylaxis studies during community outbreaks of influenza. The primary efficacy endpoint in these studies was the incidence of symptomatic, laboratory-confirmed influenza, defined as the presence of 2 or more of the following symptoms: oral temperature

≥100°F/37.8°C or feverishness, cough, headache, sore throat, and myalgia; and laboratory confirmation of influenza A or B by culture, PCR, or seroconversion (defined as a 4-fold increase in convalescent antibody titer from baseline).

Two studies assessed post-exposure prophylaxis in household contacts of an index case. Within 1.5 days of onset of symptoms in an index case, each household (including all family members ≥5 years of age) was randomized to RELENZA 10 mg inhaled once daily or placebo inhaled once daily for 10 days. In the first study only, each index case was randomized to RELENZA 10 mg inhaled twice daily for 5 days or inhaled placebo twice daily for 5 days. In this study, the proportion of households with at least 1 new case of symptomatic laboratory-confirmed influenza was reduced from 19.0% (32 of 168 households) for the placebo group to 4.1% (7 of 169 households) for the group receiving RELENZA.

In the second study, index cases were not treated. The incidence of symptomatic laboratory-confirmed influenza was reduced from 19.0% (46 of 242 households) for the placebo group to 4.1% (10 of 245 households) for the group receiving RELENZA.

Two seasonal prophylaxis studies assessed RELENZA 10 mg inhaled once daily versus placebo inhaled once daily for 28 days during community outbreaks. The first study enrolled subjects 18 years of age or greater (mean age 29 years) from two university communities. The majority of subjects were unvaccinated (86%). In this study, the incidence of symptomatic laboratory-confirmed influenza was reduced from 6.1% (34 of 554) for the placebo group to 2.0% (11 of 553) for the group receiving RELENZA.

The second seasonal prophylaxis study enrolled subjects 12 to 94 years of age (mean age 60 years) with 56% of them older than 65 years of age. Sixty-seven percent of the subjects were vaccinated. In this study, the incidence of symptomatic laboratory-confirmed influenza was reduced from 1.4% (23 of 1,685) for the placebo group to 0.2% (4 of 1,678) for the group receiving RELENZA.

CONTRAINDICATIONS

RELENZA is contraindicated in patients with a known hypersensitivity to any component of the formulation (see DESCRIPTION).

WARNINGS

RELENZA IS NOT RECOMMENDED FOR TREATMENT OR PROPHYLAXIS OF INFLUENZA IN INDIVIDUALS WITH UNDERLYING AIRWAYS DISEASE (SUCH AS ASTHMA OR CHRONIC OBSTRUCTIVE PULMONARY DISEASE) (see INDICATIONS AND USAGE).

Serious cases of bronchospasm, including fatalities, have been reported during treatment with RELENZA in patients with and without underlying airways disease. Many of these cases were reported during postmarketing and causality was difficult to assess.

RELENZA SHOULD BE DISCONTINUED IN ANY PATIENT WHO DEVELOPS BRONCHOSPASM OR DECLINE IN RESPIRATORY FUNCTION; immediate treatment and hospitalization may be required. Some patients without prior pulmonary

disease may also have respiratory abnormalities from acute respiratory infection that could resemble adverse drug reactions or increase patient vulnerability to adverse drug reactions.

Bronchospasm was documented following administration of zanamivir in 1 of 13 patients with mild or moderate asthma (but without acute influenza-like illness) in a Phase 1 study. In interim results from an ongoing treatment study in patients with acute influenza-like illness superimposed on underlying asthma or chronic obstructive pulmonary disease, more patients on zanamivir than on placebo experienced greater than 20% decline in FEV_1 or peak expiratory flow rate.

If treatment with RELENZA is considered for a patient with underlying airways disease, the potential risks and benefits should be carefully weighed. If a decision is made to prescribe RELENZA for such a patient, this should be done only under conditions of careful monitoring of respiratory function, close observation, and appropriate supportive care including availability of fast-acting bronchodilators.

PRECAUTIONS

General: Patients should be instructed in the use of the delivery system. Instructions should include a demonstration whenever possible. Patients should read and follow carefully the Patient Instructions for Use accompanying the product. Effective and safe use of RELENZA requires proper use of the DISKHALER to inhale the drug.

There is no evidence for efficacy of zanamivir in any illness caused by agents other than influenza virus A and B.

No data are available to support safety or efficacy in patients who begin treatment after 48 hours of symptoms.

Safety and efficacy of repeated treatment courses have not been studied.

Allergic Reactions: Allergic-like reactions, including oropharyngeal edema, serious skin rashes, and anaphylaxis have been reported in post-marketing experience with RELENZA. RELENZA should be stopped and appropriate treatment instituted if an allergic reaction occurs or is suspected.

Bacterial Infections: Serious bacterial infections may begin with influenza-like symptoms or may coexist with or occur as complications during the course of influenza. RELENZA has not been shown to prevent such complications.

Prevention of Influenza: Use of zanamivir should not affect the evaluation of individuals for annual influenza vaccination in accordance with guidelines of the Centers for Disease Control and Prevention Advisory Committee on Immunization Practices.

Limitations of Populations Studied: Safety and efficacy have not been demonstrated in patients with high-risk underlying medical conditions (see INDICATIONS AND USAGE: Description of Clinical Studies, and WARNINGS). No information is available regarding treatment of influenza in patients with any medical condition sufficiently severe or unstable to be considered at imminent risk of requiring inpatient management.

Information for Patients: Patients should be instructed in use of the delivery system. Instructions should include a demonstration whenever possible.

For the proper use of RELENZA, the patient should read and follow carefully the accompanying Patient Instructions for Use.

Patients should be advised that the use of RELENZA for treatment of influenza has not been shown to reduce the risk of transmission of influenza to others.

Patients should be advised of the risk of bronchospasm, especially in the setting of underlying airways disease, and should stop RELENZA and contact their physician if they experience increased respiratory symptoms during treatment such as worsening wheezing, shortness of breath, or other signs or symptoms of bronchospasm (see WARNINGS). If a decision is made to prescribe RELENZA for a patient with asthma or chronic obstructive pulmonary disease, the patient should be made aware of the risks and should have a fast-acting bronchodilator available. Patients scheduled to take inhaled bronchodilators at the same time as RELENZA should be advised to use their bronchodilators before taking RELENZA.

Drug Interactions: No clinically significant pharmacokinetic drug interactions are predicted based on data from in vitro studies.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: ***Carcinogenesis:*** In 2-year carcinogenicity studies conducted in rats and mice using a powder formulation administered through inhalation, zanamivir induced no statistically significant increases in tumors over controls. The maximum daily exposures in rats and mice were approximately 23 to 25 and 20 to 22 times, respectively, greater than those in humans at the proposed clinical dose based on AUC comparisons.

Mutagenesis: Zanamivir was not mutagenic in in vitro and in vivo genotoxicity assays which included bacterial mutation assays in *S. typhimurium* and *E. coli*, mammalian mutation assays in mouse lymphoma, chromosomal aberration assays in human peripheral blood lymphocytes, and the in vivo mouse bone marrow micronucleus assay.

Impairment of Fertility: The effects of zanamivir on fertility and general reproductive performance were investigated in male (dosed for 10 weeks prior to mating, and throughout mating, gestation/lactation, and shortly after weaning) and female rats (dosed for 3 weeks prior to mating through day 19 of pregnancy, or day 21 post partum) at IV doses 1, 9, and 90 mg/kg/day. Zanamivir did not impair mating or fertility of male or female rats, and did not affect the sperm of treated male rats. The reproductive performance of the F1 generation born to female rats given zanamivir was not affected. Based on a subchronic study in rats at a 90-mg/kg/day IV dose, AUC values ranged between 142 and 199 mcg•hr/mL (>300 times the human exposure at the proposed clinical dose).

Pregnancy: Pregnancy Category C. Embryo/fetal development studies were conducted in rats (dosed from days 6 to 15 of pregnancy) and rabbits (dosed from days 7 to 19 of pregnancy) using the same IV doses. Pre- and post-natal developmental studies were performed in rats (dosed from day 16 of pregnancy until litter day 21 to 23). In all studies, intravenous (1, 9, and 90 mg/kg/day)

instead of the inhalational route of drug administration was used. No malformations, maternal toxicity, or embryotoxicity were observed in pregnant rats or rabbits and their fetuses. Because of insufficient blood sampling timepoints in both rat and rabbit reproductive toxicity studies, AUC values were not available. However, in a subchronic study in rats at the 90-mg/kg/day IV dose, the AUC values were greater than 300 times the human exposure at the proposed clinical dose.

An additional embryo/fetal study, in a different strain of rat, was conducted using subcutaneous administration of zanamivir, 3 times daily, at doses of 1, 9, or 80 mg/kg during days 7 to 17 of pregnancy. There was an increase in the incidence rates of a variety of minor skeleton alterations and variants in the exposed offspring in this study. Based on AUC measurements, the high dose in the study produced an exposure greater than 1,000 times the human exposure at the proposed clinical dose. However, the individual incidence rate of each skeletal alteration or variant, in most instances, remained within the background rates of the historical occurrence in the strain studied.

Zanamivir has been shown to cross the placenta in rats and rabbits. In these animals, fetal blood concentrations of zanamivir were significantly lower than zanamivir concentrations in the maternal blood.

There are no adequate and well-controlled studies of zanamivir in pregnant women. Zanamivir should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Studies in rats have demonstrated that zanamivir is excreted in milk. However, nursing mothers should be instructed that it is not known whether zanamivir is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when RELENZA is administered to a nursing mother.

Pediatric Use: Safety and effectiveness of RELENZA for treatment of influenza have not been assessed in pediatric patients less than 7 years of age.

The safety and effectiveness of RELENZA have been studied in a Phase 3 treatment study in pediatric patients, where 471 children 5 to 12 years of age received zanamivir or placebo (see INDICATIONS AND USAGE: Description of Clinical Studies, ADVERSE REACTIONS, and DOSAGE AND ADMINISTRATION). In a Phase 1 study of 16 children ages 6 to 12 years with signs and symptoms of respiratory disease, 4 did not produce a measurable peak inspiratory flow rate (PIFR) through the DISKHALER (3 with no adequate inhalation on request, 1 with missing data), 9 had measurable PIFR on each of 2 inhalations, and 3 achieved measurable PIFR on only 1 of 2 inhalations. Neither of two 6-year-olds and one of two 7-year-olds produced measurable PIFR. Overall, 8 of the 16 children (including all those under 8 years old) either did not produce measurable inspiratory flow through the DISKHALER or produced peak inspiratory flow rates below the 60 L/min considered optimal for the device under standardized in vitro testing; lack of measurable flow rate was related to low or undetectable serum concentrations (see DESCRIPTION, CLINICAL PHARMACOLOGY: Pediatric Patients, and INDICATIONS AND USAGE: Description of Clinical Studies). Prescribers should carefully evaluate the ability of

young children to use the delivery system if prescription of RELENZA is considered. When RELENZA is prescribed for children, it should be used only under adult supervision and with attention to proper use of the delivery system.

Adolescents were included in the three principal Phase 3 adult treatment studies. In these studies, 67 patients were 12 to 16 years of age. No definite differences in safety and efficacy were observed between these adolescent patients and young adults.

In addition, the safety and effectiveness of RELENZA for prophylaxis of influenza have been studied in four Phase 3 studies where 273 children 5 to 11 years of age and 239 adolescents 12 to 16 years of age received RELENZA. No differences in safety and effectiveness were observed between pediatric and adult subjects.

Geriatric Use: Of the total number of patients in 6 clinical studies of RELENZA for treatment of influenza, 59 were 65 and over, while 24 were 75 and over. Of the total number of patients in 4 clinical studies of RELENZA for prophylaxis of influenza in households and community settings, 954 were 65 and over, while 347 were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

In 2 additional studies of RELENZA for prophylaxis of influenza in the nursing home setting, efficacy was not demonstrated (see INDICATIONS AND USAGE). Elderly subjects may need assistance with use of the device.

ADVERSE REACTIONS

See WARNINGS and PRECAUTIONS for information about risk of serious adverse events such as bronchospasm and allergic-like reactions, and for safety information in patients with underlying airways disease.

Because the placebo consisted of inhaled lactose powder, which is also the vehicle for the active drug, some adverse events occurring at similar frequencies in different treatment groups could be related to lactose vehicle inhalation.

Treatment of Influenza: ***Clinical Trials in Adults and Adolescents:*** Adverse events that occurred with an incidence ≥1.5% in treatment studies are listed in Table 1. This table shows adverse events occurring in patients ≥12 years of age receiving RELENZA 10 mg inhaled twice daily, RELENZA in all inhalation regimens, and placebo inhaled twice daily (where placebo consisted of the same lactose vehicle used in RELENZA).

Table 1. Summary of Adverse Events ≥1.5% Incidence During Treatment in Adults and Adolescents

Adverse Event	RELENZA 10 mg b.i.d. **Inhaled** (n = 1,132)	RELENZA All Dosing Regimens* (n = 2,289)	Placebo (Lactose Vehicle) (n = 1,520)
Body as a whole			
Headaches	2%	2%	3%
Digestive			
Diarrhea	3%	3%	4%
Nausea	3%	3%	3%
Vomiting	1%	1%	2%
Respiratory			
Nasal signs and symptoms	2%	3%	3%
Bronchitis	2%	2%	3%
Cough	2%	2%	3%
Sinusitis	3%	2%	2%
Ear, nose, and throat infections	2%	1%	2%
Nervous system			
Dizziness	2%	1%	<1%

* Includes studies where RELENZA was administered intranasally (6.4 mg 2 to 4 times per day in addition to inhaled preparation) and/or inhaled more frequently (q.i.d.) than the currently recommended dose.

Additional adverse reactions occurring in less than 1.5% of patients receiving RELENZA included malaise, fatigue, fever, abdominal pain, myalgia, arthralgia, and urticaria.

The most frequent laboratory abnormalities in Phase 3 treatment studies included elevations of liver enzymes and CPK, lymphopenia, and neutropenia. These were reported in similar proportions of zanamivir and lactose vehicle placebo recipients with acute influenza-like illness.

Clinical Trials in Pediatric Patients: Adverse events that occurred with an incidence ≥1.5% in children receiving treatment doses of RELENZA in two Phase 3 studies are listed in Table 2. This table shows adverse events occurring in pediatric patients 5 to 12 years old receiving RELENZA 10 mg inhaled twice daily, and placebo inhaled twice daily (where placebo consisted of the same lactose vehicle used in RELENZA).

Table 2. Summary of Adverse Events ≥1.5% Incidence During Treatment in Pediatric Patients*

Adverse Event	RELENZA 10 mg b.i.d. Inhaled (n = 291)	Placebo (Lactose Vehicle) (n = 318)
Respiratory		
Ear, nose, and throat infections	5%	5%
Ear, nose, and throat hemorrhage	<1%	2%
Asthma	<1%	2%
Cough	<1%	2%
Digestive		
Vomiting	2%	3%
Diarrhea	2%	2%
Nausea	<1%	2%

* Includes a subset of patients receiving RELENZA for treatment of influenza in a prophylaxis study.

In 1 of the 2 studies described in Table 2, some additional information is available from children (5 to 12 years old) without acute influenza-like illness who received an investigational prophylaxis regimen of RELENZA; 132 children received RELENZA and 145 children received placebo. Among these children, nasal signs and symptoms (zanamivir 20%, placebo 9%), cough (zanamivir 16%, placebo 8%), and throat/tonsil discomfort and pain (zanamivir 11%, placebo 6%) were reported more frequently with RELENZA than placebo. In a subset with chronic pulmonary disease, lower respiratory adverse events (described as asthma, cough, or viral respiratory infections which could include influenza-like symptoms) were reported in 7 of 7 zanamivir recipients and 5 of 12 placebo recipients.

Prophylaxis of Influenza: *Family/Household Prophylaxis Studies:* Adverse events that occurred with an incidence of ≥1.5% in the 2 prophylaxis studies are listed in Table 3. This table shows adverse events occurring in patients ≥5 years of age receiving RELENZA 10 mg inhaled once daily for 10 days.

Table 3. Summary of Adverse Events ≥1.5% Incidence During 10-Day Prophylaxis Studies in Adults, Adolescents, and Children*

Adverse Event	Contact Cases	
	RELENZA (n = 1,068)	Placebo (n = 1,059)
Lower respiratory		
Viral respiratory infections	13%	19%
Cough	7%	9%
Neurologic		
Headaches	13%	14%
Ear, nose, and throat		
Nasal signs and symptoms	12%	12%
Throat and tonsil discomfort and pain	8%	9%
Nasal inflammation	1%	2%
Musculoskeletal		
Muscle pain	3%	3%
Endocrine and metabolic		
Feeding problems (decreased or increased appetite and anorexia)	2%	2%
Gastrointestinal		
Nausea and vomiting	1%	2%
Non-site specific		
Malaise and fatigue	5%	5%
Temperature regulation disturbances (fever and/or chills)	5%	4%

* In prophylaxis studies symptoms associated with influenza-like illness were captured as adverse events; subjects were enrolled during a winter respiratory season during which time any symptoms that occurred were captured as adverse events.

Community Prophylaxis Studies: Adverse events that occurred with an incidence of ≥1.5% in 2 prophylaxis studies are listed in Table 4. This table shows adverse events occurring in patients ≥5 years of age receiving RELENZA 10 mg inhaled once daily for 28 days.

Table 4. Summary of Adverse Events ≥1.5% Incidence During 28-Day Prophylaxis Studies in Adults, Adolescents, and Children*

Adverse Event	RELENZA (n = 2,231)	Placebo (n = 2,239)
Neurologic		
Headaches	24%	26%
Ear, nose, and throat		
Throat and tonsil discomfort and pain	19%	20%
Nasal signs and symptoms	12%	13%
Ear, nose, and throat infections	2%	2%
Lower respiratory		
Cough	17%	18%
Viral respiratory infections	3%	4%
Musculoskeletal		
Muscle pain	8%	8%
Musculoskeletal pain	6%	6%
Arthralgia and articular rheumatism	2%	<1%
Endocrine and metabolic		
Feeding problems (decreased or increased appetite and anorexia)	4%	4%
Gastrointestinal		
Nausea and vomiting	2%	3%
Diarrhea	2%	2%
Non-site specific		
Temperature regulation disturbances (fever and/or chills)	9%	10%
Malaise & fatigue	8%	8%

* In prophylaxis studies symptoms associated with influenza-like illness were captured as adverse events; subjects were enrolled during a winter respiratory season during which time any symptoms that occurred were captured as adverse events.

Observed During Clinical Practice: In addition to adverse events reported from clinical trials, the following events have been identified during post-marketing use of zanamivir (RELENZA). Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to a combination of their seriousness, frequency of reporting, or potential causal connection to zanamivir (RELENZA).

General: Allergic or allergic-like reaction, including oropharyngeal edema (see PRECAUTIONS).

Cardiac: Arrhythmias, syncope.

Neurologic: Seizures.

Respiratory: Bronchospasm, dyspnea (see WARNINGS and PRECAUTIONS).

Skin: Facial edema; rash, including serious cutaneous reactions (see PRECAUTIONS).

OVERDOSAGE

There have been no reports of overdosage from administration of RELENZA. Doses of zanamivir up to 64 mg/day have been administered by nebulizer. Additionally, doses of up to 1,200 mg/day for 5 days have been administered intravenously. Adverse effects were similar to those seen in clinical studies at the recommended dose.

DOSAGE AND ADMINISTRATION

RELENZA is for administration to the respiratory tract by oral inhalation only, using the DISKHALER device provided. **Patients should be instructed in the use of the delivery system. Instructions should include a demonstration whenever possible. If RELENZA is prescribed for children, it should be used only under adult supervision and instruction, and the supervising adult should first be instructed by a healthcare professional (see PRECAUTIONS).**

Patients scheduled to use an inhaled bronchodilator at the same time as RELENZA should use their bronchodilator before taking RELENZA (see WARNINGS and PRECAUTIONS regarding patients with underlying airways disease and other medical conditions).

Treatment: The recommended dose of RELENZA for treatment of influenza in adults and pediatric patients ages 7 years of age 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. Two doses should be taken on the first day of treatment whenever possible provided there is at least 2 hours between doses. On subsequent days, doses should be about 12 hours apart (e.g., morning and evening) at approximately the same time each day. There are no data on the effectiveness of treatment with RELENZA when initiated more than 2 days after the onset of signs or symptoms.

Prophylaxis: ***Household Setting:*** The recommended dose of RELENZA for prophylaxis of influenza in adults and pediatric patients 5 years of age and older in a household setting is 10 mg once daily for 10 days. The 10-mg dose is provided by 2 inhalations (one 5-mg blister per inhalation). The dose should be administered at approximately the same time each day. There are no data on the effectiveness of prophylaxis with RELENZA in a household setting when initiated more than 1.5 days after the onset of signs or symptoms in the index case.

Community Outbreaks: The recommended dose of RELENZA for prophylaxis of influenza in adults and adolescents in a community setting is 10 mg once daily for 28 days. The 10-mg dose is provided by 2 inhalations (one 5-mg blister per inhalation). The dose should be administered at approximately the same time each day. There are no data on the effectiveness of prophylaxis with RELENZA in a community outbreak when initiated more than 5 days after the outbreak was identified in the community. The safety and effectiveness of prophylaxis with RELENZA have not been evaluated for longer than 28 days duration.

HOW SUPPLIED

RELENZA is supplied in a circular double-foil pack (a ROTADISK) containing 4 blisters of the drug. Five ROTADISKS are packaged in a white polypropylene tube. The tube is packaged in a carton with 1 blue and gray DISKHALER inhalation device (NDC 0173-0681-01).

Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) (see USP Controlled Room Temperature). Keep out of reach of children. Do not puncture any RELENZA ROTADISK blister until taking a dose using the DISKHALER.

GlaxoSmithKline
Research Triangle Park, NC 27709

March 2006 RL-2270

PATIENT INFORMATION ABOUT:

RELENZA®

(zanamivir for inhalation)

This leaflet contains important patient information about RELENZA (zanamivir for inhalation), and should be read completely before beginning treatment. It does not, however, take the place of discussions with your healthcare provider about your medical condition or your treatment. This summary does not list all benefits and risks of RELENZA. The medication described here can only be prescribed and dispensed by a licensed healthcare provider, who has information about your medical condition and more information about the drug, including how to take it, what to expect, and potential side effects. If you have any questions about RELENZA, talk with your healthcare provider.

What is RELENZA?

RELENZA (ruh-LENS-uh) is a medicine for the treatment of influenza (flu, infection caused by influenza virus) and for reducing the chance of getting the flu in community and household settings. It belongs to a group of medicines called neuraminidase inhibitors. These medications attack the influenza virus and prevent it from spreading inside your body. RELENZA treats the cause of influenza at its source, rather than simply masking the symptoms.

Important Safety Information About RELENZA

Some patients have had bronchospasm (wheezing) or serious breathing problems when they used RELENZA. Many but not all of these patients had previous asthma or chronic obstructive pulmonary disease. RELENZA has not been shown to shorten the duration of influenza in people with these diseases. Because of the risk of side effects and because it has not been shown to help them, RELENZA is not recommended for people with chronic respiratory disease such as asthma or chronic obstructive pulmonary disease.

If you develop worsening respiratory symptoms such as wheezing or shortness of breath, stop using RELENZA and contact your healthcare provider right away.

If you have chronic respiratory disease such as asthma and chronic obstructive pulmonary disease and your healthcare provider has prescribed RELENZA, you should have a fast-acting, inhaled bronchodilator available for your use. If you are scheduled to use an inhaled bronchodilator at the same time as RELENZA, use the inhaled bronchodilator **before** using RELENZA.

Read the rest of this leaflet for more information about side effects and risks.

Other kinds of infections can appear like influenza or occur along with influenza, and need different kinds of treatment. Contact your healthcare provider if you feel worse or develop new symptoms during or after treatment, or if your influenza symptoms do not start to get better.

Who should not take RELENZA?

RELENZA is not recommended for people who have chronic lung disease such as asthma or chronic obstructive pulmonary disease. RELENZA has not been shown to shorten the duration of influenza in people with these diseases, and some people have had serious side effects of bronchospasm and worsening lung function. (See the section of this Patient Information entitled **"Important Safety Information About RELENZA.")**

You should not take RELENZA if you are allergic to zanamivir or any other ingredient of RELENZA. Also tell your healthcare provider if you have any type of chronic condition including lung or heart disease, if you are allergic to any other medicines or food products, or if you are pregnant.

RELENZA was not effective in reducing the chance of getting the flu in in 2 studies in nursing home patients.

RELENZA does not treat flu-like illness that is not caused by influenza virus.

Who should consider taking RELENZA?

Adult and pediatric patients at least 7 years of age who have influenza symptoms that appeared within the previous day or two. Typical symptoms of influenza include sudden onset of fever, cough, headache, fatigue, muscular weakness, and sore throat.

RELENZA can also help reduce the chance of getting the flu in adults and children at least 5 years of age who have a higher chance of getting the flu because they spend time with someone who has the flu. RELENZA can also reduce the chance of getting the flu if there is a flu outbreak in the community.

The use of RELENZA for the treatment of flu has not been shown to reduce the risk of spreading the virus to others.

Can I take other medications with RELENZA?

RELENZA has been shown to have an acceptable safety profile when used as labeled, with minimal risk of drug interactions. Your healthcare provider may recommend taking other medications, including over-the-counter medications, to reduce fever or other symptoms while you are taking RELENZA. Before starting treatment, make sure that your healthcare provider knows if you are taking other medicines. If you are scheduled to use an inhaled bronchodilator at the same time as RELENZA, you should use the inhaled bronchodilator **before** using RELENZA.

How and when should I take RELENZA?

RELENZA is packaged in medicine disks called ROTADISKS® and is inhaled by mouth using a delivery device called a DISKHALER®. Each ROTADISK contains 4 blisters. Each blister contains 5 mg of active drug and 20 mg of lactose powder (which contains milk proteins).

You should receive a demonstration on how to use RELENZA in the DISKHALER from a healthcare provider. Before taking RELENZA, read the "Patient Instructions for Use." Make sure that you understand these instructions and talk to your healthcare provider if you have any questions. Children who use RELENZA should always be supervised by an adult who understands how to use RELENZA. Proper use of the DISKHALER to inhale the drug is necessary for safe and effective use of RELENZA.

If you have the flu the usual dose for treatment is 2 inhalations of RELENZA (1 blister per inhalation) twice daily (in the morning and evening) for 5 days. It is important that you begin your treatment with RELENZA as soon as possible from the first appearance of your flu symptoms. Take 2 doses on the first day of treatment whenever possible if there are at least 2 hours between doses.

To reduce the chance of getting the flu, the usual dose is 2 inhalations of RELENZA (1 blister per inhalation) once daily for 10 or 28 days as prescribed by your healthcare provider.

Never share RELENZA with anyone, even if they have the same symptoms. If you feel worse or develop new symptoms during treatment with RELENZA, or if your flu symptoms do not start to get better, stop using the medicine and contact your healthcare provider.

What if I miss a dose?

If you forget to take your medicine at any time, take the missed dose as soon as you remember, except if it is near the next dose (within 2 hours). Then continue to take RELENZA at the usual times. You do not need to take a double dose. If you have missed several doses, inform your healthcare provider and follow the advice given to you.

What are important or common possible side effects of taking RELENZA?

Some patients have had breathing problems while taking RELENZA. This can be very serious and need treatment right away. Most of the patients who had this problem had asthma or chronic obstructive pulmonary disease, but some did not. If you have trouble breathing or have wheezing after your dose of RELENZA, stop taking RELENZA and get medical attention.

In studies, the most common side effects with RELENZA have been headaches; diarrhea; nausea; vomiting; nasal irritation; bronchitis; cough; sinusitis; ear, nose, and throat infections; and dizziness. Other side effects that have been reported, but were not as common, include rashes and allergic reactions, some of which were severe.

This list of side effects is not complete. Your healthcare provider or pharmacist can discuss with you a more complete list of possible side effects with RELENZA. Talk to your healthcare provider promptly about any side effects you have.

Please refer to the section entitled **"Important Safety Information About RELENZA"** for additional information.

Should I get a flu shot?

RELENZA is not a substitute for a flu shot. You should receive an annual flu shot according to guidelines on immunization practices that your healthcare provider can share with you.

What if I am pregnant or nursing?

If you are pregnant or planning to become pregnant while taking RELENZA, talk to your healthcare provider before taking this medication. RELENZA is normally not recommended for use during pregnancy or nursing, as the effects on the unborn child or nursing infant are unknown.

How and where should I store RELENZA?

RELENZA should be stored at room temperature below 77°F (25°C). RELENZA is not in a childproof container. Keep RELENZA out of the reach of children. Discard the DISKHALER after finishing your treatment.

PATIENT INSTRUCTIONS FOR USE

RELENZA®

(zanamivir for inhalation)

IMPORTANT: Read Step-by-Step Instructions before using the DISKHALER®.

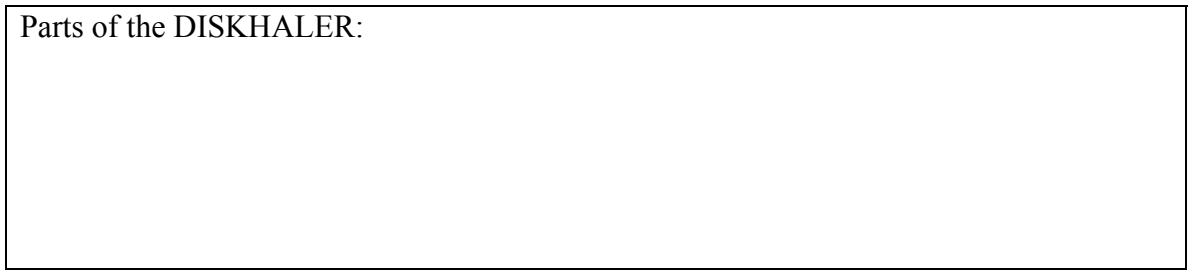
Be sure to take the dose your healthcare provider has prescribed.

BEFORE YOU START:

Please read the entire Patient Information for important information about the effects of RELENZA including the section "Important Safety Information About RELENZA" for information about the risk of breathing difficulties.

If RELENZA is prescribed for a child, dosing should be supervised by an adult who understands how to use RELENZA and has been instructed in its use by a healthcare provider.

Parts of the DISKHALER:



Step-by-step instructions for using the DISKHALER®

Step A: Load the medicine into the DISKHALER

1. Start by pulling off the blue cover.

2. **Always check inside the mouthpiece to make sure it is clear before each use. If foreign objects are in the mouthpiece, they could be inhaled and cause serious harm.**

3. Pull the white mouthpiece by the edges to extend the white tray all the way.

4. Once the white tray is extended all the way, find the raised ridges on each side of it. Press in these ridges, both sides at the same time, and **pull the whole white tray out of the DISKHALER body**.

5. Place one silver medicine disk onto the dark brown wheel, flat side up. The four silver blisters on the underside of the medicine disk will drop neatly into the four holes in the wheel.

6. Push in the white tray as far as it will go. Now the DISKHALER is loaded with medicine.

Step B: Puncture the blister

Be sure to keep the DISKHALER level.

The DISKHALER punctures one blister of medicine at a time so you can inhale the right amount. It does not matter which blister you start with. Check to make sure that the silver foil is unbroken.

1. Be sure to keep the DISKHALER level so the medicine does not spill out.

2. Locate the half-circle flap with the name "RELENZA" on top of the DISKHALER.

3. Lift this flap from the outer edge until it cannot go any farther. Flap must be **straight up** for the plastic needle to puncture both the **top** and **bottom** of the silver medicine disk inside.

4. Keeping the DISKHALER level, click the flap down into place.

Step C: Inhale

1. Before putting the white mouthpiece into your mouth, breathe all the way out (exhale).

Then put the white mouthpiece into your mouth. Be sure to keep the DISKHALER level so the medicine does not spill out.

2. Close your lips firmly around the mouthpiece. Be sure not to cover the small holes on either side of it.

3. Breathe in through your mouth steadily and as deeply as you can. Your breath pulls the medicine into your airways and lungs.

4. Hold your breath for a few seconds to help RELENZA stay in your lungs where it can work.

To take another inhalation, move to the next blister by following Step D below.

Once you've inhaled the number of blisters prescribed by your healthcare provider, replace the cover until your next dose.

Step D: Move the medicine disk to the next blister

1. **Pull** the mouthpiece to extend the white tray, without removing it.

2. Then **push** it back until it clicks. This pull-push motion rotates the medicine disk to the next blister.

3. To take your next inhalation, repeat Steps B and C.

If all four blisters in the medicine disk have been used, you are ready to start a new medicine disk (see Step A). Check to make sure that the silver foil is unbroken each time you are ready to puncture the next blister.

IMPORTANT INSTRUCTIONS

- Read this entire leaflet before using RELENZA. Even if you have had a previous prescription for RELENZA, read this leaflet to see if any information has changed.

- If you have the flu, the usual dose is 2 inhalations twice daily. To reduce the chance of getting the flu, the usual dose is 2 inhalations once daily. However, you must take the number of inhalations your healthcare provider has prescribed.

- If you feel worse or develop new symptoms during or after treatment, or if your flu symptoms do not start to improve, stop using the medicine and contact your healthcare provider.

- Keep out of reach of children.

- Always check inside the mouthpiece to make sure it is clear before each use. If foreign objects are in the mouthpiece, they could be inhaled and cause serious harm.

- Always replace the cover after each use.

- Throw away the DISKHALER after treatment is completed.

- This DISKHALER is for use only with RELENZA. Do not use the RELENZA DISKHALER device with FLOVENT® (fluticasone propionate) and do not use

RELENZA with the FLOVENT DISKHALER device.

Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) (see USP Controlled Room Temperature).

REMEMBER: This medicine has been prescribed for you by your healthcare provider. DO NOT give this medicine to anyone else.

GlaxoSmithKline
Research Triangle Park, NC 27709

March 2006 RL-2271

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021036/S-008

OFFICE DIRECTOR MEMO

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

OFFICE DIRECTOR'S BRIEF CONSULT MEMORANDUM

Date: Thursday, March 16, 2006
NDA: 21-036 SE 01
Sponsor: GSK
Proprietary Name: Relenza (zanamivir) inhalation powder
Author: Robert J. Meyer, MD, Director, ODE II

Background:

Relenza was approved in 1999 as an inhalation agent for the treatment of acute influenza A and B in adults and adolescents (ages 12 and above). I was the pulmonary consultant on this product during the original review, including at the Advisory Committee meeting. At the time of approval, there were some signals of pulmonary concern (an asthma patient in a PK study dropped their FEV_1 signficantly and in an efficacy study in asthma and COPD patients, categorical shift analyses showed the most extreme drops in lung function were associated with drug usage), but these signals certainly did not preclude approval. However, when the drug was approved, it was not indicated for use in those with significant lung disease, more because of a lack of demonstrated efficacy rather than the safety signal. Post-approval, adverse event reports were received in the treatment setting of serious respiratory events (largely bronchospasm), some with dire outcomes. While many of these were in patients with underlying diagnosed lung disease, this wasn't invariably the case. The labeling was updated with bolded warnings and precautions to highlight this possibility.

The sponsor now has presented data to support the efficacy of inhalational zanamivir for the prophylaxis of influenza. Given the current concerns over the potential for pandemic flu and the potential resistance of some human influenza A H5N1 cases to the most widely available and utilized neuraminidase, oseltamivir, this Relenza supplement is of considerable importance. According to the information given to me by the Antivirals division, the sponsor has provided adequate evidence of safety and efficacy of the drug to allow approval. However, as a matter of routine in efficacy supplements, the division requested an ODS consult to, in part, to provide an update on the AERS experience. As a part of that consultation, ODS recommended a boxed warning for the drug, in part due to the differing risk benefit that prophylaxis brings with it.

DAVP asked my opinion in consult on this recommendation of ODS, due to my clinical background and past consultations on this drug. My opinions were discussed with the division and relevant ODS personnel on March 15th, 2006, and this memorandum very briefly summarizes those discussions.

Summary:

The clinical trials for prophylaxis of influenza did not exclude patients with airways disease and there was reasonable representation in the rather substantial clinical data base (over 3800 patients overall assigned to drug treatment in these trials, with 695 patients with diagnoses of respiratory disease – 582 with asthma, 139 with COPD). A summary review of the safety data relevant to bronchospasm and pulmonary adverse effects shows a balance overall of such events between placebo and drug. The most "worrisome" case presented in the materials available to me was that a 74 year old with COPD who developed severe bronchospasm on day 2 of treatment, but in the setting of also developing active viral infection (i.e., this played out more as a case that occurred with treatment rather than prophylaxis)

In short, the clinical data do not show a worrisome signal for intolerance or poor safety in the prophylaxis setting. I should state that my expectation is that the drug would be better tolerated in the setting of a patient without active influenza (which is manifested in part as a substantially morbid URI). While the data cannot be said to fully confirm this expectation, neither do they in anyway dispel it. Even in the subset of patients with COPD and asthma, the summary data presented to me shows very reasonable safety. It is important to note that, like the original trials, patients with actively unstable disease or severe disease were not represented in the study populations in any appreciable number. Finally, the reviewers from the division tell me that efficacy was no different in the asthma and COPD population than the general population for the prophylaxis use (this was not the case in treatment).

Questions posed to me by DAVP are (note that these are paraphrased):

1. *Comment on the proposed Indications and Usage Statement:*
   "Relenza is not recommended for treatment or prophylaxis of influenza in individuals with [redacted (b) (4)] *disease (such as asthma or chronic obstructive pulmonary disease)(see WARNINGS)"*

Comment: Given the sponsor proposing to limit prophylaxis to patients without underlying airways disease, I am fine with that being a part of the I+U section. It certainly would be complicated to indicate it in these patients for prophylaxis and not for treatment. I would prefer an alternate terminology to [redacted (b) (4)]. Further, the most worrisome occurrence in the original database was a dramatic fall in FEV_1 in a patient with asthma from a PK study. That patient did not have active influenza at that time given it was a biopharm study. Therefore, not using the drug in airways disease, even for prophylaxis, seems prudent.

I would recommend using "airways" disease where it is then qualified that this includes asthma and COPD.

2. *Comment on the proposal to consolidate the Warnings and Precautions statements on the use and safety of the product in underlying lung disease.*

Comment: I support this idea and the substance of the proposed wording. Such consolidation will be necessary under the new Physician's Labeling Rule in any case. Again, I would prefer to consistently use "airways" disease, since I do not believe other forms of lung disease (e.g., pulmonary fibrosis) would have the same risk of bronchospasm as would someone with underlying asthma, COPD or other forms of airways disease (such as Cystic Fibrosis).

3. *Comment on the proposal from ODS to add a Boxed Warning.*

Comment: I do not support the addition of a boxed warning on the basis of the expanded indication to prophylaxis. While it is true that prophylaxis means a differing risk tolerance (less risk is tolerated as many patients will receive the drug without hope of benefit), I also believe the likely pulmonary safety experience in this setting will be better due to the absence of an active, severe URI. Further, the data in the supplement, as shared in summary form with me, raise no specific concerns in this regard. While it certainly makes sense to have active post-marketing surveillance for such issues, I do not find sufficient justification clinically for a boxed warning at this time . I will not opine on the potential need for a box for the treatment setting (that is, for the current indication based on the prior premarket and AERS experience), as I do not have sufficient basis to do so given the data presented to me.

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/s/

Robert Meyer
3/16/2006 12:31:33 PM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021036/S-008

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	21-036
Submission Number	008
Submission Code	SE1
Letter Date	November 4, 2005
Stamp Date	November 4, 2005
PDUFA Goal Date	May 5, 2006
Reviewer Name	Andreas Pikis, M.D.
Review Completion Date	March 28, 2006
Established Name	Zanamivir for inhalation
(Proposed) Trade Name	Relenza
Therapeutic Class	Antiviral
Applicant	GlaxoSmithKline
Priority Designation	P
Formulation	Inhaled dry powder
Dosing Regimen	10 mg inhaled once daily for ten to twenty-eight days
Indication	Prophylaxis of influenza A and B
Intended Population	≥ 5 years of age

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

The efficacy and safety data submitted in this supplemental NDA (sNDA) support the approval of zanamivir for the prevention of influenza A and B in subjects 5 years of age and older. This recommendation is based on the review of efficacy and safety data from four double-blind, randomized, placebo-controlled studies; two post-exposure prophylaxis studies conducted in a family/household setting and two seasonal prophylaxis studies conducted in a community setting. In all four studies, the incidence of symptomatic, laboratory-confirmed influenza in subjects treated with zanamivir was significantly lower compared with the incidence observed in subjects treated with placebo.

In the two post-exposure prophylaxis studies, zanamivir dosing of two inhalations (one 5 mg blister per inhalation for a total dose of 10 mg) once daily for 10 days was safe and effective in reducing household transmission of influenza regardless if the index cases received treatment with zanamivir. In the two seasonal prophylaxis studies, zanamivir dosing of two inhalations (one 5 mg blister per inhalation for a total dose of 10 mg) once daily for 28 days was safe and effective in reducing the incidence of symptomatic, laboratory-confirmed influenza during community outbreaks.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

Zanamivir was approved by FDA in 1999 for the treatment of uncomplicated influenza A and B for subjects ≥ 12 years of age. In 2000, the zanamivir treatment of uncomplicated influenza A and B was extended for children ≥ 7 years of age. No specific risk management plan was proposed by the Applicant or requested by the FDA. The Applicant continues to provide safety updates through annual reports. In addition, the Applicant continues to collect post-marketing reports of adverse events (AEs) through their Global Clinical Safety and Pharmacovigilance network, which are then submitted to FDA's Adverse Event Reporting System (AERS) database. AERS cases related to all influenza drugs are continually monitored by the Office of Drug Safety, Division of Drug Risk Evaluation (DDRE) and the results are discussed with the Division of Antiviral Drug Products.

1.2.2 Required Phase 4 Commitments

As part of their post-marketing commitments the Applicant agreed to:

I. Provide an annual update on emergence of resistance to zanamivir, as well as cross-resistance between zanamivir and other neuraminidase inhibitors, as an integrated review of information from NISN (Neuraminidase Inhibitor Surveillance Network), data collected by GSK, and information in the published literature. Each annual update will include information on the methodologies (e.g., culture, PCR) used in studies during that reporting period. Timeline: GSK will provide this annual update as part of the NDA Annual Reports due within 60 days of the original approval anniversaries in July 2007, July 2008, and July 2009.

II. Submit a postmarketing adverse drug experience report to DAVP as a "15-Day Alert Report" for each of the following serious adverse events:

- anaphylaxis
- bronchospasm or other pulmonary adverse event
- cardiovascular adverse event
- any adverse event with a fatal outcome

Consistent with 21 CFR 314.80, GSK will make diligent efforts to obtain as complete a set of information as possible, including information about antecedent and concomitant medical circumstances of the adverse experience or fatality, results of laboratory tests, a copy of any available medical records, and a copy of the autopsy report (if performed). A "15-Day Alert Report - Follow Up" will be submitted to DAVP if additional information is obtained after the deadline for submission of the initial report. The 15-Day Alert Reports due to DAVP each week will be collected and submitted as a batch, once a week, to DAVP. Each such submission will be sent to NDA 21-036 as "General Correspondence: Safety Reports per Postmarketing Commitment". Timeline: Such Alert Reports will be prepared and submitted by GSK for the specified events occurring through May 31, 2009.

III. Prepare a Wall Chart for medical practices and pharmacies on how to use the Relenza Diskhaler. This Wall Chart will be an illustration-intensive (not text intensive) aid to patient education. Versions will be prepared in English and Spanish. Timeline: GSK will submit the proposed Wall Chart and distribution plan/timeline to DAVP for review and comment no later than June 30, 2006.

IV. Meet with investigators at NIAID to develop a Concept Protocol and seek funding to assess the effects of zanamivir 10 mg inhaled once daily for 2 months on clinical laboratory measures of safety. Timeline: GSK will meet with NIAID by July 31, 2006 and provide DAVP with minutes including the outcome of the meeting by August 31, 2006.

1.2.3 Other Phase 4 Requests

Aside from those listed in the previous section, no other Phase 4 commitments are requested from the Applicant.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

This submission contains four controlled phase III studies for efficacy and six controlled phase III studies for safety. The four studies submitted for efficacy evaluation are designated as the primary phase III studies and include two post-exposure prophylaxis studies conducted in a family/household setting (Study NAI30010 and Study NAI30031), and two prophylaxis studies conducted in a community setting (Study NAIA3005 and Study NAI30034).

The safety evaluation is based on six studies; the four primary phase III studies mentioned above and two previously submitted studies conducted in a nursing home setting (Study NAIA3003 and Study NAIA3004) designated as the secondary studies.

1.3.2 Efficacy

As stated previously, FDA reviewed the clinical data from the four primary phase III studies in support of the approval of zanamivir for prophylaxis of influenza in subjects 5 years of age and older. The primary efficacy endpoint was similar across all four studies. For the family/household studies, the primary efficacy endpoint was the proportion of families/ households for which at least one randomized contact developed symptomatic, laboratory-confirmed influenza A or B infection. For the two community studies, the primary efficacy endpoint was the proportion of subjects who developed symptomatic, laboratory confirmed influenza A or B infection during prophylaxis. In all four studies, symptomatic influenza was defined as the presence of at least two of the following influenza-like symptoms from a pre-defined list for three consecutive diary card entries (36 hours): oral temperature ≥ 37.8°C or feverishness, cough, headache, sore throat, and myalgia. Laboratory confirmation of influenza was done by culture, PCR or seroconversion (defined as a 4-fold increase in convalescent titer from baseline.

The two post-exposure prophylaxis studies in a family/household setting were similar in design and randomization was performed by family/household. The main difference in study design between the two studies was the index cases were randomized to treatment in one study but not in the other. In the first study (Study NAI30010), in which index cases were treated, within 36 hours of onset of symptoms in an index case, each household (including all family members ≥ 5 years of age) was randomized to zanamivir 10 mg inhaled once daily or placebo for 10 days. Index cases were randomized to zanamivir 10 mg inhaled twice daily for five days or inhaled placebo twice daily for five days. In this study, the proportion of households with at least one new case of symptomatic, laboratory-confirmed influenza decreased significantly from 19% (32

of 168 households) in the placebo group to 4.1% (7 of 169 households) in the zanamivir group ($p < 0.001$). In the second study (Study NAI30031), in which index cases were not treated, the incidence of symptomatic, laboratory-confirmed influenza decreased from 19% (46 of 242 households) in the placebo group to 4.1% (10 of 245 households) in the zanamivir group ($p < 0.001$).

The two seasonal prophylaxis studies assessed zanamivir 10 mg inhaled once daily versus placebo inhaled once daily for 28 days during community outbreaks. The first seasonal prophylaxis study (Study NAIA3005) conducted in two university communities enrolled mainly healthy unvaccinated subjects 18 years of age or greater (mean age 28.8 years). In this study, the incidence of symptomatic, laboratory-confirmed influenza decreased from 6.1% (34 of 554 subjects) in the placebo group to 2.0% (11 of 553) in the zanamivir group ($p < 0.001$). The second seasonal prophylaxis study (Study NAI30034) enrolled subjects at high-risk for developing complications from influenza infection. In this study, the ages ranged from 12 to 94 years (mean age 60.4 years) and 56% were older than 65 years. Sixty-seven percent of subjects were vaccinated. In this study, the incidence of symptomatic, laboratory-confirmed influenza decreased from 1.4% (23 of 1685 subjects) in the placebo group to 0.2% (4 of 1678) in the zanamivir group ($p < 0.001$).

1.3.3 Safety

The safety profile of zanamivir was characterized in six double-blind, randomized, phase III prophylaxis studies (the four studies described above and in two additional studies conducted in a nursing home setting) and from the review of post-marketing data. The frequency and nature of adverse events (AEs) observed during prophylaxis studies were similar between the placebo and zanamivir groups and consistent with the known AE profile of zanamivir. Moreover, the zanamivir AE profile was consistent across subjects with different ages and in high-risk subjects. No new or unexpected safety findings were observed. The most commonly reported AEs, regardless causality, were headaches, throat and tonsil discomfort and pain, cough, nasal signs and symptoms, and temperature regulation and disturbances. Of note, in the prophylaxis studies, symptoms associated with influenza-like illness were captured as AEs.

As part of this supplement, and at the request of the FDA, the Applicant submitted an integrated summary of zanamivir post-marketing reports of AEs collected through the Global Clinical Safety and Pharmacovigilance of GlaxoSmithKline. This request was based on post-marketing reports of bronchospasm after the initial approval. Many but not all of these patients had an underlying airways disease. Some of those patients had fatal outcomes, although causality was difficult to assess. Because of the severity of this complication, in April 2000, the label statement regarding bronchospasm was changed to a 'Warnings.'

The post-marketing report by the Applicant covered the period from the first introduction of zanamivir in 1999 to January 31, 2005. A total of 779 spontaneous AE reports were received worldwide by Global Clinical Safety and Pharmacovigilance of GlaxoSmithKline involving patients who received zanamivir for either treatment or prophylaxis of influenza. The most

common AEs spontaneously reported (according to MedDRA System Organ Class) were: respiratory, thoracic, and mediastinal disorders (25%); skin and subcutaneous tissue disorders (15.5%); nervous system disorders (13.6%); general disorders and administration site conditions (10.5%); and gastrointestinal disorders (8.5%). The largest proportion of cases involved a primary event in the respiratory body system and among these the most medically significant AEs were bronchospasm, dyspnea, asthma and/or wheezing.

This post-marketing safety update summary provided by the Applicant was forwarded to the DDRE, Office of Drug Safety (ODS) and a consult was requested to assist in the review of post-marketing safety data. In addition, the DDRE independently reviewed the post-marketing reports submitted to AERS database. The DDRE consult recommended the Division consider a Box Warning regarding the risk of bronchospasm in patients with underlying airways disease receiving zanamivir for treatment or prophylaxis of influenza A and B. In addition, and based on the report of nine cases in the AERS database with anaphylactic reactions possibly related to the use of zanamivir, they recommended the addition of 'anaphylaxis' in the current statement for Allergic Reactions under the PRECAUTION section.

The issue of Box Warning was further discussed during an internal meeting on March 15, 2006, with Dr. Robert Meyer, a pulmonologist and Director of ODE II and interdisciplinary DAVP and DDRE representation. It was finally decided that at this time a Box Warning is not indicated. The decision was based on the clinical trial experience in approximately 3800 subjects assigned to drug treatment in the prophylaxis studies. A review of the safety data relevant to bronchospasm and lower respiratory events of interest shows no difference in such events between placebo and zanamivir groups. Dr Meyer stated the drug would probably be better tolerated in the absence of active influenza infection. However, it is important to note that although patients with underlying airways disease were not excluded from the prophylaxis studies, patients with severe airways disease were not represented in the studies in any appreciable number.

1.3.4 Dosing Regimen and Administration

Currently, zanamivir is approved for treatment of uncomplicated disease due to influenza A and B viruses in subjects seven years of age and older who have been symptomatic for no more than two days. The recommended dose of zanamivir for influenza treatment is two inhalations (one 5 mg blister per inhalation for a total dose of 10 mg) twice daily for five days.

The data submitted in this sNDA support the use of zanamivir in subjects five years and older for prophylaxis of influenza A and B. The recommended dose of zanamivir for prophylaxis of influenza in a family/household setting is two inhalations (one 5 mg blister per inhalation for a total dose of 10 mg) once daily for 10 days. The recommended dose of zanamivir for prophylaxis of influenza during community outbreaks is two inhalations (one 5 mg blister per inhalation for a total dose of 10 mg) once daily for 28 days.

Of note, there are no data on the effectiveness of prophylaxis with zanamivir in a household setting when drug administration is initiated more than 1.5 days after the onset of signs or symptoms in the index case. Additionally, there are no data on the effectiveness of prophylaxis

with zanamivir in a community outbreak when drug administration is initiated more than 5 days after the outbreak was identified in the community. The safety and effectiveness of prophylaxis with zanamivir have not been evaluated for longer than 28 days.

The use of less frequent dosing regimen for prophylaxis was based on previously submitted pharmacokinetic data from animal models and humans. The data demonstrated zanamivir concentrations are approximately 337- and 52-fold above the median neuraminidase IC_{50} at the epithelial layer of trachea, bronchi, and bronchioles at 12 and 24 hours, respectively, after a single 10 mg dose of zanamivir. Based on these data, the Applicant concluded that higher or more frequent dosing would not likely achieve better efficacy results.

1.3.5 Drug-Drug Interactions

Based on data from in vitro studies, no clinically significant pharmacokinetic drug interactions are predicted. Therefore, formal drug-drug interaction data were not included in the original NDA or in this supplement. In a population pharmacokinetic analyses conducted in 22 subjects, no evidence of clinically significant drug-drug interactions were observed following concurrent administered (within four hours of zanamivir) drugs for symptomatic relief including acetaminophen, dextromethorphan and guaifenesin. Given these data, zanamivir appears to have a low potential for drug-drug interactions.

1.3.6 Special Populations

Pediatrics: A total of 511 children were included in the zanamivir treatment arms in the four primary prophylaxis studies. No differences in safety and effectiveness were observed between pediatric and adult subjects. Of the 511 children, 64 were 5-6 years, 211 were 7-11 years, and 240 children were 12-16 years of age.

Geriatrics: Of the total number of subjects enrolled in the four primary studies of zanamivir for prophylaxis of influenza in households and community settings, 1911 were 65 years of age and older (placebo 957; zanamivir 954). Of the 954 subjects in the zanamivir group, 954 were ≥ 65 years of age and 347 were ≥ 75 years of age. No differences in safety and effectiveness were observed between these subjects and the overall population. Of note, in the two secondary phase III studies for zanamivir prophylaxis of influenza in a nursing home setting, efficacy was not demonstrated.

High-risk: Study NAI30034 enrolled community-dwelling subjects ≥ 12 years of age who were at high risk for developing complications from influenza. High risk was defined as subjects ≥ 65 years of age, subjects with diabetes mellitus, and subjects with chronic disorders of the pulmonary or cardiovascular systems. Of the 1678 subjects enrolled in the zanamivir arm of Study NAI30034, 946 were ≥ 65 years of age, 684 had respiratory disease, 331 had cardiovascular disease, and 359 had diabetes mellitus. There was no difference in safety and effectiveness by subject's underlying condition. However, it should be noted that the number of patients

with severe underlying airways and cardiovascular disease enrolled in Study NAI30034 was insignificant.

Race: Analysis of safety and effectiveness according to race and ethnicity revealed no differences. However, these results are interpreted with caution because the studies mainly involved Caucasian subjects. In the five placebo-controlled phase III prophylaxis studies, 92% of the enrolled subjects were Caucasians, 4% were black, 2% were American Hispanic, and 2% were Asian.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Description: Zanamivir, a neuraminidase inhibitor, is the first sialic acid analogue approved by FDA for the treatment of influenza in subjects ≥ 7 years of age. Currently, zanamivir is not approved for prophylaxis of influenza. Zanamivir is supplied as a dry powder for oral inhalation, and is delivered via a Diskhaler device. The Diskhaler device is also used for a variety of drugs for asthma. The drug is supplied in blister packs in which each blister contains 5 mg of zanamivir and 20 mg of lactose carrier. The standard dose for treatment of influenza is two inhalations twice a day for five days.

Established name and Trade name: Zanamivir (Relenza®)

Pharmacological Class: Antiviral

Indications, dosing regimens, age groups: Relenza® is approved for treatment of uncomplicated disease due to influenza A and B viruses in adults and children ≥ 7 years of age. Dosing in adults and children 7 years of age and older is two inhalations (one 5 mg blister per inhalation for a total dose of 10 mg) twice daily for five days. The proposed indication in this supplement is for prophylaxis of influenza A and B in subjects ≥ 5 years of age. The proposed dosing regimen for prophylaxis of influenza in the family/household setting is two inhalations (one 5 mg blister per inhalation for a total dose of 10 mg) once daily for 10 days. The proposed dosing regimen for prophylaxis of influenza in a community setting is two inhalations (one 5 mg blister per inhalation for a total dose of 10 mg) once daily for 28 days.

2.2 Currently Available Treatment for Indications

Two classes of antiviral medications are currently available for treatment or prophylaxis of influenza infections: the adamantanes or M2 ion channel inhibitors (amantadine and rimantadine) and neuraminidase inhibitors (oseltamivir and zanamivir). The currently available drugs for the treatment or prophylaxis of influenza infections are summarized in Table 1.

Table 1. Antiviral drugs for influenza

Drug	Adult dosage		Pediatric dosage	
	Prophylaxis	Treatment	Prophylaxis	Treatment
Influenza A				
Amantadine	100 mg PO bid or 200 mg PO once/d	same	1-9 yrs: 4.4 to 8.8 mg/kg/d PO in 2 doses (max 150 mg/d) ≥ 10 yrs: 100 mg PO bid	same
Rimantadine	100 mg PO bid	same	1-9 yrs: 5 mg/kg/d PO once/d (max 150 mg/d) ≥ 10 yrs: 100 mg PO bid	Not FDA approved
Influenza A and B				
Oseltamivir	75 mg PO once/d	75 mg PO bid	≥ 1 yr ≤ 15 kg: 30 mg PO once/d 16-23 kg: 45 mg PO once/d 24-40 kg: 60 mg PO once/d >40 kg: 75 mg once/d	≥ 1 yr ≤ 15 kg: 30 mg PO bid 16-23 kg: 45 mg PO bid 24-40 kg: 60 mg PO bid >40 kg: 75 mg PO bid
Zanamivir	Not FDA approved	2x5 mg oral inhalations bid	Not FDA approved	≥ 7 yrs 2x5 mg oral inhalations bid

Source: Antiviral drugs for prophylaxis and treatment of influenza. The Medical Letter 2005;47:93-95 (with modification).

Adamantanes:

The adamantanes exert an antiviral effect by inhibiting the activity of the matrix (M2) ion channel protein of influenza A virus. Both amantadine and rimantadine are indicated for prophylaxis and treatment of influenza A; neither is active against influenza B. Their use is limited due to the rapid development of viral resistance and their adverse effects.

Resistance to adamantanes can occur spontaneously or during treatment. A single point mutation in the codons for amino acids at positions 26, 27, 30, 31, or 34 of the M2 protein can confer resistance to both drugs. Adamantane resistant isolates are stable, transmittable and pathogenic as wild-type viruses. Approximately 10-27% of healthy adults shed adamantine resistant virus after clinical use of either of these drugs. The incidence of resistance is higher in immunocompromised subjects and in children. In the United States, the incidence of adamantine-resistant influenza A viruses increased from 1.9% during the 2001-02 influenza season to 11% during the 2004-05 season. Early findings during the 2005-06 season showed 91% of influenza A viruses tested had the S31N mutation in the M2 protein conferring resistance to adamantanes. Based on these findings, the CDC recommends neither amantadine nor rimantadine is used for the treatment or chemoprophylaxis of influenza A infections in the United States for the remainder of 2005-06 influenza season.

Amantadine is associated with CNS adverse effects including insomnia, lightheadedness, nervousness, difficulty concentrating, delirium, hallucinations and seizures. Suicide ideation and suicide attempts have also been reported. These effects occur more frequently in adults and with concurrent use of anticholinergics or older antihistamines. CNS adverse events are less common with rimantadine.

Neuraminidase inhibitors

Neuraminidase, a surface glycoprotein found in both influenza A and B viruses, cleaves terminal sialic acid from sialic acid-containing glycoproteins that serve as host cell receptors for attachment of influenza viruses. This cleavage releases the viruses which can now invade new cells. Without the presence of neuraminidase, infection could be limited to one round of replication. Neuraminidase inhibitors are sialic acid analogues inhibiting neuraminidase and subsequently viral replication. Neuraminidase inhibitors are active against both influenza A and B viruses. Influenza B viruses are approximately 10-fold less sensitive than influenza A viruses, but these viruses are still susceptible within clinically achievable concentrations.

Resistance to neuraminidase inhibitors appears less frequently than resistance to adamantanes. In controlled clinical trials, the incidence of influenza viruses with reduced susceptibility to oseltamivir ranged from 0.4-1% in adults and about 4% in children. However, in a recent report from Japan the incidence of decreased susceptibility to oseltamivir in children was 18%. Resistance to zanamivir has not been reported in immunocompetent subjects. Only one case of zanamivir resistance in an immunocompromised child infected with influenza B has been reported. Whether the neuraminidase inhibitor-resistant isolates are transmissible and pathogenic is still unknown. Generally, neuraminidase inhibitors-resistant isolates lead to a decreased pathogenicity in animal models. However, in the ferret model, resistant viruses were identified in both the index ferret and contact animals. Of great concern is the current isolation of oseltamivir-resistant influenza A (H5N1) variants from two subjects who died from the infection.

Zanamivir is the first sialic acid analogue approved by FDA for the treatment of influenza in subjects ≥ 7 years of age. Zanamivir is not approved for prophylaxis. The drug is currently supplied as a dry powder for oral inhalation, using the Diskhaler device. The Diskhaler device is also used for a variety of drugs for asthma. The drug is supplied in blister packs in which each blister contains 5 mg of zanamivir and 20 mg of lactose carrier. The standard dose is two inhalations twice a day for five days.

2.3 Availability of Proposed Active Ingredient in the United States

Zanamivir is available in the United States in a circular double-foil pack (a ROTADISK) containing 4 blisters of the drug. Five ROTADISKS are packaged in a white propylene tube which is packaged in a carton with one Diskhaler inhalation device.

2.4 Important Issues With Pharmacologically Related Products

December 2005:

Oseltamivir was approved by FDA for prophylaxis of influenza in pediatric subjects one year and older.

2.5 Presubmission Regulatory Activity

July 1999:

Zanamivir was approved by FDA for treatment of uncomplicated acute influenza A and B in adults and adolescents (≥ 12 years).

April 2000:

Zanamivir was approved by FDA for treatment of uncomplicated acute influenza A and B in children ≥ 7 years of age.

(b) (4)

March and June 2005:

Two pre-sNDA meetings were held between the Sponsor and the Division to discuss two additional studies (b) (4)

(b) (4) The two additional studies for prophylaxis of influenza included one study in a family/household setting where the index cases were not treated, and a second study in a community setting. The new community study recruited subjects considered at high risk for developing complications from influenza infection (i.e., subjects ≥ 65 years of age and subjects with chronic respiratory and cardiovascular diseases).

2.6 Other Relevant Background Information

Zanamivir is approved for prophylaxis of influenza in 22 countries. GlaxoSmithKline Europe has recently submitted an sNDA for prophylaxis of influenza A and B viruses to EMEA.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

No new chemistry and manufacturing data were submitted with this sNDA. Please refer to the original NDA reviews for background information.

3.2 Animal Pharmacology/Toxicology

No new animal pharmacology and toxicology data were submitted with this sNDA. Please refer to the original NDA reviews for background information.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

This review focuses on data from four controlled phase III studies for efficacy and six controlled phase III studies for safety. The four studies submitted for efficacy evaluation are designated as the primary phase III studies and include two post-exposure prophylaxis studies conducted in a family/household setting (Study NAI30010 and Study NAI30031), and two prophylaxis studies conducted in a community setting (Study NAIA3005 and Study NAI30034).

The safety evaluation is based on six studies; the four primary phase III studies mentioned above and the two previously submitted studies conducted in a nursing home setting (Study NAIA3003 and Study NAIA3004) designated as the secondary studies. (b) (4) As a result, the Applicant is not seeking an indication in the nursing home setting and the efficacy data were not re-reviewed for this sNDA. The two nursing home studies were

included in the integrated safety evaluation. In addition, the post-marketing safety reports submitted since July 1999 were reviewed.

4.2 Tables of Clinical Studies

The following table summarizes the clinical studies submitted in this sNDA.

Table 2. Phase III prophylaxis studies.

Study	Number of subjects (Intent-to-treat population)			Duration of Prophylaxis
	Placebo	Zanamivir	Rimantadine	
Primary Phase III Studies				
Family/ Household				
NAI30010	423[1]	414[1]	N/A	10 days[2]
NAI30031	630[1]	661[1]	N/A	10 days[2]
Community				
NAIA3005	554	553	N/A	28 days[2]
NAI30034	1685	1678	N/A	28 days[2]
Secondary Phase III Studies				
Nursing Home				
NAIA3003	13[3]	238[3]	231[3]	14 days[2]
NAIA3004	252[3]	242[3]	N/A	14 days[2]

Source: Summary of clinical efficacy, Table 1
N/A = not applicable
[1]Contact cases, rather than households
[2]10mg of inhaled zanamivir, once daily
[3]Includes all randomizations.

4.3 Review Strategy

The four primary phase III studies (two prophylaxis studies in a family/household setting and two prophylaxis studies in a community setting) were reviewed for both efficacy and safety; the two secondary phase III studies (prophylaxis studies in a nursing home setting) were reviewed only for safety. The applicant's conclusions regarding safety and efficacy were confirmed by independent FDA analyses of the data. Dr. Fraser Smith performed the statistical analysis confirming the primary endpoint and selected secondary endpoints. The Medical Officer (MO) reviewed study design, subject demographics, adverse events, and laboratory safety monitoring. Dr. Battula reviewed the virology methods and data. In this review, tables derived from applicant's presentation of the data are cited as to source in the table footnotes, while tables derived from review-generated results are not referenced. The post-marketing safety update summary provided by the Applicant was forwarded to the ODS and a consult was requested to

assist in the review of post-marketing safety data. The ODS consult was performed by Evelyn Edwards, Post-marketing Safety Evaluator, DDRE.

4.4 Data Quality and Integrity

The Good Clinical Practice Branch, Division of Scientific Investigations, FDA, conducted clinical inspections of four study sites in the United States that enrolled the greatest number of subjects for Study NAI30031 and Study NAI30034: Ann Arbor, MI and Wichita, KS for Study NAI30031; Mesa, AZ and Edmonds, WA for Study NAI30034. No major deficiencies were noted in the four inspected sites that would compromise the integrity of the studies. For more details please see Clinical Inspection Summary by Antoine El-Hage, Ph.D.

4.5 Compliance with Good Clinical Practices

The applicant states the studies were conducted according to accepted ethical standards based on the precepts established by the Declaration of Helsinki. All studies were conducted with the approval of Ethics Committees or Institutional Review Boards and Informed Consent was obtained for all subjects.

4.6 Financial Disclosures

The applicant submitted financial disclosure information for studies NAI30031, NAI30034, NAI30010, NAIA3004, and NAIA3003. The applicant did not submit financial disclosure information for study NAIA3005 because this study was completed (March 8, 1998) prior to implementation of the Financial Disclosure Rule on February 2, 1999.

Based on available financial data, the $25,000 threshold for "payments of other sorts" was exceeded by two principle investigators: (b) (6) The majority of payments assigned to (b) (6) were made to his affiliated institution. Such payments to (b) (6) affiliated institution were attributed not only to him, but also to any subinvestigator at that institution who took part in study NAI30010. As a result, seven subinvestigators received greater than $25,000 in "payment of other sorts."

At (b) (6) placebo and (b) (6) zanamivir families had a contact case with symptomatic, laboratory confirmed influenza. At (b) (6) placebo and (b) (6) zanamivir families had a contact case with symptomatic, laboratory-confirmed influenza. These data are similar to the overall effect observed across centers and are not expected to bias the clinical study outcome.

The $50,000 threshold for equity interest was exceeded in the case of the following clinical investigators:

(b) (6) principle investigator in study NAI30034. (b) (6) site enrolled (b) (6) of the 3363 subjects (b) (6) in the ITT population. None of the subjects in this site had a positive

laboratory-confirmed influenza. This site is not expected to potentially bias the outcome of the study.

(b) (6) principle investigator in study NAI30034. (b) (6) site enrolled (b) (6) of the 3363 subjects (b) (6) in the ITT population. Only one subject in this site had a positive laboratory-confirmed influenza. This site is not expected to bias the outcome of the study.

(b) (6), sub-investigator of (b) (6) in study NAI30034. (b) (6) site enrolled (b) (6) of the 3363 subjects (b) (6) in the ITT population. Only one subject in this site had a positive laboratory-confirmed influenza. This site is not expected to bias the outcome of the study.

(b) (6) principle investigator in study NAI30010. Previously to his participation in the study, (b) (6), which continues operations as GlaxoSmithKline, Inc. As a retired employee, he benefits from provisions made for retirees. No effort has been made to quantify (b) (6) retirement benefits. (b) (6) site enrolled (b) (6) (b) (6) of 1158 subjects in study NAI30010.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

No new pharmacokinetic, pharmacodynamic or exposure-response relationship data were submitted with this sNDA. Please refer to original NDA reviews for background information.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The indication under consideration in this sNDA is the following: zanamivir is indicated in adults and pediatric subjects ≥ 5 years of age for prophylaxis of influenza.

Four primary phase III studies were used to support the efficacy of zanamivir for prophylaxis of influenza A and B infections in subjects 5 years of age and older. More specifically, data from studies NAI30010 and NAI30031 were used to support the efficacy of zanamivir to reduce transmission of influenza A and B among individuals in households with an infected person. Data from studies NAIA3005 and NAI30034 were used to support the efficacy of zanamivir for prophylaxis of influenza A and B infections during community outbreaks.

Zanamivir is currently approved for treatment of uncomplicated influenza A and B infections in subjects ≥ 7 years of age.

6.1.1 Methods

Four primary phase III studies (two prophylaxis studies in a family/household setting and two prophylaxis studies in a community setting) were reviewed for efficacy. The Applicant's conclusions regarding efficacy were confirmed by independent FDA analyses of the data as described in the Statistical review conducted by Dr. Fraser Smith.

In this review, analyses and presentation of the efficacy data are grouped by setting as follows:

- Efficacy data from the two household studies (Study NAI30010 and Study NAI30031).
- Efficacy data from the two community studies (Study NAIA3005 and Study NAI30034).

6.1.2 General Discussion of Endpoints

The primary efficacy endpoint was similar across the four primary phase III studies. For the family/household studies, the primary efficacy endpoint was the proportion of families/ households for which at least one randomized contact developed symptomatic, laboratory-confirmed influenza A or B infection. For the two community studies, the primary efficacy endpoint was the proportion of subjects who developed symptomatic, laboratory-confirmed influenza A or B infection during prophylaxis.

In all four studies, symptomatic influenza was defined as the presence of at least two influenza-like symptoms from a pre-defined list for three consecutive diary card entries (36 hours). There were minor differences among the studies in the pre-defined list of influenza-like symptoms provided to subjects on diary cards. These differences are shown in the following table.

Table 3. Influenza-like symptoms (at least two) required for primary endpoint: family/household and community studies.

Influenza-like symptoms	**Family/Household Studies**		**Community Studies**	
	NAI30010	**NAI30031**	**NAIA3005**	**NAI30034**
Fever ≥37.8°C	X		X	
Feverishness	X		X	
Fever ≥37.8°C or feverishness		X		X
Cough	X	X	X	X
Headache	X	X	X	X
Sore throat	X	X	X	X
Myalgia	X		X	
Muscle/joint aches and pains		X		X

Source: Summary of clinical efficacy, Table 3.

Laboratory confirmation of influenza required a positive viral culture, seroconversion or PCR in Study NAI30010 and NAI30031, and a positive viral culture or seroconversion in Study

NAIA3005 and NAI30034. A positive result by seroconversion was defined as a four-fold increase in antibody titer.

In the family/household studies clinical symptoms were recorded via a diary card for all index and contact cases. Subjects recorded symptoms (headache, sore throat, feverishness, muscle/join aches and pains, nasal symptoms, weakness, loss of appetite, and cough plus an overall symptom assessment) twice daily, temperature twice daily, and use of relief medication once daily.

In the community studies, subjects completed a diary card for at least 28 days. Similar data were collected as in the household studies.

Routine laboratory tests were not performed in the two family/household studies and in one of the community studies (Study NAI30034). Routine laboratory tests for the other community study were performed at Baseline and at one week after the last dose of study medication (Day 35). In the two nursing home studies routine laboratory tests were performed at Baseline and on Day 14.

6.1.3 Study Design

Prophylaxis studies in family/household settings: Protocols NAI30010 and NAI30031

The two post-exposure prophylaxis studies in a family/household setting were similar in design and randomization was performed by family/household. The main difference between the two family/household studies was in Study NAI30010 index cases were randomized to treatment with zanamivir, but in Study NAI30031 index cases did not receive treatment with zanamivir. Please refer to the Appendix for specific details.

Both studies were adequate and well-controlled and provide a reasonable assessment of benefit for zanamivir versus placebo for the prophylaxis of influenza in the household setting. Both studies were double-blind, randomized, placebo-controlled trials designed to evaluate the efficacy of inhaled zanamivir administered 10 mg once daily for 10 days compared with placebo in the prevention of symptomatic, laboratory-confirmed influenza A and B infections in the family/household setting. The study was randomized by family. Eligible families were recruited and consented prior to influenza season. When a suspected case of influenza-like illness was identified within the family (index case) at a time influenza was known to be circulating in the community, all eligible family members and the index case were randomized to receive study medication. Children < 5 years of age were enrolled and could be the index case but did not receive study drug.

In Study NAI30010, the index cases received two inhalations of 5 mg zanamivir or placebo twice a day for 5 days, and the contact cases received two inhalations of 5 mg zanamivir or placebo once a day for 10 days, whereas in Study NAI30031 the index cases were not treated with any influenza antiviral therapy.

Primary community studies: Protocols NAIA3005 and NAI30034

Study NAIA3005: This study was conducted in two university communities in the United States (Ann Arbor, MI and Columbia, MO). The study was designed to evaluate the efficacy of inhaled zanamavir 10 mg once daily for 28 days compared with placebo in the prevention of influenza A and B infections in community-dwelling adults ≥ 18 years of age.

Once influenza was determined in the community, eligible subjects were stratified according to their immunization status and randomized to receive either inhaled zanamivir 10 mg once daily for 28 days or inhaled placebo once daily for 28 days. Subjects completed diary cards twice a day for at least 28 days. Following the first prophylaxis clinic on Day 1, subjects attended the clinic on Days 7, 14, 21, 28, and at post-prophylaxis visit on Day 35.

Study NAI30034 was almost identical to study NAIA3005. The main difference between the two studies was the subject population. Study NAI30034 enrolled community-dwelling subjects ≥ 12 years of age who were at high risk for developing complications from influenza. High risk was defined as subjects ≥ 65 years of age, subjects with diabetes mellitus, and subjects with chronic disorders of the pulmonary or cardiovascular systems. In comparison, Study NAIA3005 enrolled healthy adults ≥ 18 years of age.

6.1.4 Efficacy Findings

PRIMARY FAMILY/HOUSEHOLD STUDIES

Please refer to the Appendix for specific details regarding description of the studies, baseline demographics, and disposition of subjects. The primary efficacy endpoint in family/household studies was the proportion of randomized families in whom at least one randomized contact developed symptomatic, laboratory-confirmed (by culture, serology or PCR) influenza A or B infection. The results of the primary efficacy endpoint analyses for Studies NAI30010 and NAI30031 are summarized in Table 4. The study population used for the analysis of efficacy was the intent-to-treat population. The intent-to-treat population is defined as all randomized subjects regardless if study medication was received or if the subject completed the planned duration of the study.

Table 4. Summary of primary efficacy analysis - relative risk of laboratory-confirmed, symptomatic influenza: NAI30010 and NAI30031 (ITT population).

Study	Cases of influenza		*P*-value	Approximate relative risk[1] (95% CI)
	Placebo, n (%)	Zanamivir, n (%)		
NAI30010[2]	32/168 (19.0)	7/169 (4.1)	< 0.001	0.21 (0.11, 0.43)
NAI30031[2]	42/242 (19.0)	10/245 (4.1)	< 0.001	0.19 (0.10, 0.36)

[1]Approximate relative risk = risk on zanamivir/risk on placebo
[2]In at least one contact case in the family/household

Comment: Nineteen percent (19.0%) of the households in the placebo treatment groups in both studies NAI30010 and NAI30031 had symptomatic, laboratory-confirmed influenza in at least one contact case, while 4.1% of the households in the zanamivir treatment groups in both studies NAI30010 and NAI30031 had symptomatic, laboratory-confirmed influenza in at least one contact case.

The zanamivir treatment effect was highly significant ($p<0.001$, odds ratios and relative risks were approximately 0.20) in both studies.

Interestingly, the outcomes of the two studies were identical regardless if the index case received antiviral treatment or not. The FDA asked the Applicant to provide copies of the serology source documents from 68 subjects enrolled in Study NAI30031 in order to verify the results. The serology results shown on the source documents were consistent with the serology results submitted with the electronic datasets.

Major secondary efficacy endpoints in family/household studies

a) Proportion of randomized families in whom at least one randomized contact developed laboratory-confirmed (symptomatic or asymptomatic) influenza infection.

The summary of households in which at least one contact case developed laboratory-confirmed (symptomatic or asymptomatic) influenza infection is shown in Table 5.

Table 5. Summary of households in which at least one contact case developed laboratory-confirmed (symptomatic or asymptomatic) influenza infection in Study NAI30010 and NAI30031.

	Placebo	Zanamivir	***P*-value**	Relative Odds (95% CI)	Approximate Relative Risk (95% CI)
Study NAI30010					
Intent-to-Treat Number (%) of households	N=168 47 (28)	N=169 22 (13)	0.001	0.39 (0.21, 0.70)	0.47 (0.30, 0.73)
Index Influenza Positive Number (%) of households	N=87 33 (38)	N=78 15 (19)	0.014	0.39 (0.18, 0.85)	0.52 (0.32, 0.85)
Per Protocol Number (%) of households	N=164 45 (27)	N=165 19 (12)	<0.001	0.35 (0.19, 0.65)	0.43 (0.27, 0.68)
Study NAI30031					
Intent-to-Treat Number (%) of households	N=242 75 (31)	N=245 35 (14)	<0.001	0.34 (0.20, 0.55)	0.44 (0.31, 0.62)
Index Influenza Positive Number (%) of households	N=153 67 (44)	N=129 27 (21)	<0.001	0.31 (0.17, 0.57)	0.46 (0.32, 0.67)
Per Protocol Number (%) of households	N=228 72 (32)	N=232 34 (15)	<0.001	0.32 (0.19 0.54)	0.43 (0.30, 0.61)

Source: Section 7.2.1 and 7.1.3 of the Clinical Study Report

Comment: In each of the three populations in studies NAI30010 and NAI30031, the percentage of zanamivir households in which at least one contact case developed laboratory-confirmed (symptomatic or asymptomatic) influenza was significantly lower than the corresponding percentage of placebo households. As in other analyses presented in this review, these findings were consistent regardless of which population was evaluated (ITT, Index Influenza Positive or Per Protocol Population).

b) Proportion of families in whom at least one randomized contact developed symptomatic, laboratory confirmed influenza where symptoms developed any time from 1 day after start of treatment to Day 11 for the ITT , Index Influenza Positive and Per Protocol Populations

Table 6 summarizes the proportion of randomized families in whom at least one randomized subject developed symptomatic, laboratory-confirmed influenza. Subjects who developed symptoms at any time from one day after start of treatment to Day 11 were included in the ITT, Index Influenza Positive and Per Protocol populations analyses, respectively, in Study NAI30010 and Study NAI30031.

Table 6. Summary of households in which at least one contact case developed symptomatic, laboratory-confirmed influenza at any time from 1 day after start of treatment to Day 11 in Study NAI30010 and Study NAI30031.

	Placebo	**Zanamivir**	***P*-value**	**Relative Odds (95% CI)**	**Approximate Relative Risk (95% CI)**
Study NAI30010					
Intent-to-Treat Number (%) of households	N=168 25 (19%)	N=169 4 (2%)	<0.001	0.14 (0.03, 0.41)	0.16 (0.06, 0.38)
Index Influenza Positive Number (%) of households	N=87 20 (23%)	N=78 3 (4%)	<0.001	0.13 (0.02, 0.49)	0.18 (0.07, 0.47)
Per Protocol Number (%) of households	N=164 25 (15%)	N=165 4 (2%)	<0.001	0.14 (0.03, 0.42)	0.16 (0.07, 0.39)
Study NAI30031					
Intent-to-Treat Number (%) of households	N=242 46 (19%)	N=245 10 (4%)	<0.001	0.17 (0.07, 0.37)	0.19 (0.10, 0.36)
Index Influenza Positive Number (%) of households	N=153 44 (29%)	N=129 8 (6%)	<0.001	0.18 (0.07, 0.43)	0.21 (0.11, 0.43)
Per Protocol Number (%) of households	N=228 41 (18%)	N=232 9 (4%)	<0.001	0.17 (0.07, 0.38)	0.19 (0.10, 0.36)

Source: Section 7.1 of the Clinical Study Report

Comment: The treatment effect of zanamivir in both Study NAI30010 and Study NAI30031 was highly significant in all three populations (ITT, Index Influenza Positive and Per Protocol Populations). Zanamivir effectiveness was demonstrated in contact cases who developed symptomatic, laboratory-confirmed influenza at any time from Day 1 after start of treatment to Day 11.

Additional efficacy analysis:

- **Missing data sensitivity analysis**

To evaluate the impact of missing data the Applicant performed sensitivity analyses for missing data. Missing data were imputed at the placebo rate for both treatment groups. Events for families/households with missing data were imputed at the placebo rate for both treatment groups, rounding up to the nearest integer, if necessary. Results are summarized in the following table.

Table 7. Summary of Applicant's sensitivity analysis data (ITT population)

Study	Number of households with influenza, including imputed events			Approximate Relative Risk[1] (95% CI)
	Placebo n (%)	Zanamivir n (%)	*P*-value	
NAI30010	33 (20)	8 (5)	<0.001	0.24 (0.12, 0.46)
NAI30031	48 (20)	11 (4)	<0.001	0.20 (0.11, 0.37)

Source: Summary of clinical efficacy, Table 20
[1]Approximate relative risk = risk on zanamivir/risk on placebo

Comment: Results of these analyses demonstrate the primary efficacy analyses are robust to reasonable assumptions regarding missing data.

Dr. Smith, the statistical reviewer, performed additional sensitivity analyses assuming 1, 2 and 3 times the placebo incidence rates for contact cases who discontinued from the study. The zanamivir treatment effect remained highly significant using these assumptions. Please refer to statistical review for more details.

- **Efficacy analyses by contact case rather than household**

In both family/household studies the 'household' was the defined unit of randomization and outcome was assessed accordingly. In this analysis the Applicant used 'each contact case' as the basis for assessing the outcome.

Table 8. Efficacy analysis by 'household' compared with 'each contact case' in Study NAI30010 and Study NAI30031 (ITT population)**.**

Study	Cases of influenza			Approximate Relative Risk[3] (95% CI)
	Placebo n/N (%)	Zanamivir n/N (%)	***P***-value	
NAI30010[1]	32/168 (19.0)	7/169 (4.1)	<0.001	0.21 (0.11, 0.43)
NAI30010[2]	40/423 (9.4)	7/414 (1.7)	<0.001	0.19 (0.09, 0.37)
NAI30031[1]	46/242 (19.0)	10/245(4.0)	<0.001	0.19 (0.10, 0.36)
NAI30031[2]	55/630 (8.7)	12/661 (1.8)	<0.001	0.18 (0.10, 0.32)

[1]Results presented by household
[2]Results presented by contact case
[3]Approximate relative risk = risk on zanamivir/risk on placebo

Comment: This analysis showed zanamivir treatment effect was also highly statistically significant when the effect was assessed using 'each contact case' as the unit for assessing outcome.

- **Efficacy analysis by influenza type**

Both family/household studies (Study NAI30010 and Study NAI30031) were also analyzed by influenza type (A or B) to determine whether zanamivir demonstrated prophylactic efficacy against both influenza A and B viruses. Analyses were performed using 'each contact case' and 'household' as the units to assess the outcome. The results of these analyses are shown in Table 9.

Table 9. Summary of laboratory-confirmed, symptomatic influenza by influenza type and by contact case and by influenza type and by household (ITT Population).

Study	Influenza Type	Contact Cases of Influenza			Approximate Relative Risk[1] (95% CI)
		Placebo n/N (%)	Zanamivir n/N (%)	*P*-value	
By contact case					
NAI30010	A	26/423 (6)	4/414 (<1)	<0.001	0.17 (0.07, 0.41)
NAI30010	B	14/423 (3)	3/414 (<1)	0.014	0.23 (0.07, 0.68)
By household					
NAI30010[2]	A	20/168 (12)	4/169 (2)	<0.001	0.19 (0.08, 0.49)
NAI30010[2]	B	13/168 (8)	3/169 (2)	0.016	0.23 (0.07, 0.69
By contact case					
NAI30031	A	32/630 (5)	7/661 (1)	<0.001	0.21 (0.10, 0.45)
NAI30031	B	23/630 (4)	5/661 (<1)	<0.001	0.13 (0.05, 0.36)
By household					
NAI30031[3]	A	27/242 (11)	6/245 (2)	<0.001	0.22 (0.10, 0.49)
NAI30031[3]	B	20/242 (8)	4/245 (2)	<0.001	0.15 (0.06, 0.41)

[1]Approximate relative risk = risk on zanamivir/risk on placebo.
[2]Total number of households on placebo with a case was 32, with 1 of these 32 households having emergent cases of both influenza A and B.
[3]Total number of households on placebo with a case was 46, with 1 of these 46 households having emergent cases of both influenza A and B.

Comment: The results indicate that zanamivir is effective for prophylaxis against both influenza A and influenza B viruses. Analysis by 'each contact case' as the defined unit provided similar results to analysis by 'household' as the defined unit.

- **Efficacy analysis by match between index case and contact case (ITT population)**

An analysis was performed to determine the relative risk of zanamivir versus placebo for contact cases whose influenza type matched that of the index case, and for contact cases whose influenza type differed from that of the index case.

Table 10. Summary of relative risk of laboratory-confirmed, symptomatic influenza by contact case according to whether influenza types of index cases and contact cases match (ITT population).

Study	Influenza type match[1]	Placebo n/N (%)	Zanamivir n/N (%)	*P*-value	Approximate relative risk[2]
NAI30010	Yes	29/423 (7)	5/414 (1)	<0.001	0.18
NAI30010	No	11/423 (3)	2/414 (<1)	0.036	0.21
NAI30031	Yes	46/630 (7)	9/661 (1)	<0.001	0.19
NAI30031	No	9/630 (1)	3/661 (<1)	0.021	0.11

Source: Summary of clinical efficacy, Table 24
[1]A match is considered to be an index case with influenza type A plus a contact case with influenza type A, or an index case with influenza type B plus a contact case with influenza type B. All other combinations were considered to be not a match (including those cases where the index case was negative).
[2]Approximate relative risk = risk on zanamivir/risk on placebo

Comment: In most cases, it was more common for the type of influenza of the contact case to match that of the index case within the same household. Matching was observed in 72% (34/47) of contact cases in Study NAI30010 and in 82% (55/67) of contact cases in Study NAI30031.

Zanamivir was effective in preventing influenza regardless of whether the influenza virus was acquired from the index case or from an infected individual outside the household.

- **Efficacy analysis by age (ITT population)**

Analyses were performed in the two family/household studies to determine the zanamivir relative efficacy across all age groups. The results of these analyses are summarized in the following table.

Table 11. Summary of efficacy analyses by age in family/household studies (ITT population)

Study	Age group (years)	Contact cases/subjects with symptomatic, laboratory-confirmed influenza	
		Placebo n/N (%)	Zanamivir n/N (%)
Study NAI30010	5-7	4/48 (8)	1/47(2)
	8-16	9/140 (6)	4/135 (3)
	17-34	4/53 (8)	1/58 (2)
	35-49	21/160 (13)	1/151 (<1)
	50+	2/22 (9)	0/23
Study NAI30031	5-7	5/43 (12)	1/45 (2)
	8-16	23/211 (11)	6/237 (3)
	17-34	6/100 (6)	3/91 (3)
	35-49	20/240 (8)	2/250 (<1)
	50+	1/36 (3)	0/38

Source: Statistical Reviewer's Analysis

Comment: The incidence of symptomatic, laboratory-confirmed influenza is consistently higher in the placebo group across all age groups. Prophylaxis with zanamivir appears effective across all age groups. Importantly, zanamivir efficacy was demonstrated in younger subjects (such as ages 5-7). Given their age, these subjects inherently may have difficulties using the Diskhaler inhalation device. Nevertheless, detailed subject instruction regarding the proper use of the Diskhaler is imperative.

- **Efficacy analyses by immunization status**

Table 12 summarizes the analyses of the two family/household studies by vaccination status.

Table 12. Summary of efficacy analyses by vaccination status (ITT population)

Study	Vaccination Status	Contact cases/subjects with symptomatic, laboratory-confirmed influenza	
		Placebo n/N (%)	Zanamivir n/N (%)
NAI30010	Yes	5/78 (6)	0/57
NAI30010	No	35/345 (10)	7/357 (2)
NAI30031	Yes	7/60(12)	1/72(1)
NAI30031	No	48/570 (8)	11/589 (2)

Source: Summary of clinical efficacy, Table 29

Comment: Compared to the zanimavir treatment group, the percentage of contact cases with symptomatic, laboratory-confirmed influenza is consistently higher in the placebo treatment group regardless of vaccination status.

Several additional analyses were conducted using the primary endpoint in the two family/ household studies. All these analyses confirmed the robustness of the zanamivir efficacy data. Please refer to statistical review by Dr. Fraser Smith for further details.

PRIMARY COMMUNITY STUDIES

As previously described and as described in the Appendix, the two community studies were similar in design. The main difference between the two studies was the study population. Study NAIA3005 was conducted in a two university communities and recruited predominantly healthy subjects ≥ 18 years of age. Study NAI30034 recruited subjects considered at high risk for developing complications from influenza infection (see Appendix, Table 8).

The primary endpoint in both studies was the proportion of randomized subjects who developed symptomatic, laboratory-confirmed influenza. The results of the primary efficacy analyses are shown in Table 13.

Table 13. Summary of primary efficacy analysis - relative risk of laboratory-confirmed, symptomatic influenza: NAIA3005 and NAI30034 (ITT population).

Study	**Cases of influenza**		***P*-value**	**Approximate relative risk[1] (95% CI)**
	Placebo n/N (%)	**Zanamivir n/N (%)**		
NAIA3005	34/554 (6.1)	11/542 (2.0)	< 0.001	0.33 (0.17, 0.61)
NAI30034	23/1685 (1.4)	4/1678 (0.2)	< 0.001	0.17 (0.07, 0.44)

[1]Approximate relative risk = risk on zanamivir/risk on placebo

Comment: The protective efficacy of zanamivir administered once daily for 28 days was demonstrated in both studies. It is noteworthy that in Study NAI30034 statistical significant difference was noted despite a low influenza attack rate.

The FDA asked the Applicant to provide copies of the serology source documents from 81 subjects enrolled in Study NAI30034 in order to verify the results. The serology results shown on the source documents were consistent with the serology results submitted with the electronic datasets.

Additional efficacy analysis:

- **Missing data sensitivity analysis**

To evaluate the impact of missing data the Applicant performed sensitivity analysis for missing data. In this analysis, missing data were imputed at the placebo rate for both treatment groups.

Results are summarized in the following table.

Table 14. Summary of Applicant's sensitivity analysis data (ITT population)

Study	Number of households with influenza, including imputed events			Approximate relative risk[1] (95% CI)
	Placebo n n (%)	Zanamivir n (%)	*P*-value	
NAI3005[2]	36 (6)	12 (2)	<0.001	0.34 (0.18, 0.62)
NAI30034[2]	25 (1)	6 (< 1)	<0.001	0.24 (0.11, 0.54)

Source: Summary of clinical efficacy, Table 20
[1]Approximate relative risk = risk on zanamivir/risk on placebo
[2]Events for subjects with missing data were imputed at the placebo rate for both treatment groups, rounding up to the nearest integer, if necessary.

Comment: Results of these analyses demonstrated the efficacy results are robust to reasonable assumptions regarding missing data.

Additional sensitivity analyses assuming 1, 2 and 3 times the placebo incidence rates for contact cases who discontinued from the study were performed. The zanamivir treatment effect remained highly significant using these assumptions. Please refer to statistical review for more details.

- **Asymptomatic, laboratory confirmed influenza in community studies**

Table 15 summarizes the proportion of cases who were asymtomatic and seroconverted in the two community studies.

Table 15. Summary of seroconversion in asymptomatic subjects in the community studies (ITT population.

	Asymptomatic, serologically positive subjects	
	Placebo [n(%)]	Zanamivir [n(%)]
Community studies		
NAIA3005	43 (8%)	42 (8%)
NAI30034	29 (2%)	34 (2%)

Source: Summary of clinical efficacy, Table 26

Comment: The proportion of subjects who seroconverted but remained asymptomatic was similar between placebo and zanamivir groups in both studies. These results suggest that treatment with zanamivir not only prevents current disease but also allows development of seroconversion that is potentially protective against future infection with the same virus.

- **Efficacy analysis by age**

Analyses were performed in the two community studies to determine the relative efficacy across all age groups. The results of these analyses are summarized in the following table.

Table 16. Summary of efficacy analyses by age in community studies (ITT population)

Study	Age group (years)	Contact cases/subjects with symptomatic, laboratory-confirmed influenza	
		Placebo n/N (%)	Zanamivir n/N (%)
Community Studies			
NAIA3005	17-34	27/416 (6)	9/416 (2)
	35-49	5/116 (4)	2/105 (2)
	50+	2/22 (9)	0/32
NAI30034	12-16	3/55 (5)	1/51 (2)
	17-34	4/114 (4)	1/123 (<1)
	35-49	7/246 (3)	1/228 (<1)
	50-64	4/320 (1)	0/330
	65-79	4/829 (<1)	0/818
	80+	1/121 (1)	1/128 (1)

Comment: Zanamivir efficacy was demonstrated across the various age groups assessed. The percentage of subjects with symptomatic, laboratory-confirmed influenza appears consistently higher in the placebo treatment group in each age group with the possible exception of subjects 80 years of age and older. The ability to use the Diskhaler inhalation device, particularly in older subjects, may have impacted effectiveness. As stated in the PRECAUTIONS: Geriatric Use section of the package insert, elderly subjects may need assistance with the use of the device.

- **Efficacy analyses by immunization status**

Table 17 summarizes the analyses of the two community studies by vaccination status.

Table 17. Summary of efficacy analyses by vaccination status (ITT population)

Study	Vaccination Status	Subjects with symptomatic, laboratory-confirmed Influenza	
		Placebo n/N (%)	Zanamivir n/N (%)
NAIA3005	Yes	6/79 (8)	0/80
NAIA3005	No	28/475 (6)	11/473 (2)
NAI30034	Yes[1]	4/916 (<1)	1/903 (<1)
NAI30034	No	19/768 (2)	3/775 (<1)

Source: Summary of Clinical Efficacy Table 29
[1]Excludes subjects vaccinated less than 21 days before the start of the study.

Comment: Regardless of vaccination status, zanamivir efficacy was demonstrated in the two community studies. The percentage of contact cases with symptomatic,

laboratory-confirmed influenza appears consistently higher in the placebo treatment group than in the zanamivir group in both studies.

- **Efficacy analyses by high-risk category**

Study NAI30034 was conducted in a community setting and recruited subjects who were considered high-risk of developing complications after influenza infection. In this study, high-risk subjects were defined as subjects ≥ 65 years of age, subjects with respiratory disease, cardiovascular disease, and subjects with diabetes mellitus.

Table 18. Summary of efficacy analyses by high-risk category (ITT population)

Study	High-risk category	Subjects with symptomatic, laboratory-confirmed influenza	
		Placebo n/N (%)	**Zanamivir n/N (%)**
NAI30034	All subjects	23/1685 (1.4)	4/1678 (0.2)
	Subjects aged ≥65 years	5/950 (<1)	1/946 (<1)
	Subjects with respiratory disease	17/695 (2)	3/684 (<1)
	Subjects with cardiovascular disease	1/307 (<1)	0/331
	Subjects with diabetes mellitus	3/370 (<1)	0/359

Source: Summary of clinical efficacy, Table 30

Comment: There was no difference in efficacy according to subject's underlying condition. Of note, efficacy was demonstrated in subjects with underlying respiratory disease; whereas, in the treatment studies, efficacy was not demonstrated in this population. Nevertheless, zanamivir is not recommended for treatment or prophylaxis of influenza in subjects with underlying airways. This recommendation is based on lack of efficacy in the treatment setting and is based on reported cases of bronchospasm and decline in lung function. These issues are highlighted in the INDICATIONS AND USAGE and WARNINGS section of the package insert.

Several additional analyses were also conducted using the primary endpoint in the two community studies. All these analyses confirmed the robustness of the zanamivir efficacy data. Please refer to statistical review by Dr. F. Smith for further details.

6.1.5 Clinical Microbiology

As a component of zanamivir prophylaxis studies, the Applicant conducted virology substudies to determine whether influenza resistant virus emerged in subjects receiving zanamivir for up to 28 days. The resistance evaluations involved phenotypic assessment of neuraminidase susceptibility of viral isolates before and after treatment with zanamivir and genotypic assessment by sequencing the neuraminidase gene and the hemagglutinin 1 subunit (which contains the binding site for the sialic acid receptor) of the hemagglutinin gene. The Applicant

stated no evidence for emergence of resistance to zanamivir as measured by phenotyping of neuraminidase activity and by genotyping of neuraminidase and hemagglutinin 1 subunit of the hemagglutinin was observed in the prophylaxis studies. For additional details please see the Microbiology review by Dr. Narayana Battula.

6.1.6 Efficacy Conclusions

The protective efficacy of zanamivir in the prophylaxis of influenza was demonstrated in two studies conducted in a family/household setting and in two studies conducted in a community setting. In all four studies, the incidence of symptomatic, laboratory-confirmed influenza in subjects treated with zanamivir was significantly lower compared with the incidence observed in subjects treated with placebo. Several additional analyses were conducted using the primary endpoint. All these analyses confirmed the robustness of the zanamivir efficacy data.

The benefit of zanamivir prophylaxis was also shown across all ages studied and was irrespective of vaccination status and current smoking status. Additionally, the benefit of zanamivir prophylaxis was not affected by underlying high-risk condition in Study NAI30034. The zanamivir prophylactic efficacy was similar in the prevention of influenza A and B. Moreover, zanamivir resistant isolates were not observed in these studies.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

The safety evaluation of this sNDA is based on six phase III studies. The two post-exposure prophylaxis studies conducted in a family/household setting (Study NAI30010 and Study NAI30031), the two seasonal prophylaxis studies conducted in a community setting (Study NAIA3005 and Study NAI30034), and the two nursing home studies (Study NAIA3003 and Study NAIA3004). Adverse event (AE) and serious AE data were pooled for the two family/ household studies and for the two seasonal prophylaxis studies. AEs from the two nursing home studies were not pooled because Study NAIA3003 compared zanamivir with the standard of care (rimantadine for influenza A and placebo for influenza B) rather than placebo. In addition, AE data from all five placebo-controlled studies were pooled with the AE data from Study NAIA3003 presented in a side-by-side fashion.

All safety analyses were performed using the safety population. The safety population includes all subjects randomized to treatment who took at least one dose of study drug. The ITT was used for summaries of subjects discontinuing study and study drug. The ITT population was defined as all randomized subjects, regardless of whether or not the study drug was actually taken or if the subject completed study procedures. All clinical studies and subject populations are summarized in the following table. Overall, the adverse event profile was similar between the placebo and zanamivir groups and consistent with the known AE profile described for zanamivir in the treatment of influenza.

Table 19. Summary of clinical studies (safety population)

Study	Number of subjects (safety population)			Duration of prophylaxis
	Placebo	Zanamivir	Rimantadine	
Primary phase III studies				
Family/ Household				
NAI30010	430	407	N/A	10 days
NAI30031	629	661	N/A	10 days
Community				
NAIA3005	554	553	N/A	28 days
NAI30034	1685	1678	N/A	28 days
Secondary Phase III Studies				
Nursing Home				
NAIA3003	13	238	231	14 days
NAIA3004	252	242	N/A	14 days

7.1.1 Deaths

No deaths were reported during the prophylaxis period in any of the primary or secondary phase III studies. Six deaths (five in the nursing home studies and one in the community studies) occurred after the prophylaxis period; three of the six subjects received inhaled zanamivir, two inhaled placebo, and one rimantadine. All deaths were considered unrelated to study drugs. Below are brief summaries of the six subjects who died:

Subject 12870 (Study NAIA3003), an 83-year-old male, was randomized to receive inhaled zanamivir. Five days after initiating treatment he developed influenza A infection characterized by upper respiratory symptoms. Three days later, he deteriorated and he was diagnosed with left lower lobe pneumonia and dehydration. He was treated with intravenous antibiotics and fluids. Study drug was discontinued on Day 8. His respiratory distress and dehydration improved. However, he experienced recurrent dehydration and died 30 days after his initial presentation.

Subject 12797 (Study NAIA3003), was an 82-year-old female with a history of multiple chronic cardiovascular, endocrine, metabolic, renal and neurologic problems. She was randomized to receive rimantadine. Study medication was discontinued after two days. Five days after study drug discontinuation and two days after undergoing left leg amputation she developed post-operative bilateral pneumonia. Approximately two weeks after surgery she died.

Subject 14266, a 68-year-old male enrolled in Study NAIA3004, was receiving inhaled zanamivir. Study medication was permanently discontinued on Day 12 when he was diagnosed with liver cirrhosis and severe heart failure. He died 6 months after completing the study.

Subject 50906 (Study NAIA3004), a 63-year-old male, was randomized to placebo. The subject was concurrently diagnosed with ischemic heart disease, hypertension, atherosclerotic encephalopathy, chronic alcoholism, chronic bronchitis, and obesity. Three days after completing study drug treatment he experienced a myocardial infarction which lead to a fatal cardiac arrest.

Subject 14820 (Study NAIA3004), a 57-year-old male, was randomized to placebo. About 10 days after completing the study treatment he was hospitalized with exudative pleural effusion, acute cholecystitis with cholelithiasis, jaundice and possible lung cancer. He died approximately 2½ months after completing the study.

Subject 72577 (Study NAI30034), was a 57-year-old female, randomized to receive inhaled zanamivir. The subject had a history of diabetes mellitus, hypertension, and hypercholesterolemia. Five days after the last study dose she was hospitalized in the intensive care unit for myocardial infarction. A few days after she was discharged from the hospital she had another myocardial infarction and she died.

7.1.2 Other Serious Adverse Events

The incidence of non-fatal serious AEs in the placebo and zanamivir groups in the pooled data of the five phase III placebo-controlled studies was < 1% in both groups. Three serious AEs reported in two subjects enrolled in Study NAI30034 were considered related to study drug; both subjects were randomized to inhaled placebo (cardiac arrhythmia in one subject, dyspnea and cough in the other subject). All other serious AEs were considered by investigators not related to study drugs. The most common serious AEs reported across all six phase III studies were fractures (4 subjects), chest symptoms (4 subjects), and chronic obstructive airways disease (3 subjects). The following table summarizes all serious AEs observed during prophylaxis in all six phase III studies.

Table 20. Summary of serious AEs for the six phase III studies: during prophylaxis (safety population).

Serious Adverse Event	**NAIA3004, NAIA3005, NAI30010, NAI30031, NAI30034 combined**		**NAIA3003**		
	Placebo (N=3550)	**Zanamivir (N=3541)**	**Placebo (N=13)**	**Rimantadine (N=231)**	**Zanamivir (N=238)**
No. (%) subjects with at least one SAE	16 (<1%)	19 (<1%)	0	0	2 (<1%)
Cardiovascular:					
Cerebrovascular accidents	2 (<1%)	0	0	0	0
Arrhythmias	1 (<1%)	0	0	0	0
Coronary artery disorders	1 (<1%)	0	0	0	0
Thrombosis	1 (<1%)	0	0	0	0
Biventricular heart failure	0	1 (<1%)	0	0	0
Tachyarrhythmias	0	1 (<1%)	0	0	0
Thrombophlebitis	0	1 (<1%)	0	0	0
Drug interaction, overdose and trauma:					
Fractures	2 (<1%)	2 (<1%)	0	0	0
Ear, Nose, and Throat:					
Bacterial Ear Nose & Throat Infections	1 (<1%)	0	0	0	0
Endocrine & Metabolic:					
Fluid disturbances	0	1 (<1%)	0	0	1 (<1%)
Hyperglycemia	1 (<1%)	0	0	0	0
Hypoglycemia	1 (<1%)	0	0	0	0
Gastrointestinal:					
Gastrointestinal Obstructions	1 (<1%)	1 (<1%)	0	0	0
Enterocolitis	0	1 (<1%)	0	0	0
Esophagitis	0	1 (<1%)	0	0	0
Gastroenteritis	0	1 (<1%)	0	0	0
Hepatobiliary Tract & Pancreas:					
Gallbladder Disorders	0	1 (<1%)	0	0	0
Hepatic Cirrhosis	0	1 (<1%)	0	0	0
Pancreatitis	0	1 (<1%)	0	0	0
Lower Respiratory:					
Chronic Obstructive Airways Disease	1 (<1%)	2 (<1%)	0	0	0
Asthma	1 (<1%)	0	0	0	0
Breathing Disorders	1 (<1%)	0	0	0	0
Cough	1 (<1%)	0	0	0	0
Pneumonia	0	0	0	0	1 (<1%)
Viral Respiratory	0	0	0	0	1 (<1%)

Infections					
Neurology:					
Headaches	0	1 (<1%)	0	0	0
Non-site Specific:					
Chest Symptoms	1 (<1%)	3 (<1%)	0	0	0
Non-Specific Conditions	1 (<1%)	0	0	0	0
Temperature Regulation Disturbances[1]	1 (<1%)	0	0	0	0
Bacterial Infections	0	1 (<1%)	0	0	0
Infections	0	1 (<1%)	0	0	0
Psychiatry:					
Anxiety	1 (<1%)	0	0	0	0
Bipolar Disorders	0	1 (<1%)	0	0	0
Reproduction:					
Cysts lumps & masses of female reproductive tract	1 (<1%)	0	0	0	0
Primary malignant breast neoplasia	0	1 (<1%)	0	0	0
Skin:					
Primary malignant skin neoplasia	0	0	0	0	1 (<1%)
Renal impairment	1 (<1%)	0	0	0	0
Urinary calculi	1 (<1%)	0	0	0	0

Source Data: Summary of clinical safety, Table 24
Data for NAI30010 and NAI30031 include contact cases only
Data for NAIA3003 and NAIA3004 include all randomizations
[1]Temperature regulation disturbances included fever, intermittent fever, chills, and intermittent chills

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

Please refer to Section 10: Appendices, Tables 3, 4, 5, 6, 9, 10, 12, and 13 for the primary reasons for study and study drug discontinuations for the individual studies summarized by setting. The following table provides a pooled summary of study drug discontinuation for the six phase III studies.

Table 21. Summary of study drug discontinuation for the six phase III studies (ITT population).

	NAIA3004, NAIA3005, NAI30010, NAI30031, NAI30034 combined		NAIA3003		
	Placebo (N=3544)	**Zanamivir (N=3548)**	**Placebo (N=13)**	**Rimantadine (N=231)**	**Zanamivir (N=238)**
Study Drug					
Discontinued study drug prematurely	295 (8%)	269 (8%)	0	21 (9%)	13 (5%)
Completed study drug	3249 (92%)	3279 (92%)	13 (100%)	210 (91%)	225 (95%)
Reason for premature discontinuation					
Adverse event	60 (2%)	54 (2%)	0	12 (5%)	11 (5%)
Consent withdrawn	42 (1%)	32 (<1%)	0	1 (<1%)	0
Lost to follow up	13 (<1%)	7 (<1%)	0	0	0
Protocol violation	55 (2%)	54 (2%)	0	1 (<1%)	1 (<1%)
Other[1]	125 (4%)	122 (3%)	0	7 (3%)	1 (<1%)

Source Data: Summary of clinical safety, Table 6 (modified)
Data for NAI30010 and NAI30031 include contact cases only
Data for NAIA3003 and NAIA3004 include all randomizations
[1]Other category includes: twice daily dosing instead of once daily on some/all days; lost study drug, missed last dose.

Comment: For the five placebo-controlled phase III studies combined, 3544 subjects received placebo and 3548 subjects received zanamivir. Overall, 8% of subjects in those studies discontinued study drug for any reason. Numbers of discontinuations and reasons for premature discontinuations were similar across treatment groups.

7.1.3.2 Adverse events associated with dropouts

The frequency of AEs leading to discontinuation of study drug was low and similar across the treatment groups. Overall, for the five placebo-controlled phase III studies combined, 2% of subjects in both the placebo and zanamivir groups prematurely discontinued study drug due to an AE. The most common AEs leading to drug discontinuation were cough, throat and tonsil discomfort, headaches, malaise and fatigue, and temperature regulation and disturbances. The following table summarizes the AEs leading to discontinuation in three or more subjects.

Table 22. Summary of AEs leading to discontinuation of study drug in three or more subjects in the six phase III studies: During prophylaxis (safety population)

AE leading to discontinuation of study drug	NAIA3004, NAIA3005, NAI30010, NAI30031, NAI30034 combined		NAIA3003		
	Placebo (N=3550)	Zanamivir (N=3541)	Placebo (N=13)	Rimantadine (N=231)	Zanamivir (N=238)
No. (%) subjects with at least one AE leading to withdrawal	60 (2%)	54 (2%)	0	12 (5%)	11 (5%)
Cough	11 (<1%)	8 (<1%)	0	6 (3%)	5 (2%)
Throat and tonsil discomfort and pain	6 (<1%)	5 (<1%)	0	5 (2%)	4 (2%)
Headaches	3 (<1%)	7 (<1%)	0	3 (1%)	2 (<1%)
Malaise and fatigue	2 (<1%)	0	0	6 (3%)	6 (3%)
Temperature regulation disturbances[1]	1 (<1%)	3 (<1%)	0	4 (2%)	4 (2%)
Nasal signs and symptoms	2 (<1%)	1 (<1%)	0	6 (3%)	3 (1%)
Asthma	7 (<1%)	5 (<1%)	0	0	0
Breathing disorders	5 (<1%)	3 (<1%)	0	1 (<1%)	1 (<1%)
Chest symptoms	5 (<1%)	3 (<1%)	0	1 (<1%)	0
Dizziness	3 (<1%)	4 (<1%)	0	0	2 (<1%)
Vocal cord disorders	0	0	0	3 (1%)	4 (2%)
Nausea and vomiting	2 (<1%)	1 (<1%)	0	2 (<1%)	2 (<1%)
Viral respiratory infections	6 (<1%)	0	0	0	1 (<1%)
Chest sounds	2 (<1%)	0	0	2 (<1%)	1 (<1%)
Muscle pain	1 (<1%)	1 (<1%)	0	2 (<1%)	1 (<1%)
Nasal inflammation	0	0	0	2 (<1%)	2 (<1%)
Diarrhea	1 (<1%)	2 (<1%)	0	0	1 (<1%)
Bronchitis	2 (<1%)	1 (<1%)	0	1 (<1%)	0
Skin rashes	3 (<1%)	1 (<1%)	0	0	0
Hypertension	3 (<1%)	0	0	0	0
Chronic obstructive airways disease	1 (<1%)	2 (<1%)	0	0	0
Confusion	2 (<1%)	0	0	0	1 (<1%)
Pain	0	0	0	1 (<1%)	2 (<1%)

Source Data: Summary of clinical safety, Table 28
Data for NAI30010 and NAI30031 include contact cases only
Data for NAIA3003 and NAIA3004 include all randomizations.
[1]Temperature regulation disturbances included fever, intermittent fever, chills, and intermittent chills

7.1.3.3 Other significant adverse events

After the approval of zanamivir for the treatment of influenza infection, bronchospasm and bronchospasm-like symptoms were reported through the post-marketing surveillance system. Many, but not all of these subjects, had underlying airways disease. Some of those subjects had fatal outcome, although causality was difficult to assess. Because of the severity of this complication, the Applicant was asked during the pre-NDA face-to-face meetings to examine the incidence of bronchospasm in the phase III prophylaxis studies.

Several analyses were performed to examine the incidence of bronchospasm during the phase III prophylaxis studies. The following steps were taken: a) identify lower respiratory events of interest based on adverse event coded terms, b) identify bronchospasm-like events based on the investigator text, c) identify events that map to the term 'Airways constriction and obstruction,' and d) identify adverse events containing the specific term 'bronchospasm.'

a) Lower respiratory events of interest

Coded adverse event terms were reviewed to determine the terms possibly related to bronchospasm or bronchospasm-like illness. Lower respiratory events of interest consisted of the following coded terms: asthma, breathing disorders, bronchitis, chest sounds, airways constriction and obstruction, lower respiratory signs and symptoms, chronic obstructive airways disease, lung disorders, allergic lower respiratory disorders, lower respiratory failure, and chest symptoms.

These analyses are summarized in the following table.

Table 23. Summary of the frequency of lower respiratory events of interest based on coded term for the six phase III studies: During prophylaxis (safety population)

Adverse Event	NAIA3004, NAIA3005, NAI30010, NAI30031, NAI30034 combined		NAIA3003		
	Placebo (N=3550)	Zanamivir (N=3541)	Placebo (N=13)	Rimantadine (N=231)	Zanamivir (N=238)
No. (%) subjects with at least one lower respiratory event of interest	**135 (4%)**	**107 (3%)**	**0**	**17 (7%)**	**11 (5%)**
Bronchitis	38 (1%)	36 (1%)	0	1 (<1%)	0
Asthma	33 (<1%)	22 (<1%)	0	0	0
Breathing disorders	28 (<1%)	11 (<1%)	0	8 (3%)	8 (3%)
Chest symptoms	21 (<1%)	22 (<1%)	0	2 (<1%)	4 (2%)
Chronic obstructive airways disease	10 (<1%)	11 (<1%)	0	2 (<1%)	0
Lower respiratory signs and symptoms	6 (<1%)	13 (<1%)	0	0	1 (<1%)
Chest sounds	8 (<1%)	2 (<1%)	0	4 (2%)	4 (2%)
Airways constriction and obstruction	4 (<1%)	3 (<1%)	0	0	0
Lung disorders	1 (<1%)	1 (<1%)	0	1 (<1%)	0
Allergic lower respiratory disorders	2 (<1%)	0	0	0	0
Lower respiratory failure	1 (<1%)	0	0	0	0

Source Data: Summary of clinical safety, Table 29
Data for Study NAI30010 and Study NAI30031 include contact cases only
Data for Study NAIA3003 and Study NAIA3004 include all randomizations

Comment: For the five placebo-controlled phase III studies combined, a total of 242 subjects experienced a lower respiratory event; a total of 135 subjects (4%) in the placebo group and 107 subjects (3%) in the zanamivir group. The most common AEs were bronchitis, asthma, breathing disorders, and chest symptoms. The presentation of lower respiratory events was similar between zanamivir and placebo groups.

b) Bronchospasm-like events

Following the initial review of lower respiratory events, a further review was undertaken to identify adverse events indicative of bronchospasm. In this analysis, a case-by-case review of the investigator text for each adverse event was conducted within the coded terms identified as 'lower respiratory events of interest' as presented in the previous table. All AEs identified as bronchospasm-like AEs in this review are shown in Table 24.

Table 24. Summary of the frequency of 'bronchospasm-like' events based on AE investigator text review for the six phase III studies: During prophylaxis (safety population)

Adverse Event	**NAIA3004, NAIA3005, NAI30010, NAI30031, NAI30034 combined**		**NAIA3003**		
	Placebo (N=3550)	**Zanamivir (N=3541)**	**Placebo (N=13)**	**Rimantadine (N=231)**	**Zanamivir (N=238)**
No. (%) subjects with at least one 'Bronchospasm-like' AE	**87 (2%)**	**57 (2%)**	**0**	**15 (6%)**	**10 (4%)**
Asthma	33 (<1%)	22 (<1%)	0	0	0
Breathing disorders	26 (<1%)	11 (<1%)	0	8 (3%)	8 (3%)
Chronic obstructive airways disease	10 (<1%)	11 (<1%)	0	2 (<1%)	0
Chest symptoms	8 (<1%)	11 (<1%)	0	1 (<1%)	0
Chest sounds	6 (<1%)	2 (<1%)	0	4 (2%)	2 (<1%)
Airways constriction and obstruction	4 (<1%)	3 (<1%)	0	0	0
Bronchitis	4 (<1%)	0	0	1 (<1%)	0
Lower respiratory signs and symptoms	1 (<1%)	1 (<1%)	0	0	0
Allergic lower respiratory disorders	1 (<1%)	0	0	0	0

Source: Summary of clinical safety, Table 31
Data for NAI30010 and NAI30031 include contact cases only
Data for NAIA3003 and NAIA3004 include all randomizations

Comment: For the six phase III prophylaxis studies combined, a total of 169 subjects (2%) experienced any broncospasm-like AE. Similarly, for the five placebo-controlled phase III prophylaxis studies combined, 2% of subjects in each treatment arm experienced any broncospasm-like AE. The most common broncospasm-like AEs were asthma, breathing disorders, and chronic obstructive airway disease.

c) Events coded under the term 'Airways constriction and obstruction'

For the five placebo-controlled phase III studies, AEs mapping to the term 'Airways constriction and obstruction' were reported in four cases (< 1%) in the placebo group, and in three cases (< 1%) in the zanamivir group. No cases mapping this term were identified in Study NAIA3003.

d) Events containing the specific term 'Bronchospasm'

The last step with this approach was to identify only those AEs with investigator text containing the specific term 'broncospasm.' In this analysis, only two subjects had bronchospasm reported as an AE during the prophylaxis studies. One subject in the placebo group (Study NAI30031) and one in the zanamivir group (NAI30034). Below is a brief summary of the two cases with bronchospasm.

Subject 96394 (Study NAI30034), a 74-year-old male, had severe bronchospasm one day after initiating treatment with zanamivir. This AE was considered study drug related by the Investigator. Study drug discontinued on Day 6. The subject had a history of severe COPD for which he was taking medications. He also started having mild influenza-like symptoms after 12 hours which peaked on Days 3 and 4. Laboratory testing confirmed influenza A infection.

Subject 68142 (Study NAI30031), a 43-year-old female, was randomized to receive placebo. Subject's other illnesses included type 1 diabetes, mild asthma and allergic rhinitis. Three days after initiating study treatment, she developed influenza-like symptoms. She was hospitalized for moderate wheezing, associated symptoms of lower respiratory infection, and worsening asthma with an element of bronchospasm. She was also found to have mild ketoacidosis. All these symptoms resolved after four days. However, she was also found to have bacterial sinusitis with an underlying anatomical deformity. The subject completed study drug treatment and there was no laboratory diagnosis of influenza. The Investigator considered the events unrelated to study drug.

In conclusion, there was no increased risk of bronchospasm in subjects receiving inhaled zanamivir compared with those receiving placebo during the phase III prophylaxis studies.

7.1.4 Other Search Strategies

Because the placebo consisted of inhaled lactose powder, which is also the vehicle for the active drug, it is very difficult to identify from the zanamivir clinical trials the extent to which the dry powder itself may contribute to AEs. To evaluate the potential association of inhalation of lactose dry powder and lower respiratory AEs, the FDA requested additional information from Applicant's sponsored studies in the respiratory therapeutic area. The Applicant selected studies from the GlaxoSmithKline US Asthma Database to assess placebo as a dry powder and placebo in an alternative formulation such as aerosol/metered dose inhalers. This analysis included 16 studies of salmeterol, fluticasone propionate and fluticasone propionate/salmeterol combination. The selected studies included a placebo group and had some similarity in the study design to the zanamivir trials. The incidence of lower respiratory AEs and reports of bronchospasm and bronchospasm-like events occurred in studies using lactose dry powder as placebo were compared with those from studies using alternative formulation as placebo. The results of this comparison are shown in the following table.

Table 25. Frequency of lower respiratory events of interest by body system in previous studies of inhaled respiratory medications (ITT population).[1]

	Placebo Dry Powder (N=530)	**Placebo Aerosol (N=1018)**
No. (%) Subjects with at least one AE	14 (3%)	67 (7%)
Lower Respiratory, any event	6 (1%)	50 (5%)
Bronchitis	3 (<1%)	23 (2%)
Acute bronchitis	1 (<1%)	9 (<1%)
Status asthmaticus	0	6 (<1%)
Asthmatic bronchitis	1 (<1%)	3 (<1%)
Exacerbation of asthma	1 (<1%)	1 (<1%)
Shortness of breath	0	2 (<1%)
Wheeze	0	2 (<1%)
Breathing disorder	0	1 (<1%)
Choking sensation	0	1 (<1%)
Exacerbation of dyspnea	0	1 (<1%)
Exacerbation of wheezing	0	1 (<1%)
Respiratory arrest	0	1 (<1%)
Rhonchi	0	1 (<1%)
Respiratory[2], any event	8 (2%)	9 (<1%)
Bronchitis	4 (<1%)	4 (<1%)
Chest tightness	2 (<1%)	1 (<1%)
Wheezing	1 (<1%)	2 (<1%)
Asthma	2 (<1%)	0
Dyspnea	0	2 (<1%)
Non-Site Specific, any event	0	8 (<1%)
Chest tightness	0	8 (<1%)
Ear Nose & Throat, any event	0	1 (<1%)
Tightness of throat	0	1 (<1%)

Source: Summary of clinical safety, Table 35
[1] These formulations were not compared in the same studies
[2]This body system represents AEs coded under the DISS coding dictionary.

Comment: Fewer lower respiratory adverse events were reported in the group treated with placebo dry powder than with the placebo aerosol formulation. No adverse event mapped to the coded term of 'airways constriction and obstruction' and no investigator text contained the term 'bronchospasm.' The Applicant concluded these results appear to show that subjects inhaling dry powder placebo (such as lactose) do not show any signal of a greater frequency of respiratory AEs than placebos not containing lactose. Therefore, the AEs may be due to the inhaled product itself and may not be specific to the vehicle such as lactose.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

Adverse events were recorded at each study visit. The investigator was responsible for the detection and documentation of events meeting the definition of an AE or serious AE. In addition to solicitation of AEs by study staff at clinic or home visits, study participants used diary cards to record symptoms of influenza-like illness twice daily. Symptoms of influenza-like illness were considered as AEs. All AEs were recorded in the CRF and in the subject's medical record.

As previously stated, because the duration of zanamivir prophylaxis was different between the post-exposure prophylaxis studies and seasonal prophylaxis studies, AE and serious AE data were pooled by setting. AEs from the two nursing home studies were not pooled because Study NAIA3003 compared zanamivir with the standard of care (rimantadine for influenza A and placebo for influenza B) rather than placebo. In addition, AE data from all five placebo-controlled studies were pooled with the AE data from Study NAIA3003 presented in a side-by-side fashion.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

The AE categorizations provided in this sNDA appear appropriate.

7.1.5.3 Incidence of common adverse events

An overall summary of AEs, regardless causality, occurred during the prophylaxis period in the family/household studies combined, community studies combined , and nursing home studies are shown in Tables 26, 27, and 28, respectively.

Table 26. Summary of the most commonly reported AEs (≥ 1.5%), regardless causality, for the family/household prophylaxis studies (Study NAI30010 and NAI30031 combined data) by decreasing frequency: During prophylaxis (safety population).

Adverse Event	**Placebo Contact cases (N=1059)**	**Zanamivir Contact cases (N=1068)**
No. (%) subjects with at least one AE	539 (51%)	455 (43%)
Viral respiratory infections	202 (19%)	140 (13%)
Headaches	150 (14%)	138 (13%)
Nasal signs and symptoms	129 (12%)	126 (12%)
Throat and tonsil discomfort and pain	94 (9%)	89 (8%)
Cough	96 (9%)	80 (7%)
Malaise and fatigue	54 (5%)	58 (5%)
Temperature regulation disturbances[1]	45 (4%)	50 (5%)
Muscle pain	35 (3%)	34 (3%)
Feeding problems[2]	26 (2%)	25 (2%)
Nasal inflammation	22 (2%)	11 (1%)
Nausea and vomiting	19 (2%)	14 (1%)

Source: Summary of clinical safety, Table 12.
[1]Temperature regulation disturbances included fever, intermittent fever, chills, and intermittent chills
[2]Feeding problems included decreased and increased appetite, anorexia, and recurrent anorexia

Comment: In the two family/household studies the frequency of AEs was similar between the placebo and the zanamivir groups. Fifty-one percent of subjects in the placebo group and 43% of subjects in the zanamivir group had at least one AE. The most common AEs were viral respiratory infections, headaches, nasal signs and symptoms, and throat and tonsil discomfort and pain.

Table 27. Summary of the most commonly reported AEs (≥ 1.5%), regardless causality, for the community prophylaxis studies (Study NAIA3005 and NAI30034 combined data) by decreasing frequency: During prophylaxis (safety population).

Adverse Event	Placebo (N=2239)	Zanamivir (N=2231)
No. (%) subjects with at least one AE	1268 (57%)	1264 (57%)
Headaches	571 (26%)	544 (24%)
Throat and tonsil discomfort and pain	445 (20%)	420 (19%)
Cough	414 (18%)	378 (17%)
Nasal signs and symptoms	288 (13%)	277 (12%)
Temperature regulation disturbances[1]	216 (10%)	202 (9%)
Muscle pain	170 (8%)	177 (8%)
Malaise and fatigue	170 (8%)	170 (8%)
Musculoskeletal pain	132 (6%)	129 (6%)
Feeding problems[2]	96 (4%)	79 (4%)
Viral respiratory infections	81 (4%)	77 (3%)
Nausea and vomiting	62 (3%)	52 (2%)
Diarrhea	55 (2%)	48 (2%)
Ear, nose and throat infections	48 (2%)	42 (2%)
Arthralgia and articular rheumatism	17 (<1%)	34 (2%)

Source: Summary of clinical safety, Table 14
[1]Temperature regulation disturbances included fever, intermittent fever, chills, and intermittent chills
[2]Feeding problems included decreased and increased appetite, anorexia, and recurrent anorexia

Comment: In the community studies, the frequency of reported AEs regardless causality was similar between the placebo and zanamivir groups. Fifty-seven percent of subjects in each group had at least one AE. The most common AEs were headaches, throat and tonsil discomfort and pain, cough, nasal signs and symptoms.

Table 28. Summary of the most commonly reported AEs (≥ 1.5%), regardless causality, for the nursing home prophylaxis studies (Study NAIA3003 and NAIA3004) by decreasing frequency: During prophylaxis (safety population).

Adverse Event	NAIA3003			NAIA3004	
	Placebo (N=13)	Rimantadine (N=231)	Zanamivir (N=238)	Placebo (N=252)	Zanamivir (N=242)
No. (%) subjects with at least one AE	6 (46%)	128 (55%)	137 (58%)	92 (37%)	78 (32%)
Cough	1 (8%)	39 (17%)	38 (16%)	22 (9%)	20 (8%)
Nasal signs and symptoms	1 (8%)	31 (13%)	30 (13%)	21 (8%)	24 (10%)
Headaches	3 (23%)	15 (6%)	25 (11%)	22 (9%)	14 (6%)
Malaise and fatigue	1 (8%)	19 (8%)	22 (9%)	18 (7%)	13 (5%)
Throat and tonsil discomfort and pain	1 (8%)	21 (9%)	18 (8%)	12 (5%)	8 (3%)
Temperature regulation disturbances[1]	1 (8%)	10 (4%)	10 (4%)	21 (8%)	9 (4%)
Musculoskeletal pain	2 (15%)	8 (3%)	19 (8%)	1 (<1%)	3 (1%)
Vocal cord disorders	0	9 (4%)	13 (5%)	7 (3%)	2 (<1%)
Diarrhea	1 (8%)	9 (4%)	13 (5%)	2 (<1%)	4 (2%)
Gastrointestinal signs and symptoms	0	14 (6%)	14 (6%)	1 (<1%)	0
Nausea and vomiting	1 (8%)	12 (5%)	7 (3%)	2 (<1%)	4 (2%)
Muscle pain	1 (8%)	6 (3%)	5 (2%)	8 (3%)	6 (2%)
Breathing disorders	0	8 (3%)	8 (3%)	6 (2%)	2 (<1%)
Constipation	0	8 (3%)	13 (5%)	2 (<1%)	0
Nasal inflammation	0	7 (3%)	9 (4%)	5 (2%)	2 (<1%)
Dizziness	0	2 (<1%)	11 (5%)	2 (<1%)	5 (2%)
Increased white cells	0	0	1 (<1%)	6 (2%)	9 (4%)
Chronic obstructive airways disease	0	2 (<1%)	0	5 (2%)	8 (3%)
Hypertension	0	1 (<1%)	0	9 (4%)	4 (2%)
Arthralgia and articular rheumatism	1 (8%)	2 (<1%)	6 (3%)	1 (<1%)	3 (1%)
Pain	0	4 (2%)	7 (3%)	0	1 (<1%)
Hyposalivation	0	6 (3%)	0	0	0

Source:Summary of clinical safety, Table 16
[1]Temperature regulation disturbances included fever, intermittent fever, chills, and intermittent chills

Comment: In the nursing home studies, the frequency of reported AEs regardless causality was similar among the placebo, rimantadine, and zanamivir groups. It should be

noted that the number of subjects who received placebo in Study NAIA3003 was very small. As observed in the other settings, the most commonly reported AEs across the nursing home studies were cough, nasal signs and symptoms, headaches, malaise and fatigue, and throat and tonsil discomfort and pain.

The following table summarizes the frequency and nature of the most commonly reported AEs (≥ 3%) for the five phase III placebo-controlled studies. Overall, for the five placebo-controlled phase III studies combined, the reported AEs regardless causality to study drugs were 53% of subjects in the placebo group and 51% in the zanamivir groups. The most common AEs were headaches, throat and tonsil discomfort and pain, cough, nasal signs and symptoms, and temperature regulation and disturbances.

Table 29. Summary of the most common AEs regardless causality for the six phase III studies: During prophylaxis (safety population).

Adverse Event	**NAIA3004, NAIA3005, NAI30010, NAI30031, NAI30034 combined**		**NAIA3003**		
	Placebo (N=3550)	**Zanamivir (N=3541)**	**Placebo (N=13)**	**Rimantadine (N=231)**	**Zanamivir (N=238)**
No. (%) subjects with at least one AE	1899 (53%)	1797(51%)	6 (46%)	128 (55%)	137 (58%)
Headaches	743(21%)	696 (20%)	3 (23%)	15 (6%)	25 (11%)
Throat and tonsil discomfort and pain	551 (16%)	517 (15%)	1 (8%)	21 (9%)	18 (8%)
Cough	532 (15%)	478 (13%)	1 (8%)	39 (17%)	38 (16%)
Nasal signs and symptoms	438 (12%)	427 (12%)	1 (8%)	31 (13%)	30 (13%)
Temperature regulation disturbances[1]	282 (8%)	261 (7%)	1 (8%)	10 (4%)	10 (4%)
Malaise and fatigue	242 (7%)	241 (7%)	1 (8%)	19 (8%)	22 (9%)
Viral respiratory infections	283 (8%)	217 (6%)	0	0	1 (<1%)
Muscle pain	213 (6%)	217 (6%)	1 (8%)	6 (3%)	5 (2%)
Musculoskeletal pain	148 (4%)	147 (4%)	2 (15%)	8 (3%)	19 (8%)
Feeding problems[2]	122 (3%)	106 (3%)	1 (8%)	2 (<1%)	3 (1%)
Nausea and vomiting	83 (2%)	70 (2%)	1 (8%)	12 (5%)	7 (3%)
Diarrhea	63 (2%)	64 (2%)	1 (8%)	9 (4%)	13 (5%)
Arthralgia and articular rheumatism	22 (<1%)	42 (1%)	1 (8%)	2 (<1%)	6 (3%)
Nasal inflammation	31 (<1%)	19 (<1%)	0	7 (3%)	9 (4%)
Gastrointestinal signs and symptoms	15 (<1%)	13 (<1%)	0	14 (6%)	14 (6%)
Breathing disorders	28 (<1%)	11 (<1%)	0	8 (3%)	8 (3%)
Pain	23 (<1%)	21 (<1%)	0	4 (2%)	7 (3%)
Dizziness	20 (<1%)	21 (<1%)	0	2 (<1%)	11 (5%)
Vocal cord disorders	10 (<1%)	9 (<1%)	0	9 (4%)	13 (5%)
Constipation	11 (<1%)	5 (<1%)	0	8 (3%)	13 (5%)
Hyposalivation	9 (<1%)	3 (<1%)	0	6 (3%)	0

Source Data: Summary of clinical safety, Table 18
Data for Study NAI30010 and Study NAI30031 include contact cases only
Data for Study NAIA3003 and Study NAIA3004 include all randomizations
[1]Temperature regulation disturbances included fever, intermittent fever, chills, and intermittent chills
[2]Feeding problems included decreased and increased appetite, anorexia, and recurrent anorexia

7.1.5.4 Common adverse event tables

In section 7.1.5.3, Tables 26-28 summarize the AEs (regardless causality) reported in ≥ 1.5% of subjects in the different settings. The ≥1.5% cut-off was chosen based on the available data in the package insert. The current package insert displays AEs ≥ 1.5% during treatment in adults, adolescents, and pediatric subjects ≥ 7 years of age. Applicant's analyses of adverse events were confirmed by FDA. Minor differences were noted between Applicant's and FDA analyses but were not significant to alter Applicant's conclusions.

7.1.5.5 Identifying common and drug-related adverse events

The most common (occurring in at least 3% of subjects in any treatment group) AEs considered by investigators as drug-related are summarized in the following table. In the five phase III placebo-controlled studies, the incidence of drug-related AEs was 8% in each the two treatment arms (placebo and zanamivir). The most commonly reported AEs were headaches, cough, and throat and tonsil discomfort and pain.

Table 30. Summary of the most common (≥ 3%) drug-related AEs (per Investigator's assessment) for the six phase III studies: During prophylaxis (safety population)

Drug-related adverse event	NAIA3004, NAIA3005, NAI30010, NAI30031, NAI30034 combined		NAIA3003		
	Placebo (N=3550)	Zanamivir (N=3541)	Placebo (N=13)	Rimantadine (N=231)	Zanamivir (N=238)
No. (%) subjects with at least one drug-related AE	268 (8%)	272 (8%)	5 (38%)	74 (32%)	80 (34%)
Headaches	70 (2%)	83 (2%)	3 (23%)	8 (3%)	11 (5%)
Cough	64 (2%)	57 (2%)	0	14 (6%)	17 (7%)
Throat and tonsil discomfort and pain	50 (1%)	47 (1%)	0	6 (3%)	6 (3%)
Nasal signs and symptoms	18 (<1%)	9 (<1%)	0	8 (3%)	11 (5%)
Nausea and vomiting	9 (<1%)	14 (<1%)	1 (8%)	6 (3%)	3 (1%)
Diarrhea	12 (<1%)	9 (<1%)	1 (8%)	5 (2%)	5 (2%)
Gastrointestinal signs and symptoms	2 (<1%)	4 (<1%)	0	12 (5%)	13 (5%)
Malaise and fatigue	6 (<1%)	3 (<1%)	1 (8%)	6 (3%)	9 (4%)
Constipation	4 (<1%)	0	0	6 (3%)	12 (5%)
Dizziness	3 (<1%)	8 (<1%)	0	1 (<1%)	7 (3%)
Hyposalivation	7 (<1%)	2 (<1%)	0	6 (3%)	0

Source: Summary of clinical safety, Table 19
Data for NAI30010 and NAI30031 include contact cases only
Data for NAIA3003 and NAIA3004 include all randomizations

7.1.5.6 Additional analyses and explorations

Additional safety analyses were performed for special groups such as pediatric subjects, elderly subjects, smokers and high-risk subjects. A summary of these analyses are shown in the following table. Overall, the safety profile of zanamivir was similar to that of placebo and did not differ across all these special groups. However, it is important to note that although patients with underlying airways disease were not excluded from the studies, patients with severe airways disease were not represented in the studies in any appreciable number.

Table 31. Summary of AE data in specific subject groups for the five placebo-controlled phase III studies: during prophylaxis (safety population).

Study population	Subjects reporting any AE	
	Placebo N(%)	Zanamivir N(%)
Combined studies; all subjects	1899 (53)	1797 (51)
Combined studies; subjects ≥ 65 years	524 (46)	515 (47)
Combined studies; subjects age 5-11 years	148 (53)	130 (48)
Combined studies; subjects age 12-16 years	118 (54)	103 (43)
Current smokers: NAI30010, NAI30031, NAIA3005, and NAI30034	202 (58)	184 (54)
Subjects ≥ 65 years: NAI30034	458 (48)	462 (49)
Subjects with respiratory disease: NAI30034	379 (55)	368 (54)
Subjects with cardiovascular disease: NAI30034	139 (45)	144 (44)
Subjects with diabetes mellitus: NAI30034	180 (49)	206 (57)

7.1.6 Laboratory Findings

7.1.6.1 Overview of laboratory testing in the development program

Safety laboratory evaluations were not performed in the two family/household studies and in one of the community studies (NAI30034). Routine laboratory tests were performed for the other community study (Study NAIA3005) and the two nursing home studies. For the two nursing home studies, laboratory tests were obtained at Baseline and on Day 14 (last day of dosing); for the community study, laboratory tests were obtained at Baseline and at one week after the last dose of study medication (Day 35).

Laboratory data analyses for the three studies with available data revealed that, across study drug groups, the majority of subjects demonstrated unchanged chemistry and hematology values. A few marginal shifts in laboratory values occurred but these were similar for both groups and clinically insignificant.

7.1.7 Vital Signs

7.1.7.1 Overview of vital signs testing in the development program

Family/household studies: Only temperature was recorded at Day 1, Day 5, at the end of treatment (Day 11), and at post-treatment follow-up (Day 28). In addition, temperature was recorded twice daily as part of subject's diary card. Other vital signs were not recorded during these studies.

Community studies: Only temperature was recorded twice daily as part of subject's diary card.

Nursing home studies: Vital signs were recorded at baseline only.

7.1.8 Electrocardiograms (ECGs)

ECGs were not monitored in these studies. Please see original review for background information.

7.1.9 Immunogenicity

No information regarding immunogenicity is presented in this sNDA.

7.1.10 Human Carcinogenicity

No new animal carcinogenicity data were submitted with this sNDA. Please refer to the original NDA reviews for background information.

7.1.11 Special Safety Studies

No special safety studies were requested or submitted with this sNDA.

7.1.12 Withdrawal Phenomena and/or Abuse Potential

Zanamivir is not known to have abuse potential or to be associated with withdrawal phenomena.

7.1.13 Human Reproduction and Pregnancy Data

Zanamivir is considered Pregnancy Category C and current label suggests zanamivir should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

7.1.14 Assessment of Effect on Growth

Zanamivir has a low systemic bioavailability and has been administered in pediatric subjects ≥ 5 years of age for a relatively short period (5 days for treatment, 10 days for post-exposure prophylaxis or 28 days for seasonal prophylaxis). Consequently, effects on growth are considered unlikely. No formal assessment of growth has been conducted.

7.1.15 Overdose Experience

There have been no reports with overdose of zanamivir. Doses of zanamivir up to 64 mg/day have been administered by nebulizer. Doses up to 1,200 mg/day have been administered intravenously. Adverse effects were similar to those seen in clinical studies at the recommended doses.

7.1.16 Postmarketing Experience

See section 7.2.2.2

7.2 Adequacy of Subject Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

Please refer to Table 2, which summarizes the clinical sources reviewed for this sNDA. Please also refer to the Appendix for summaries of the studies.

7.2.1.1 Study type and design/subject enumeration

See section 7.2.1

7.2.1.2 Demographics

Table 30 summarizes the baseline demographic characteristics of subjects enrolled in the six phase III prophylaxis studies. Overall, in the five placebo-controlled phase III studies, the baseline characteristics are similar between the placebo and zanamivir groups.

Table 30. Demographic characteristics for the six phase III studies (safety population)

Characteristics	NAIA3004, NAIA3005, NAI30010, NAI30031, NAI30034 combined		NAIA3003		
	Placebo (N=3550)	**Zanamivir (N=3541)**	**Placebo (N=13)**	**Rimantadine (N=231)**	**Zanamivir (N=238)**
Age (yrs)					
5-11	279 (8%)	273 (8%)	0	0	0
12-16	220 (6%)	239 (7%)	0	0	0
17-34	698 (20%)	700 (20%)	0	0	0
35-49	783 (22%)	752 (21%)	0	4 (2%)	2 (<1%)
50-64	440 (12%)	470 (13%)	3 (23%)	18 (8%)	23 (10%)
65 -74	729 (21%)	675 (19%)	1 (8%)	79 (34%)	76 (32%)
≥ 75	401 (11%)	432 (12%)	9 (69%)	130 (56%)	137 (58%)
Age (yrs)					
Mean (SD)	45.9 (23.2)	45.8 (23.3)	74.8 (10.6)	75.9 (10.2)	76.3 (10.1)
Median	45.5	45.0	76.0	76.0	76.0
(Min. - Max.)	(5–107)	(5 – 96)	(53 – 87)	(44 – 99)	(45 – 102)
Sex					
Female	2012 (57%)	1987 (56%)	2 (15%)	68 (29%)	71 (30%)
Male	1538 (43%)	1554 (44%)	11 (85%)	163 (71%)	167 (70%)
Race					
Asian	58 (2%)	60 (2%)	0	0	1 (<1%)
Black	138 (4%)	135 (4%)	0	2 (<1%)	0
American	59 (2%)	59 (2%)	0	0	0
Hispanic					
White	3251 (92%)	3251 (92%)	13 (100%)	229 (99%)	237 (>99%)
Other	44 (1%)	36 (1%)	0	0	0
Vaccinated prior to randomization[1]					
Yes	1156 (33%)	1134 (32%)	12 (92%)	201 (87%)	216 (91%)
No	2164 (61%)	2188 (62%)	1 (8%)	6 (3%)	2 (<1%)
Missing	230 (6%)	219 (6%)	0	24 (10%)	20 (8%)
Current Smoker[2]					
Yes	351 (11%)	340 (10%)	--	--	--
No	2945 (89%)	2955 (90%)			

Source: Summary of clinical safety, Table 11
Data for Study NAI30010 and Study NAI30031 include contact cases only
Data for Study NAIA3003 and Study NAIA3004 include all randomizations
[1]For Study NAI30034, excludes subjects vaccinated less than 21 days before the start of the study
[2]Subject smoking status was not available for Study NAIA3003 and Study NAIA3004

7.2.1.3 Extent of exposure (dose/duration)

As previously described, the two post-exposure prophylaxis studies (Study NAI30010 and Study NAI30031) conducted in a family/household setting, were similar in design and randomization was performed by family/household. The main difference between the two family/household studies was in Study NAI30010 the index cases were randomized to treatment with zanamivir, but in Study NAI30031 index cases did not receive treatment with zanamivir. In these two studies, contact cases were randomized by family to receive zanamivir two inhalations of 5 mg or placebo once a day for 10 days. In Study NAI30010, a total of 414 contacts were randomized to receive zanamivir. In Study NAI30031, 661 contacts were randomized to receive zanamivir.

In the two seasonal prophylaxis studies (Study NAIA3005 and Study NAI30034), conducted in a community setting, subjects were randomized to receive zanamivir two inhalations of 5 mg or placebo once a day for 28 days. In Study NAI3005, 553 subjects were randomized to receive zanamivir; in Study NAI30034 the number of subjects randomized to receive zanamivir was 1595. Please refer to Appendix for specific details regarding the studies.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

The safety evaluation of zanamivir was characterized in six double-blind, randomized, phase III prophylaxis studies. The four primary phase III studies mentioned above and the two previously submitted studies (Study NAIA3003 and Study NAIA3004) conducted in a nursing home setting and designated as the secondary studies. In the two nursing home studies subjects were randomized to receive zanamivir two inhalations of 5 mg or placebo once a day for 14 days. A total of 424 subjects were randomized to receive zanamivir in the two nursing home studies; 184 subjects in Study NAIA3003 and 240 subjects in Study NAIA3004.

7.2.2.1 Other studies

No other studies besides those listed in Table 2 were reviewed.

7.2.2.2 Postmarketing experience

Zanamivir was approved by FDA in 1999 for treatment of uncomplicated influenza A and B in adults and adolescents. Although there was no clinical pattern of adverse events, the major safety concern raised by zanamivir studies was the possibility of bronchospasm due to decreases in pulmonary function tests in subjects receiving zanamivir compared with pulmonary function tests in subjects receiving placebo. The original label stated these concerns without having a ‘Warning’ section.

After the approval, bronchospasm and broncospasm-like symptoms were reported through the post-marketing surveillance system. Many but not all of these events occurred in subjects with underlying airways disease. Some of those subjects had fatal outcomes, although causality was difficult to assess. Because of the severity of this complication, the label statement regarding bronchospasm was changed to a ‘Warning.’ Based on these observations, the FDA asked the

Applicant to submit an integrated summary of zanamivir post-marketing reports of AEs collected through their Global Clinical Safety and Pharmacovigilance network.

The post-marketing report by the Applicant covered the period from the first introduction of zanamivir in 1999 to January 31, 2005. A total of 779 spontaneous AE reports were received worldwide by Global Clinical Safety and Pharmacovigilance of GlaxoSmithKline involving patients who received zanamivir for either treatment or prophylaxis of influenza. The most common AEs spontaneously reported (according to MedDRA System Organ Class) were: respiratory, thoracic, and mediastinal disorders (25%); skin and subcutaneous tissue disorders (15.5%); nerous system disorders (13.6%); general disorders and administration site conditions (10.5%); and gastrointestinal disorders (8.5%). The largest proportion of cases involved a primary event in the respiratory body system and among these the most medically significant AEs were bronchospasm, dyspnea, asthma and/or wheezing.

As previously stated, following evaluation of a signal related to post-marketing reports of bronchospasm, discussions were conducted between the Applicant and FDA and the label statement regarding bronchospasm was changed to a 'Warning.' From January 10, 2000 to July 31, 2005, there were 66 additional reports of bronchospasm. Twenty-nine of the 66 cases were considered as serious AEs. Outcome was known in 59 (89%) of reports and included four reports of fatal outcomes.

Other AEs of specific medical significance covering the period from the first introduction of zanamivir in 1999 to January 31, 2005, included: deaths (31 reports); anaphylaxis (4 reports); myocarditis (six cases); Stevens-Johnson syndrome and Toxic Epidermal Necrolysis (two reports), and pulmonary fibrosis (1 report).

Deaths

The Applicant's analysis included 31 reports of fatal outcomes. Twenty reports were considered to have adequate information. All fatal cases occurred in subjects receiving zanamivir for treatment. No fatal cases occurred in children or adolescents. Most of the patients who died had other diseases and they were diagnosed with events compatible or indicative exacerbations or complications of influenza infection.

In a few cases, in the absence of underlying disease and symptoms indicative of exacerbation of influenza infection, a causal relationship with zanamivir could not be ruled out. However, a definitive assessment of the role of zanamivir was not possible due to lack of key information.

This post-marketing safety update summary provided by the Applicant was forwarded to the DDRE, Office of Drug Safety (ODS) and a consult was requested to assist in the review of post-marketing safety data. In addition, the DDRE independently reviewed the post-marketing reports submitted to AERS database. The DDRE consult recommended the Division consider a Box Warning regarding the risk of bronchospasm in patients with underlying airways disease receiving zanamivir for treatment or prophylaxis of influenza A and B. In addition, and based on the report of nine cases in the AERS database with anaphylactic reactions possibly related to the

use of zanamivir, they recommended the addition of 'anaphylaxis' in the current statement for Allergic Reactions under the PRECAUTION section.

The issue of Box Warning was further discussed during an internal meeting on March 15, 2006, with Dr. Robert Meyer, a pulmonologist and Director of ODE II and interdisciplinary DAVP and DDRE representation. It was finally decided that at this time a Box Warning is not indicated. The decision was based on the clinical trial experience in approximately 3800 subjects assigned to drug treatment in the prophylaxis studies. A review of the safety data relevant to bronchospasm and lower respiratory events of interest shows no difference in such events between placebo and zanamivir groups. Dr Meyer stated the drug would probably be better tolerated in the absence of active influenza infection. However, it is important to note that although patients with underlying airways disease were not excluded from the prophylaxis studies, patients with severe airways disease were not represented in the studies in any appreciable number.

The addition of 'anaphylaxis' in the current statement for Allergic Reactions was discussed with the Applicant and they agreed for this label change.

7.2.2.3 Literature

Not applicable.

7.2.3 Adequacy of Overall Clinical Experience

Overall, the data presented in this sNDA support the approval of zanamivir in subjects five years and older for prophylaxis of influenza A and B. The recommended dose of zanamivir for prophylaxis of influenza in a family/household setting is two inhalations (one 5 mg blister per inhalation for a total dose of 10 mg) once daily for 10 days. The recommended dose of zanamivir for prophylaxis of influenza during community outbreaks is two inhalations (one 5 mg blister per inhalation for a total dose of 10 mg) once daily for 28 days.

The AE profile was comparable between the placebo and zanamivir arms of the studies and consistent with the known AE profile of zanamivir. No new or unexpected AEs were identified. The most commonly reported AEs, regardless causality, were headaches, throat and tonsil discomfort and pain, cough, nasal signs and symptoms, and temperature regulation and disturbances which are typical signs and symptoms of influenza and influenza-like diseases. Moreover, no signs of increased bronchospasm or bronchospasm-like symptoms were identified in the prophylaxis studies. The zanamivir adverse event profile was also consistent across subjects with different ages and in high-risk subjects.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

No new pharmacology/toxicology data were submitted in this sNDA.

7.2.5 Adequacy of Routine Clinical Testing

See section 7.1.6.1

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

No new pharmacokinetic data were submitted in this sNDA.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

The evaluation of potential AEs presented in this sNDA appears adequate. No new or unexpected AEs were identified during the review.

7.2.8 Assessment of Quality and Completeness of Data

The quality and completeness of the submitted data are adequate.

7.2.9 Additional Submissions, Including Safety Update

Zanamivir safety data in subjects with renal insufficiency:

During the review process, the Applicant was asked to submit an integrated summary of all AEs observed in subjects with renal insufficiency enrolled in the phase III prophylaxis studies. Generally, systemic exposure after zanamivir oral inhalation is limited. However, pharmacokinetic studies after a single intravenous dose of 4 mg or 2 mg of zanamivir in volunteers with mild/moderate or severe renal insufficiency showed significant decreases in renal clearance and significant increases in half-life (normals 3.1 hr, mild/moderate 4.7 hr, and severe 18.5 hr; median values). These findings indicate that drug accumulation cannot be ruled out, particularly, in patients with severe renal insufficiency who received inhaled zanamivir for a prolonged time. Below is a brief summary of the data provided by the Applicant:

As previously stated, laboratory data were performed at baseline and at the end of treatment in the two nursing home studies (NAIA3003 and NAIA3004) and in one of the community studies (NAIA3005). The creatinine clearance for the subjects enrolled in these studies was estimated by using the Cockcroft-Gault formula (Annals of Oncology 2004;15:291-295). The results of these calculations were used to group subjects by degree of renal insufficiency:

Normal renal function: creatinine clearance > 80 ml/min
Mild renal impairment: creatinine clearance 50-80 ml/min
Moderate renal impairment: creatinine clearance 30-50 ml/min
Severe renal impairment: creatinine clearance < 30 ml/min

This approach identified 515 subjects with mild renal failure, 242 with moderate renal failure and 54 with severe renal failure (Table 31)

Table 31. Summary of subjects with renal insufficiency enrolled in Studies NAIA3003, NAIA3004, and NAIA3005.

Study Number	Number of subjects with				Total number of subjects with renal insufficiency/Total number subjects (%)
	Normal renal function	Mild renal impairment	Moderate renal impairment	Severe renal impairment	
NAIA3005	1022	81	0	0	81/1103 (7.3%)
NAIA3003	95	214	132	40	386/481 (80.2%)
NAIA3004	148	220	110	14	344/492 (69.9%)
Total for three prophylaxis studies	1265	515	242	54	811/2076 (39.1%)

Note. It was not possible to classify 4 subjects in NAIA3005 (two had missing creatinine at baseline and another two had missing weight), one subject in NAIA3003 (missing creatinine at baseline), and two subjects in NAIA3004 (missing creatinine at baseline); these data are needed for the Cockcroft-Gault formula.

Among the 811 subjects with some degree of renal failure, 404 subjects received zanamivir, 185 subjects received rimantadine, and 222 subjects received placebo. All subjects with moderate and severe renal failure were enrolled in the two nursing home studies.

The frequency and nature of the clinical AEs observed during prophylaxis therapy in subjects with renal failure were generally similar between the placebo/rimantadine and zanamivir groups. The frequency and nature of AEs were also similar for each category of renal failure. Moreover, the frequency and nature of AEs in subjects with various degrees of renal insufficiency were similar to the frequency and nature of AEs in subjects with normal renal function. Similarly, the rates of zanamivir discontinuation due to an AE did not vary by degree of renal impairment and did not differ for groups receiving placebo, rimantadine and zanamivir. Many of the most common AEs observed in these subpopulations were consistent with the symptoms of influenza or other upper respiratory infections.

Across the three prophylaxis studies, changes in laboratory test results in subjects who received zanamivir did not differ from changes in laboratory results from patients who received placebo/rimantadine. No clinically significant laboratory abnormalities were documented during the course of each study. As expected, clinical chemistry laboratory changes outside the normal range for creatinine, urea, and bicarbonate and hematology laboratory abnormalities for hemoglobin/hematocrit, were more common in subjects with renal impairment. However, these results are interpreted with caution because no subjects with moderate and severe renal impairment received inhaled zanamivir for four weeks.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

The data presented in this sNDA showed that inhaled zanamivir had an acceptable AE profile in prophylaxis studies. Overall, the AE profile reported in the prophylaxis studies is similar to the known zanamivir AE profile described in the treatment studies. A higher incidence of AEs was noticed in the prophylaxis studies than in the treatment studies. However, this difference is not unexpected based on the designs of the studies. A possible explanation could be the longer duration of treatment and the fact that enrolled subjects in the prophylaxis studies were asymptomatic at baseline. Therefore, any subsequent symptom was reported as an AE.

In the five placebo-controlled phase III prophylaxis studies there were no significant differences between the zanamivir and the placebo groups. The most commonly reported AEs during prophylaxis, regardless causality, were headaches, throat and tonsil discomfort and pain, cough, and nasal signs and symptoms which are typical signs and symptoms of influenza and influenza-like illness. The frequency of serious AEs (< 1%), drug-related AEs (8%), and study drug discontinuations due to AEs (2%) were similar between the zanamivir and the placebo groups. No deaths were reported during the prophylaxis period.

Further analyses for special groups of interest (i.e., pediatric subjects, elderly subjects, smokers, subjects at high risk for developing complications after influenza infection) showed that the safety profile of zanamivir was similar to that of placebo and did not differ across all these special groups. Safety analysis concentrated on lower respiratory events of interest and bronchospasm-like events showed no signs of increased frequency in the zanamivir group compared to placebo.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

AE and serious AE data were pooled for the two family/household studies and for the two seasonal prophylaxis studies. Adverse events from the two nursing home studies were not pooled because Study NAIA3003 compared zanamivir with the standard of care (rimantadine for influenza A and placebo for influenza B) rather than placebo. In addition, adverse event data from all five placebo-controlled studies were pooled with the adverse event data from Study NAIA3003 presented in a side-by-side fashion.

7.4.1.1 Pooled data vs. individual study data

Please see the Integrated Review of Safety.

7.4.1.2 Combining data

Please see the Integrated Review of Safety.

7.4.2 Explorations for Predictive Factors

7.4.2.1 Explorations for dose dependency for adverse findings

Not applicable.

7.4.2.2 Explorations for time dependency for adverse findings

Exploratory analyses for time dependency for adverse events drug-disease were not performed by Applicant for this sNDA.

7.4.2.3 Explorations for drug-demographic interactions

Please see the Integrated Review of Safety.

7.4.2.4 Explorations for drug-disease interactions

Exploratory analyses for drug-disease interaction were not performed by Applicant for this sNDA.

7.4.2.5 Explorations for drug-drug interactions

Not applicable

7.4.3 Causality Determination

Based on the data and clinical narratives the causality determinations for the safety analyses are acceptable.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The data submitted in this sNDA support the use of zanamivir in subjects five years and older for prophylaxis of influenza A and B. The recommended dose of zanamivir for prophylaxis of influenza in a family/household setting is two inhalations (one 5 mg blister per inhalation for a total dose of 10 mg) once daily for 10 days. The recommended dose of zanamivir for prophylaxis of influenza during community outbreaks is two inhalations (one 5 mg blister per inhalation for a total dose of 10 mg) once daily for 28 days.

The use of less frequent dosing regimen for prophylaxis was based on previously submitted pharmacokinetic data from animal models and humans. The data demonstrated zanamivir concentrations are approximately 337- and 52-fold above the median neuraminidase IC_{50} at the

epithelial layer of trachea, bronchi, and bronchioles at 12 and 24 hours, respectively, after a single 10 mg dose of zanamivir. Based on these data, the Applicant concluded that higher or more frequent dosing would not likely achieve better efficacy results.

8.2 Drug-Drug Interactions

Based on data from in vitro studies, no clinically significant pharmacokinetic drug interactions are predicted. Therefore, no formal drug-drug interaction data were included in the original NDA or in this supplement.

8.3 Special Populations

Study NAI30034 enrolled community-dwelling subjects ≥ 12 years of age who were at high risk for developing complications from influenza. High risk was defined as subjects ≥ 65 years of age, subject with diabetes mellitus, and subjects with chronic disorders of the pulmonary or cardiovascular systems. Of the 1678 subjects enrolled in the zanamivir arm of the study, 946 were ≥ 65 years of age, 684 had respiratory disease, 331 had cardiovascular disease, and 359 had diabetes mellitus. There was no difference in safety and effectiveness by subject's underlying condition. However, it is important to note that although patients with underlying airways disease were not excluded from the prophylaxis studies, patients with severe airways disease were not represented in the studies in any appreciable number.

8.4 Pediatrics

A total of 515 children were included in the zanamivir treatment arms in the four primary prophylaxis studies. Of the 511 children, 64 were 5-6 years, 211 were 7-11 years, and 240 children were 12-16 years of age. No differences in safety and effectiveness were observed between pediatric and adult subjects.

8.5 Advisory Committee Meeting

This sNDA was not discussed at an Advisory Committee meeting.

8.6 Literature Review

A literature review focused on resistance of influenza virus to available drugs.

8.7 Postmarketing Risk Management Plan

In this sNDA, no specific risk management plan was proposed by the Applicant or requested by the FDA. Please see Section 9.3 for post-marketing commitments requested by FDA.

8.8 Other Relevant Materials

Not applicable.

9 OVERALL ASSESSMENT

9.1 Conclusions

In this submission the Applicant sought approval of zanamivir for the prevention of influenza A and B based on four double-blind, randomized, placebo-controlled studies; two post-exposure prophylaxis studies conducted in a family/household setting and two seasonal prophylaxis studies conducted in a community setting. The primary efficacy endpoint was similar across all these studies. For the family/household studies the primary efficacy endpoint was the proportion of families/households for which at least one randomized contact developed symptomatic, laboratory-confirmed influenza A or B infection. For the two community studies the primary efficacy endpoint was the proportion of subjects who developed symptomatic, laboratory-confirmed influenza A or B infection during prophylaxis. In all four studies, symptomatic influenza was defined as the presence of at least two of the following influenza-like symptoms from a pre-defined list for three consecutive diary card entries (36 hours): oral temperature ≥ 37.8°C or feverishness, cough, headache, sore throat, and myalgia. Laboratory confirmation of influenza was done by culture, PCR or seroconversion (defined as a 4-fold increase in convalescent titer from baseline.

The two post-exposure prophylaxis studies conducted in a family/household setting were similar in design and randomization was performed by family/household. The main difference in study design between the two studies was that index cases were randomized to treatment in one study but not in the other. In the first study, in which index cases were treated, within 36 hours of onset of symptoms in an index case, each household (including all family members ≥ 5 years of age) was randomized to zanamivir 10 mg inhaled once daily or placebo for 10 days. Index cases were randomized to zanamivir 10 mg inhaled twice daily for five days or inhaled placebo twice daily for five days. In this study, the proportion of households with at least one new case of symptomatic, laboratory-confirmed influenza decreased significantly from 19% (32 of 168 households) in the placebo group to 4.1% (7 of 169 households) in the zanamivir group ($p < 0.001$). In the second study, where index cases were not treated, the incidence of symptomatic, laboratory-confirmed influenza decreased from 19% (46 of 242 households) in the placebo group to 4.1% (10 of 245 households) in the zanamivir group ($p < 0.001$).

The two seasonal prophylaxis studies assessed zanamivir 10 mg inhaled once daily versus placebo inhaled once daily for 28 days during community outbreaks. The first seasonal prophylaxis study conducted in two university communities, enrolled mainly healthy unvaccinated subjects 18 years of age or greater (mean age 28.8 years). In this study, the incidence of symptomatic, laboratory-confirmed influenza decreased from 6.1% (34 of 554 subjects) in the placebo group to 2.0% (11 of 553) in the zanamivir group ($p < 0.001$). The

second seasonal prophylaxis study enrolled high-risk subjects for developing complications from influenza infection. Their age ranged from 12 to 94 years of age (mean age 60.4 years) with 56% of them older than 65 years. Sixty-seven percent of them were vaccinated. In this study, the incidence of symptomatic, laboratory-confirmed influenza decreased from 1.4% (23 of 1685 subjects) in the placebo group to 0.2% (4 of 1678) in the zanamivir group ($p < 0.001$).

No new or unexpected AEs were identified. The overall AE profile was comparable between the placebo and zanamivir arms of the studies and consistent with the known AE profile of zanamivir. The most commonly reported AEs, regardless causality, were headaches, throat and tonsil discomfort and pain, cough, nasal signs and symptoms, and temperature regulation and disturbances which are typical signs and symptoms of influenza and influenza-like diseases. The zanamivir adverse event profile was also consistent across subjects with different ages and in high-risk subjects.

9.2 Recommendation on Regulatory Action

The efficacy and safety data submitted in this supplemental NDA (sNDA) support the approval of zanamivir for the prevention of influenza A and B in subjects 5 years of age and older. This recommendation is based on the review of efficacy and safety data from four double-blind, randomized, placebo-controlled studies; two post-exposure prophylaxis studies conducted in a family/household setting and two seasonal prophylaxis studies conducted in a community setting. In all four studies, the incidence of symptomatic, laboratory-confirmed influenza in subjects treated with zanamivir was significantly lower compared with the incidence observed in subjects treated with placebo.

In the two post-exposure prophylaxis studies, zanamivir dosing of two inhalations (one 5 mg blister per inhalation for a total dose of 10 mg) once daily for 10 days was safe and effective in reducing household transmission of influenza regardless treatment with zanamivir of the index cases. In the two seasonal prophylaxis studies, zanamivir dosing of two inhalations (one 5 mg blister per inhalation for a total dose of 10 mg) once daily for 28 days was safe and effective in reducing the incidence of symptomatic, laboratory-confirmed influenza during community outbreaks.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

No specific risk management plan has been proposed by the Applicant or requested by the FDA.

9.3.2 Required Phase 4 Commitments

As part of their post-marketing commitments the Applicant agreed to:

I. Provide an annual update on emergence of resistance to zanamivir, as well as cross-resistance between zanamivir and other neuraminidase inhibitors, as an integrated review of information from NISN (Neuraminidase Inhibitor Surveillance Network), data collected by GSK, and information in the published literature. Each annual update will include information on the methodologies (e.g., culture, PCR) used in studies during that reporting period. Timeline: GSK will provide this annual update as part of the NDA Annual Reports due within 60 days of the original approval anniversaries in July 2007, July 2008, and July 2009.

II. Submit a postmarketing adverse drug experience report to DAVP as a "15-Day Alert Report" for each of the following serious adverse events:

- anaphylaxis
- bronchospasm or other pulmonary adverse event
- cardiovascular adverse event
- any adverse event with a fatal outcome

Consistent with 21 CFR 314.80, GSK will make diligent efforts to obtain as complete a set of information as possible, including information about antecedent and concomitant medical circumstances of the adverse experience or fatality, results of laboratory tests, a copy of any available medical records, and a copy of the autopsy report (if performed). A "15-Day Alert Report - Follow Up" will be submitted to DAVP if additional information is obtained after the deadline for submission of the initial report. The 15-Day Alert Reports due to DAVP each week will be collected and submitted as a batch, once a week, to DAVP. Each such submission will be sent to NDA 21-036 as "General Correspondence: Safety Reports per Postmarketing Commitment". Timeline: Such Alert Reports will be prepared and submitted by GSK for the specified events occurring through May 31, 2009.

III. Prepare a Wall Chart for medical practices and pharmacies on how to use the Relenza Diskhaler. This Wall Chart will be an illustration-intensive (not text intensive) aid to patient education. Versions will be prepared in English and Spanish. Timeline: GSK will submit the proposed Wall Chart and distribution plan/timeline to DAVP for review and comment no later than June 30, 2006.

IV. Meet with investigators at NIAID to develop a Concept Protocol and seek funding to assess the effects of zanamivir 10 mg inhaled once daily for 2 months on clinical laboratory measures of safety. Timeline: GSK will meet with NIAID by July 31, 2006 and provide DAVP with minutes including the outcome of the meeting by August 31, 2006.

9.3.3 Other Phase 4 Requests

No additional phase 4 studies were requested.

9.4 Labeling Review

The proposed label submitted with this sNDA has been reviewed by all disciplines involved in the review. Modifications of the proposed label have been discussed with and agreed by the Applicant. The major changes in the modified label involve the following sections:

(b) (4)

5 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

10 APPENDICES

10.1 Review of Individual Study Reports

PRIMARY FAMILY/HOUSEHOLD STUDIES: PROTOCOLS NAI30010 and NAI30031

Protocol NAI30010, "A double-blind, randomized, placebo-controlled, parallel-group, multicenter study to investigate the efficacy and safety of inhaled zanamivir 10 mg administered onca a day for 10 days in the prevention of transmission of symptomatic influenza A and B viral infections within families."

This phase III study, conducted in the United States, Canada, United Kingdom, and Finland, was designed to evaluate the efficacy of inhaled zanamivir administered 10 mg once daily for 10 days compared with placebo in the prevention of symptomatic, laboratory-confirmed influenza A and B infections in the family/household setting. The study was randomized by family. Eligible families were recruited and consented prior to influenza season. When a suspected case of influenza-like illness was identified within the family (index case) at a time influenza was known to be circulating in the community, all eligible family members and the index case were randomized to receive study medication. Children < 5 years of age were enrolled and could be the index case but did not receive study drug. The index cases received two inhalations of 5 mg zanamivir or placebo twice a day for 5 days, and the contact cases received two inhalations of 5 mg zanamivir or placebo once a day for 10 days. The first dose of study medication was administered within 36 hours of symptom onset in the index cases. The first dose was observed by the study site on Day 1. Family participants were observed at the study site at Day 1, at the end of treatment (Day 11), and post-treatment (Day 28). Family participants were also contacted by telephone during treatment (Day 5) and post-treatment (Day 14). The index cases with influenza like illness attended a visit during treatment (Day 5) and an additional visit on Day 14 if moderate to severe symptoms persisted.

Samples (throat swab, throat/nasal swab, nasopharyngeal swab, nasal wash or nasal aspirate were collected on Day 1 from all index cases for the diagnosis of influenza. Throat swabs for culture or PCR were collected anytime during the study from contact cases within 2-3 days of onset of influenza like illness. On Day 1 and Day 28 serum samples were collected from all study subjects to evaluate influenza antibodies.

Contacts completed diary twice daily as described previously.

Study objectives

- To evaluate the efficacy of inhaled zanamivir compared with placebo in the prevention of symptomatic, laboratory-confirmed influenza A and B viral infections.

- To evaluate the safety and tolerability of inhaled zanamivir compared with placebo in the prevention of symptomatic, laboratory-confirmed influenza A and B viral infections.
- To assess the impact of inhaled zanamivir for the prevention of symptomatic, laboratory-confirmed influenza A and B viral infections on subject productivity and healthcare resource use.

Inclusion criteria

A family was eligible for participation in this study only if all of the following criteria applied:

- Consisted of at least 2-5 members, who were living in the home for the duration of the study period, with at least one adult, ≥18 years of age, AND one child, 5-17 years of age. (This included families with additional members that were <5 years of age.)

  A female was eligible to enter and participate in this study if she was of:

  1. Non-childbearing potential, i.e., physiologically incapable of becoming pregnant, including any female who is pre-menarchal or post-menopausal. (Menarche is defined as the beginning of menstrual function; the first menstrual period of an individual.) or,
  2. Childbearing potential who had a negative pregnancy test (urine) at the First Treatment Visit (Day 1) before receiving study medication. Those at risk of pregnancy had (in the opinion of the investigator) to be taking contraceptive precautions during the study.

- Subjects were able to take the first dose of study medication within 36 hours (1.5 days) of symptom onset in the index case.

- Subjects were able to use the DISKHALER satisfactorily. Assistance could be given if necessary and available.

- Subjects were willing and able to adhere to the procedures stated in to protocol. The Diary CARD had to be completed by the subject or his/her parent or legally acceptable representative. Assistance in completing the Diary Card could be given if necessary; however, subjects had to be able to provide the responses to all items in the Diary Card and assistance had to be restricted to reading the questions and/or written completion of the subject's response.

- Subjects who, in the opinion of the Investigator, could be managed on an outsubject basis and were not medically compromised by their participation in the study.

- Subjects were fluent and literate in the language spoken by the Investigator and staff.

- Subjects were willing and able to give written informed consent to participate in the study. If the subject was below the legal age of consent, the legally acceptable representative had to also provide consent. Where appropriate, written assent was also be obtained from the subject.

Exclusion Criteria

A family member was not eligible for participation in this study if any of the following criteria applied:

- Females who were pregnant, breast-feeding or at risk of becoming pregnant during the study.

- Subjects who were known or suspected to be hypersensitive to any component of the study medication and relief medications.

- Subjects with evidence or history of alcoholism, drug abuse, psychiatric disorders, or any other medical condition that could have affected their ability to complete the study or confound the evaluation of safety or efficacy data.

- Subjects who were immunocompromised, for example as a result of HIV infection of systematic chemotherapy treatment.

Study endpoints

Primary endpoint

The primary endpoint was the proportion of randomized families in whom at least one randomized contact developed symptomatic, laboratory-confirmed (by culture, serology or PCR) influenza A or B infection. Symptomatic influenza was defined as the presence of at least two of the following symptoms: fever ≥ 37.8°C, cough, headache, sore throat, myalgia, feverishness. Symptoms had to be present concurrently for three consecutive Diary Card entries (≥ 36 hours) during days 1-11 inclusive.

Secondary endpoints

The secondary endpoints consisted of the following:

- The proportion of randomized families in whom at least one randomized contact developed laboratory-confirmed influenza infection.

- The proportion of randomized families in whom at least one randomized contact developed symptomatic, laboratory-confirmed influenza infection and where symptoms began anytime from start of treatment to Day 11.

- The proportion of randomized families in whom at least one randomized contact developed febrile illness during Days 1 to 11. A febrile illness was defined as a temperature of ≥37.8°C.

- The proportion of randomized families in whom at least one contact case (including non-treated contact cases <5 years of age) developed laboratory-confirmed influenza infection.

- Time to alleviation of clinically significant symptoms for randomized index cases. Clinically significant symptoms of influenza were defined as fever, headache, myalgia, sore throat, cough and feverishness. Alleviation was defined as no fever (temperature <37.8°C and feverishness recorded as "absent/minimal"), cough as "none" or "mild", and headache, myalgia, sore throat recorded as "absent/minimal". All of these were to be maintained for a further 24 hours.

- Time to alleviation of clinically significant and no use of relief medication for randomized index cases. As well as showing alleviation of clinically significant symptoms (as defined above), the index case recorded no use of relief medication. All of these had to be maintained for a further 24 hours.

- The number of days out of 28 at least one member of the family (including the index case) was unable to perform all their normal activities.

- The number of days out of 28 at least one member of the family (including the index case) recorded use of relief medication.

- The proportion of randomized families in whom at least one randomized member developed a secondary complication of influenza.

- Temperature of randomized index case as measured at the clinic visit on Study Day 5.

Primary statistical analysis was performed on the Intent-to-Treat Population of all families randomized to treatment. The analysis was repeated on a secondary population of all randomized families in which the index case or any contact case had laboratory confirmation of influenza infection.

Protocol NAI30031, "A double-blind, randomized, placebo-controlled, parallel-group, multi-center study to investigate the efficacy and safety of inhaled zanamivir 10 mg administered once a day for 10 days in the prevention of transmission of symptomatic influenza A and B viral infections within households".

This study was almost identical to study NAI30010. The main difference in the design of study 30031 was that index cases (≥ 5 years of age) were provided with relief medication only and were not randomized to study drug.

Family/household studies: Study population

A summary of families and subjects randomized in Study NAI30010 and Study NAI30031 is shown in Table 1.

Table 1. Summary of families and subjects randomized into studies NAI30010 and NAI30031: Intent-to-treat populations.

	Placebo	Zanamivir	Total
Study NAI30010			
Total families	168	169	337
Total no. of subjects	581	577	1158
Index cases	158	163	321
Contact cases	423	414	837
Study NAI30031			
Total no. of subjects	872	906	1778
Index cases	242	245	487
Contact cases	630	661	1291

Baseline characteristics: Subject demographics for the two family/household studies are shown in Table 2.

Table 2. Summary of demographic data and vaccination status: family/household studies (contact cases, ITT population).

	NAI30010	**NAI30031**
Sex - males, n (%) - females, n (%)	 376 (45) 461 (55)	 592 (46) 699 (54)
Age - mean (years)	26.2	27.3
Vaccinated prior to randomization, n (%)	135 (16)	132 (10)
Race - White, n (%) - Black, n (%) - Asian, n (%) - American Hispanic, n (%) - Other, n (%)	 749 (89) 45 (5) 9 (1) 13 (2) 21 (3)	 1210 (94) 26 (2) 31 (2) 12 (<1) 12 (<1)

Source: Summary of clinical efficacy, Table 7.

Comment: Overall the baseline characteristics were similar between the two trials and well balanced between the treatment groups within each study. The studies enrolled

predominantly Caucasians. Approximately 90% of the subjects in study NAI30010 were Caucasians, while 5% were black, 2% were American Hispanic, 1% were Asian and the remaining 3% were other races. In study NAI30031, 95% of the subjects were Caucasians, while 2% were black and 2% were Asian.

Sixteen percent (16%) of the subjects in study NAI30010 and 10% of the subjects in study NAI30031 were vaccinated prior to randomization.

Disposition of subjects:

Study discontinuations.

Study and study drug discontinuations of contact and index cases of Study NAI30010 are summarized in Tables 3 and 4, respectively.

Table 3. Summary of contact and index cases who discontinued Study NAI30010: Intent-to-treat population.

	Contact cases		Index cases	
	Placebo N=423	Zanamivir N=414	Placebo N=158	Zanamivir N=163
Discontinued study prematurely	5 (1%)	3 (< 1%)	2 (< 1%)	1 (< 1%)
Completed study	418 (99%)	411 (99%)	156 (99%)	162 (99%)
Reason for premature discontinuation				
Adverse event	0	1 (< 1%)	0	0
Consent withdrawn	1 (< 1%)	0	0	0
Lost to follow-up	2 (< 1%)	1 (< 1%)	1 (< 1%)	1 (< 1%)
Protocol violation	2 (< 1%)	1 (< 1%)	1 (< 1%)	0

Source: Section 6.1 of the Clinical Study Report

Comment: The percentage of contact and index cases who discontinued Study NAI30010 prematurely was ≤ 1%.

Table 4. Summary of contact and index cases who discontinued study medication in Study NAI30010: Intent-to treat population.

	Contact cases		Index cases	
	Placebo N=423	Zanamivir N=414	Placebo N=158	Zanamivir N=163
Discontinued study prematurely	7 (2%)	9 (2%)	1 (< 1%)	1 (< 1%)
Completed study	416 (98%)	405 (98 %)	157 (99%)	162 (99%)
Reason for premature discontinuation				
Adverse event	1 (< 1%)	2 (< 1%)	0	0
Consent withdrawn	1 (< 1%)	0	0	0
Lost to follow-up	2 (< 1%)	0	1 (< 1%)	0
Protocol violation	2 (< 1%)	1 (< 1%)	0	0
Other	1 (< 1%)	6 (1%)	0	1 (< 1%)

Comment: Seven (2%) contact cases in the placebo group and nine (2%) contact cases in the zanamivir group discontinued study medication in protocol NAI30010. Only one index case in each group discontinued study medication in protocol NAI30010.

Study discontinuations of contact and index cases of Study NAI30031 are summarized in Table 5.

Table 5. Summary of contact and index cases who discontinued Study NAI30031: Intent-to-treat population.

	Contact cases		Index cases	
	Placebo N=630	Zanamivir N=661	Placebo N=242	Zanamivir N=245
Discontinued study prematurely	11 (2%)	6 (2%)	4 (2%)	3 (1%)
Completed study	619 (98%)	655 (99 %)	238 (98%)	242 (99%)
Reason for premature discontinuation				
Adverse event	0	0	0	0
Consent withdrawn	6 (< 1%)	2 (< 1%)	3 (1%)	1 (< 1%)
Lost to follow-up	2 (< 1%)	2 (< 1%)	1 (< 1%)	1 (< 1%)
Protocol violation	2 (< 1%)	1 (< 1%)	0	1 (< 1%)
Other	1 (< 1%)	1 (1%)	0	0

Source: Section 6.1.1 of the Clinical Study Report

Comment: Only 2% of the contact cases in the placebo group and 2% of the contact cases in the zanamivir group discontinued prematurely from Study NAI30031. Similar percentages were observed among the index cases. No subjects prematurely discontinued study due to an AE.

Study drug discontinuations of contact cases of Study NAI30031 are summarized in Table 6.

Table 6. Summary of contact cases who discontinued study medication in Study NAI30031: Intent-to-Treat Population.

	Contact cases	
	Placebo N=630	Zanamivir N=661
Discontinued study prematurely	18 (3%)	8 (1%)
Completed study	612 (97%)	653 (99 %)
Reason for premature discontinuation		
Adverse event	4 (< 1%)	1 (< 1%)
Consent withdrawn	5 (< 1%)	2 (< 1%)
Lost to follow-up	1 (< 1%)	0
Protocol violation	2 (< 1%)	2 (< 1%)
Other	6 (< 1%)	3 (1%)

Source: Section 6.1.2 of the Clinical Study Report

Comment: Eighteen (3%) contact cases of the placebo group and eight (1%) contact cases of the zanamivir group discontinued study medication in protocol NAI30031.

Results

For discussion of the efficacy and safety results please refer to the Integrated Review of efficacy and safety sections.

PRIMARY COMMUNITY STUDIES: PROTOCOLS NAIA3005 and NAI30034

Protocol NAIA3005, "A double-blind, randomized, placebo-controlled, parallel-group, multi-center study to investigate the efficacy and safety of zanamivir 10 mg administered once a day for 28 days in the prevention of symptomatic influenza A and B viral infections in community-dwelling adults."

This study was conducted in two university communities in the United States (Ann Arbor, MI and Columbia, MO). The study was designed to evaluate the efficacy of inhaled zanamivir 10 mg once daily for 28 days compared with placebo in the prevention of influenza A and B infections in community-dwelling adults ≥ 18 years of age.

Once an influenza was determined in the community, eligible subjects were stratified according to their immunization status and randomized to receive either inhaled zanamivir 10 mg once daily for 28 days or inhaled placebo once daily for 28 days. Subjects completed diary cards twice

a day for at least 28 days. Following the first prophylaxis clinic on Day 1, subjects attended the clinic on Days 7, 14, 21, 28, and at post-prophylaxis visit on Day 35.

The primary efficacy endpoint was the proportion of randomized subjects who developed symptomatic, laboratory-confirmed influenza A and B infection during prophylaxis. The non-vaccinated population was the primary population of the analysis. Definition for symptomatic influenza is described in Section 6.1.2 (Table 3). Laboratory confirmation of influenza was based on serology and culture results. Serum samples were obtained at baseline and on Day 35. A nasopharyngeal and/or throat swab for influenza culture was collected if a subject was returned to the study center within 2-3 days of the onset of influenza-like symptoms. Unlike the family/household studies, PCR was not performed in the community studies.

Study objectives

- To evaluate the efficacy of inhaled zanamivir compared with placebo in the prevention of symptomatic, laboratory-confirmed influenza A and B viral infections.
- To evaluate the safety and tolerability of inhaled zanamivir compared with placebo in the prevention of symptomatic, laboratory-confirmed influenza A and B viral infections.
- To assess the impact of inhaled zanamivir for the prevention of symptomatic, laboratory-confirmed influenza A and B viral infections on subject productivity and healthcare resource use.

Inclusion criteria

A subject was eligible for participation in this study only if all of the following criteria applied:

- Males or females ≥ 18 years of age from a university community.

  Women of childbearing potential had to have a negative pregnancy test (urine) at the First Treatment Visit (Day 1) before receiving study medication. Those at risk of pregnancy had (in the opinion of the investigator) to be taking contraceptive precautions during the study.

- Subjects were able to take the first dose of study medication within 72 hours (1.5 days) following notification of an influenza outbreak and complete four weeks of treatment while in the university community.

- Subjects were able to use the DISKHALER satisfactorily. Assistance could be given if necessary and available.

- Subjects were willing and able to adhere to the procedures stated in to protocol. The Diary CARD had to be completed by the subject. Assistance in completing the Diary Card could be given if necessary; however, subjects had to be able to provide the

responses to all items in the Diary Card and assistance had to be restricted to reading the questions and/or written completion of the subject's response.

- Subjects who, in the opinion of the Investigator, could be managed on an outsubject basis and were not medically compromised by their participation in the study.

- Subjects were fluent and literate in the language spoken by the Investigator and staff.

- Subjects were willing and able to give written informed consent to participate in the study.

Exclusion Criteria

A subject was not eligible for participation in this study if any of the following criteria applied:

- Females who were pregnant, breast-feeding or at risk of becoming pregnant during the study.

- Subjects who were known or respected to be hypersensitive to any component of the study medication and relief medications.

- Subjects with evidence or history of alcoholism, drug abuse, psychiatric disorders, or any other medical condition that could have affected their ability to complete the study or confound the evaluation of safety or efficacy data.

- Subjects who were immunocompromised, for example as a result of HIV infection of systematic chemotherapy treatment.

Study endpoints

Primary endpoint

The primary endpoint was the proportion of non-vaccinated randomized subjects who developed symptomatic, laboratory-confirmed (by culture, serology or PCR) influenza A or B infection during prophylaxis. Definition of symptomatic influenza was similar to that in the family/ household studies.

Secondary endpoints

The secondary endpoints consisted of the following:

- The proportion of randomized subjects who developed laboratory-confirmed influenza infection.

- The proportion of randomized subjects who, during Days 3-28 prophylaxis, developed symptomatic, laboratory-confirmed influenza infection.

- The proportion of randomized subjects who, during prophylaxis, developed a febrile illness with laboratory confirmation of influenza infection. A febrile illness was defined as a temperature of ≥37.8°C.

- The proportion of randomized subjects who, during prophylaxis, developed a febrile illness irrespective of laboratory confirmation of influenza infection.

- The maximum recorded score during Days 1-28 for each of the symptoms recorded on the Diary Card.

- The number of days out of 28 the subject was unable to perform all their normal activities.

- The number of days out of 28 the subject recorded use of relief medication.

- The proportion of randomized subjects who, during prophylaxis, developed a secondary complication of influenza and had subsequent associated laboratory confirmation of influenza infection.

- The proportion of randomized subjects who, during prophylaxis, developed a secondary complication of influenza, irrespective of laboratory confirmation of influenza.

- The proportion of randomized subjects who required antibiotics.

- The proportion of randomized subjects who required an OTC medication.

- The proportion of randomized subjects who required a prescribed medication.

- The proportion of randomized subjects who had an unscheduled healthcare contact plus the mean number of unscheduled healthcare contacts.

- The proportion of randomized subjects confined to bed/incapacitated plus the mean duration of incapacity because of influenza.

- The proportion of randomized subjects who missed at least half day from work/school because of influenza and the mean duration missed from work/school.

Protocol NAI30034, "A double-blind, randomized, placebo-controlled, parallel-group, multicenter study to investigate the efficacy and safety of inhaled zanamivir 10 mg administered once a day for 28 days in the prevention of symptomatic influenza A and B viral infections in community-dwelling high risk subjects aged ≥ 12 years."

This study was almost identical to study NAIA3005. The main difference between the two studies was the subject population. Subjects enrolled in Study NAI30034 were vaccinated (67%), community-dwelling subjects ≥ 12 years of age who were at high risk of complications from influenza. High risk was defined as subjects ≥ 65 years of age, subjects with diabetes mellitus and subjects with chronic disorders of the pulmonary or cardiovascular systems. In comparison, Study NAIA3005 enrolled healthy adults ≥ 18 year of age.

Community studies: Study population-Baseline characteristics:

A summary of subjects randomized in Study NAIA3005 and Study NAI30034 is shown in Table 7.

Table 7. Summary of demographic data and vaccination status: Community studies (ITT population)

Characteristics	**NAIA3005**	**NAI30034**
Sex		
- males, n (%)	449 (41)	1417 (42)
- females, n (%)	658 (59)	1946 (58)
Age - mean (years)	28.8	60.4
Vaccinated prior to randomization, n (%)	159 (14)	1819 (54)
Race		
- White, n (%)	915 (83)	3135 (93)
- Black, n (%)	80 (7)	122 (4)
- Asian, n (%)	59 (5)	19 (<1)
- American Hispanic, n (%)	17 (2)	76 (2)
- Other, n (%)	36 (3)	11 (<1)

Source: Summary of clinical efficacy, Table 11

Comment: Approximately 40% of the subjects in each of the two community studies were male. The mean age in the first community study (NAIA3005) was 29 years of age while the mean age in the second community study (NAI30034) was 60 years of age.

Fourteen percent (14%) of the subjects in study NAIA3005 were vaccinated prior to randomization while 54% of the subjects in NAI30034 were vaccinated prior to randomization.

Eighty-three percent (83%) of the subjects in study NAIA3005 were Caucasian, while 7% were black, 5% were Asian, 2% were American Hispanic and 3% were other races.

Ninety-three percent (93%) of the subjects in study NAI30034 were Caucasian, while 4% were black and 2% were American Hispanic.

High-risk conditions:

Table 8 summarizes the number and percentage of subjects recruited in Study NAI30034 with high-risk conditions: elderly (> 65 years), respiratory disease, cardiovascular disease, and diabetes.

Table 8. Summary of high-risk conditions and severity for subjects in Study NAI30034 (ITT population)

Risk factor	**Placebo** (N=1685)	**Zanamivir** (N=1678)	**Total** (N=3363)
Elderly (aged ≥65 years), n (%)	950 (56%)	946 (56%)	1896 (56%)
Respiratory Disease, n (%)	695 (41%)	684 (41%)	1379 (41%)
Asthma, n (%)	582 (35%)	564 (34%)	1146 (34%)
Mild, n (%)	329 (57%)	306 (54%)	635 (55%)
Moderate, n (%)	252 (43%)	258 (46%)	510 (45%)
Severe[1], n (%)	1 (<1%)	0	1 (<1%)
COPD, n (%)	139 (8%)	147 (9%)	286 (9%)
Mild, n (%)	62 (45%)	63 (43%)	125 (44%)
Moderate, n (%)	51 (37%)	52 (35%)	103 (36%)
Severe, n (%)	26 (19%)	32 (22%)	58 (20%)
Cardiovascular Disease, n (%)	307 (18%)	331 (20%)	638 (19%)
Mild, n (%)	164 (53%)	182 (55%)	346 (54%)
Moderate, n (%)	132 (43%)	133 (40%)	265 (42%)
Severe, n (%)	11 (4%)	16 (5%)	27 (4%)
Diabetes, n (%)	370 (22%)	359 (21%)	729 (22%)
Insulin dependent, n (%)	108 (29%)	127 (35%)	235 (32%)
Non-insulin dependent[2], n (%)	261 (71%)	232 (65%)	493 (68%)

Source: Table 9 and 10 of the Clinical study report
[1]Patiet had severe asthma condition, but was not considered sufficiently severe at baseline to be a protocol violator;
[2]Subjects receiving oral medication for diabetes.

Comment: Fifty-six percent (56%) of the high-risk subjects in study NAI30034 were ≥ 65 years of age, 41% had respiratory disease, the majority with mild or moderate asthma. Nineteen percent (19%) had cardiovascular disease, the majority with mild or moderate disease. The majority of diabetic subjects were non-insulin dependent.

In addition, 6% of the high-risk subjects in study NAI30034 had endocrine disease, 5% had neurological disease, 2% had renal disease, 1% had hepatic disease and 53% had other diseases (data not shown in Table 18).

The underlying diseases were well balanced between the two treatment groups.

Disposition of subjects:

Subjects who discontinued Study NAI3005 and Study NAI30034 are summarized in Table 9.

Table 9. Summary of subjects who discontinued Study NAIA3005 and Study NAI30034: Intent-to-treat population

	Study NAIA3005		**Study NAI30034**	
	Placebo N=554	**Zanamivir N=553**	**Placebo N=1685**	**Zanamivir N=1678**
Discontinued study prematurely	17 (3%)	10 (2%)	91 (5%)	83 (5%)
Completed Study	537 (97%)	543 (98%)	1594 (95%)	1595 (95%)
Reason for premature discontinuation:				
Adverse event	6 (1%)	4 (<1%)	36 (2%)	32 (2%)
Consent Withdrawn	3 (<1%)	1 (<1%)	34 (2%)	29 (2%)
Lost to follow-up	7 (1%)	5 (<1%)	5 (<1%)	4 (<1%)
Protocol violation	0	0	7 (<1%)	6 (<1%)
Other	1 (<1%)	0	9 (<1%)	11 (<1%)
Missing	0	0	0	1 (<1%)

Source: Section 6.1 of the Clinical Study Report

Comment: The majority of subjects completed studies. The percentage of subjects who discontinued studies was similar between the placebo and the zanamivir groups in both studies.

The percentage of subjects who discontinued studies due to an AE ranged from 1 to 2% and was similar between the placebo and the zanamivir groups in both studies.

Study drug discontinuations. Study drug discontinuations of subjects enrolled in Study NAIA3005 and Study NAI30035 are summarized in Tables 10.

Table 10. Summary of subjects who discontinued study medication in Study NAIA3005 and Study NAI30034: Intent-to-treat population

	Study NAIA3005		Study NAI30034	
	Placebo N=554 N(%)	**Zanamivir N=553 N(%)**	**Placebo N=1685 N(%)**	**Zanamivir N=1678 N(%)**
Discontinued study medication prematurely	73 (13%)	60 (11%)	91 (5%)	83 (5%)
Completed Study Medication	481 (87%)	493 (89%)	1594 (95%)	1595 (95%)
Reason for premature discontinuation:				
Adverse event	7 (1%)	4 (<1%)	36 (2%)	32 (2%)
Consent withdrawn	4 (<1%)	2 (<1%)	34 (2%)	29 (2%)
Lost to follow-up	6 (<1%)	4 (<1%)	5 (<1%)	4 (<1%)
Protocol violation	0	0	7 (<1%)	6 (<1%)
Missing	5 (<1%)	0	0	1 (<1%)
Other	56 (10%)	50 (9%)	9 (<1%)	11 (<1%)

Source: Clinical study reports

Comment: In study NAI3005, 133 subjects discontinued study medication prematurely. The main reasons for premature discontinuation of study medication were in the 'other' category. The majority of these subjects run out of study medication on the last day of treatment because inadvertently they took an additional dose on a previous day.

In study NAI30034, 5% of the placebo and zanamivir subjects discontinued study medication prematurely. The main reasons for discontinuation from the study medication were adverse events and withdrawal of consent.

Results

For discussion of the efficacy and safety results please refer to the Integrated Review of Efficacy and safety sections.

SECONDARY STUDIES: NURSING HOME STUDIES (PROTOCOLS NAIA3003 and NAIA3004)

Protocol NAIA3003, "A double-blind, randomized, parallel-group, multi-center study to investigate the efficacy and safety of zanamivir 10 mg administered once a day compared to the standard of care in controlling nursing home outbreaks."

This phase III study, conducted in United States nursing homes, was designed to investigate the efficacy of inhaled zanamivir administered 10 mg once daily for 14 days compared with the

standard of care in the prevention of influenza A and B infections. Standard of care was rimantadine 100 mg administered once daily during an influenza A outbreak and placebo (lactose powder vehicle) during outbreaks of influenza B.

Study objectives

The study objectives were to:

- Evaluate the efficacy of inhaled zanamivir compared with the standard of care in the prevention of influenza infections in the nursing home setting.
- Evaluate the safety and tolerability of inhaled zanamivir compared with the standard of care in the prevention of influenza infections in the nursing home setting.
- Assess the emergence and transmission of resistant virus during influenza outbreaks in the nursing home setting.
- Assess the pharmacoeconomic impact of influenza in the nursing home.

Inclusion criteria

Subjects were eligible for participation in this study only if all of the following criteria applied:

- The subject was a resident of the nursing home
- The subject was able to use the DISKHALER satisfactorily (with assistance)
- The subject was willing and able to adhere to the procedures stated in the protocol
- The subject was willing and able to give written informed consent to participate in the study. For those subjects with legally authorized representatives (Power of Attorney or guardian), those representatives must have been willing to give consent for an assenting subject
- The subject was able to fully comprehend the language spoken by the investigator and staff.

Subjects were eligible for randomization to study drug if both of the following applied on the day of randomization:

- The inclusion criteria listed above still applied
- An influenza outbreak was declared in the EU.

Exclusion Criteria

Subjects were not eligible for participation in the study if any of the following applied:

- The subject was known or suspected to be hypersensitive to any component of the study medication
- The subject was a female of childbearing potential
- In the opinion of the investigator, the subject was unable to complete the study or had any medical condition that could confound the evaluation of safety or efficacy
- The subject was immunocompromised, e.g., conditions associated with malignancy, Acquired Immune Deficiency Syndrome (AIDS), or chemotherapy other than hormonal therapy (such as tamoxifen or anti-androgen). Subjects on chronic systemic steroids for chronic airway disease were not excluded.

Subjects were not eligible for randomization to study drug if any of the following applied on the day of randomization:

- Any of the exclusion criteria listed above applied
- Had received any influenza antiviral in the previous 7 days
- Had received an investigational drug in the previous 30 days
- Had influenza-like illness.

Study endpoints

Primary endpoint

The primary endpoint was the proportion of randomized subjects who, during prophylaxis, developed a new sign or symptom and had laboratory confirmation of influenza infection. Onset of a new sign or symptom was any sign or symptom observed after randomization which prompted a sample of influenza culture. Laboratory confirmation of influenza infection was a positive result by any of the following methods: culture, PCR, or seroconversion. If a laboratory test was missing, confirmation of influenza infection was required from one of the other methods for a subject to be considered influenza positive.

Secondary endpoints

The secondary endpoints included the following:

- The proportion of randomized subjects who, during prophylaxis, developed febrile illness (defined as a temperature of ≥99.0°F or ≥37.2°C) and had subsequent associated laboratory confirmation of influenza infection. In addition, febrile illness and subsequent associated laboratory confirmation of influenza infection using the standard definition of fever for non-elderly individuals (temperature of ≥100.0°F or ≥37.8°C) was assessed.

- The proportion of randomized subjects who, during prophylaxis (Days 1-15) or anytime during the study (Days 1-28), developed complications of influenza and had subsequent associated laboratory confirmation of influenza infection.

- The proportion of randomized subjects who, during prophylaxis (Days 1-15) or anytime during the study (Days 1-28), took an antibiotic due to complications of influenza and had subsequent associated laboratory confirmation of influenza infection.

- The proportion of randomized who, during Days 3-15 of prophylaxis, developed a new sign or symptom with subsequent associated laboratory confirmation of influenza infection. In addition, the proportion of randomized subjects who developed a new sign or symptom with subsequent associated laboratory confirmation of influenza infection on Days 2-15 or anytime during the study (Days 1-28) was assessed.

- The proportion of randomized subjects, who during prophylaxis, had laboratory-confirmed influenza infection.

Protocol NAIA3004, "A double-blind, randomized, placebo-controlled, parallel-group, multi-center study to investigate the efficacy and safety of zanamivir 10 mg administered once a day in controlling nursing home influenza outbreaks."

This was a randomized, double-blind, placebo-controlled, parallel group, multicenter study conducted in twelve nursing homes in Lithuania, the Netherlands and Israel. The goal of the study was to investigate the efficacy, safety, and tolerability of inhaled zanamivir 10 mg administered once daily for 14 days, compared with placebo, in the prevention of influenza A and B infections in a predominantly unvaccinated, high risk population.

Study objectives, inclusion and exclusion criteria were similar to Study NAIA3003.

Nursing home studies: Study population-baseline characteristics:

Demographic characteristics and vaccination status for subjects in the two nursing home studies are summarized in Table 11.

Table 11. Demographic characteristics for nursing home prophylaxis studies (Study NAIA3003 and Study NAIA3004 combined data) (safety population)

	NAIA3003			NAIA3004	
Demographic Characteristic	**Placebo (N=13)**	**Rimantadine (N=231)**	**Zanamivir (N=238)**	**Placebo (N=252)**	**Zanamivir (N=242)**
Age (yrs)					
17-34	0	0	0	15 (6%)	12 (5%)
35-49	0	4 (2%)	2 (<1%)	20 (8%)	19 (8%)
50-64	3 (23%)	18 (8%)	23 (10%)	44 (17%)	58 (24%)
65 -74	1 (8%)	79 (34%)	76 (32%)	76 (30%)	68 (28%)
≥ 75	9 (69%)	130 (56%)	137 (58%)	97 (38%)	85 (35%)
Age (yrs)					
Mean (SD)	74.8 (10.6)	75.9 (10.2)	76.3 (10.1)	67.3 (15.9)	66.7 (15.7)
Median	76.0	76.0	76.0	70.0	69.0
(Min. - Max.)	(53 – 87)	(44 – 99)	(45 – 102)	(23 – 107)	(20 – 96)
Sex					
Female	2 (15%)	68 (29%)	71 (30%)	122 (48%)	114 (47%)
Male	11 (85%)	163 (71%)	167 (70%)	130 (52%)	128 (53%)
Race					
Asian	0	0	1 (<1%)	0	0
Black	0	2 (<1%)	0	0	0
White	13 (100%)	229 (99%)	237 (>99%)	252 (100%)	242 (100%)
Vaccinated prior to randomization					
Yes	12 (92%)	201 (87%)	216 (91%)	22 (9%)	23 (10%)
No	1 (8%)	6 (3%)	2 (<1%)	0	0
Missing	0	24 (10%)	20 (8%)	230 (91%)	219 (90%)

Source: Clinical safety summary, Table 9

Comment: More males (61%) than females (39%) were enrolled in the nursing home studies. In both studies, most of the subjects were Caucasians (99%). The majority of subjects in Study NAIA3003 were vaccinated against influenza prior to randomization. Vaccination data were missing for the majority of subjects in Study NAIA3004.

Disposition of subjects:

Study discontinuation:

Study discontinuations for subjects in Study NAIA3003 and Study NAIA3004 are summarized in Table 12.

Table 12. Summary of subjects who discontinued Study NAIA3003 and Study NAIA3004 (combined data, ITT population)

	NAIA3003			NAIA3004	
	Placebo (N=13)	**Rimantadine (N=231)**	**Zanamivir (N=238)**	**Placebo (N=252)**	**Zanamivir (N=242)**
Study					
Randomized (ITT Population)	13	231	238	252	242
Discontinued study prematurely	0	5 (2%)	4 (2%)	7 (3%)	5 (2%)
Completed study	13 (100%)	226 (98%)	234 (98%)	245 (97%)	237 (98%)
Reason for premature discontinuation					
Adverse event	0	3 (1%)	2 (<1%)	1 (<1%)	2 (<1%)
Consent withdrawn	0	1 (<1%)	1 (<1%)	6 (2%)	3 (1%)
Protocol violation	0	1 (<1%)	1 (<1%)	0	0

Source: Summary of clinical safety, Table 5 (modified)
Data for NAIA3003 and NAIA3004 includes all randomizations

Comment: The percentage of subjects who completed studies was ≥ 97%. The percentage of subjects who discontinued studies due to an adverse event was ≤ 1%.

Study drug discontinuation:

Study drug discontinuations of cases of Study NAIA3003 and NAIA3004 are summarized in the following table.

Table 13. Summary of subjects who discontinued study medication in Study NAIA3003 and Study NAIA3004 (combined data, ITT population)

	NAIA3003			NAIA3004	
	Placebo (N=13)	**Rimantadine (N=231)**	**Zanamivir (N=238)**	**Placebo (N=252)**	**Zanamivir (N=242)**
Study Drug					
Discontinued study drug prematurely	0	21 (9%)	13 (5%)	5 (2%)	9 (4%)
Completed study drug	13 (100%)	210 (91%)	225 (95%)	247 (98%)	233 (96%)
Reason for premature discontinuation					
Adverse event	0	12 (5%)	11 (5%)	2 (<1%)	6 (2%)
Consent withdrawn	0	1 (<1%)	0	2 (<1%)	1 (<1%)
Protocol violation	0	1 (<1%)	1 (<1%)	0	0
Other	0	7 (3%)	1 (<1%)	1 (<1%)	2 (<1%)

Source: Summary of clinical safety, Table 5 (modified)
Data for NAIA3003 and NAIA3004 includes all randomizations

Comment: The numbers of subjects who discontinued study drug was low in both studies. In Study NAIA3003, 7% of subjects discontinued study drug foe any reason. In Study NAIA3004, 3% of subjects discontinued study drug for any reason.

In Study NAIA3003, 5% of subjects discontinued study drug due to an AE. In Study NAIA3004, the percentage of patients who discontinued study drug was 2% for the zanamivir group and < 1% in the placebo group.

Results

As previously stated, data from the two nursing home studies were analyzed only for safety. For discussion of the safety results please refer to the Integrated Review of safety section.

10.2 Line-by-Line Labeling Review

Please see section 9.4.

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1. Moscona A. Neuraminidase inhibitors for influenza. N Engl J Med 2005;353:1363-1373.

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Andreas Pikis, M.D.
Medical Reviewer

Concurrences:
DAVP/TL/Struble
DAVP/DivDir/Birnkrant

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Andreas Pikis
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MEDICAL OFFICER

Kimberly Struble
3/29/2006 09:56:47 AM
MEDICAL OFFICER

Debra Birnkrant
3/29/2006 10:02:15 AM
MEDICAL OFFICER

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: **March 17, 2006**

FROM: Debra Birnkrant, MD, Division Director
Kimberly A. Struble, PharmD, Medical Team Leader
Division of Antiviral Products

TO: **Division File**

SUBJECT: Division Director/Group Leader Memo for NDA 21-036 SE1-008 Efficacy Supplements for RELENZA (zanamivir) inhaled dry powder for prophylaxis of influenza

1.0 BACKGROUND:

RELENZA is the tradename for zanamivir, which is an inhibitor of influenza virus neuraminidase. The purpose of this memorandum is to summarize the basis of approval for RELENZA for prophylaxis of influenza in the household and community settings. In addition, noteworthy efficacy and safety findings are highlighted.

Regulatory History:

RELENZA was approved on July 26, 1999, for treatment of uncomplicated acute illness due to influenza A and B virus in adults and pediatric patients 12 years of age and older who have been symptomatic for no more than two days. On April 26, 2000, the patient population for the treatment indication was expanded to include pediatric patients seven years of age and older. (b) (4)

[redacted]

The Division advised GSK on the design of additional studies to support a prophylaxis indication. Subsequently GSK conducted two additional studies; one study in the household setting where the index case was not treated with antiviral medication and a second study in subjects at high risk for developing complications from influenza infection. The basis for the prophylaxis indication are two studies in the household setting and two studies in the community setting, of which one study is in a university community and another is in subjects at high risk for developing complications from influenza. In addition, the safety data from the two nursing home studies were resubmitted in support of safety in elderly patients. Overall, in the six studies submitted, 3779 subjects received at least one dose of zanamivir and 3794 subjects received placebo or rimantadine. For complete details, please refer to the medical officer review by Dr. Andreas Pikis, and the biometrics review by Dr. Frasier Smith.

2.0 SUMMARY OF RESULTS:

Efficacy:

Four studies were submitted in support of efficacy for prophylaxis of influenza in the household and community settings. All four studies were adequate and well-controlled and provide an

assessment of benefit for zanamivir versus placebo. All studies were double-blind, randomized, and placebo-controlled.

The two studies in the household setting were identical in design with one exception. In Study NAI30010 the index cases received zanamivir treatment, whereas in Study NAI30031, the index cases were not treated with zanamivir. Both studies were randomized by family. All contacts (≥ 5 years of age) received inhaled zanamivir 10 mg once daily for 10 days. The two community studies were also similar in design. The difference between the two studies was the patient population enrolled. In study NAI3005, subjects ≥ 18 years of age from two university communities were enrolled; whereas in study NAI30034, subjects ≥ 12 years of age who were at high risk for developing complications from influenza were enrolled. High risk was defined as subjects ≥ 65 years of age, subjects with diabetes mellitus, and subjects with chronic disorders of the pulmonary or cardiovascular systems.

The primary endpoint for the household and community studies was symptomatic, laboratory-confirmed (by culture, serology or PCR) influenza A or B infection. For the primary efficacy analyses the intent-to-treat population defined as all randomized subjects regardless if study medication was received or if the subject completed the planned duration of the study was used for three studies (NAI30010, NAI30031 and NAI30034). The non-vaccinated population was the primary efficacy population defined in the community study NAI3005. Below is a summary of the results for the primary efficacy analyses for the four pivotal trials.

		Placebo	Zanamivir	p-value	Relative Odds (95% CI)	Approximate Relative Risk (95% CI)
Household	**Study NAI30010**[1]	N=168	N=169			
	Number (%) of households	32 (19.0%)	7 (4.1%)	<0.001	0.18 (0.06, 0.43)	0.21 (0.11, 0.43)
	Study NAI30031[1]	N=242	N=245			
	Number (%) of households	46 (19.0%)	10 (4.1%)	<0.001	0.17 (0.07, 0.37)	0.19 (0.10, 0.36)
Community	**Study NAIA3005**[2]	N=475	N=473			
	Number (%) of subjects	28 (6%)	11 (2%)	0.009	0.38 (0.1, 0.80)	0.40 (0.20, 0.76)
	Study NAI30034[3]	N=1685	N=1678			
	Number (%) of subjects	23 (1.4%)	4 (0.2%)	<0.001	0.17 (0.04, 0.50)	0.17 (0.07, 0.44)

[1] ITT Population
[2] Non-vaccinated population
[3] Excludes subjects vaccinated within 21 days of randomization or during the study

The studies in the household and community settings demonstrate the effectiveness of zanamaivir for the prophylaxis of influenza A and B. In all four studies statistically significant reductions in the incidence of symptomatic, laboratory-confirmed influenza illness were demonstrated. These findings in the household and community settings are impressive for

several reasons. First, the results were consistent regardless of which population was evaluated, ITT, index influenza positive or per protocol. Secondly, in several sensitivity analyses conducted to evaluate the impact of missing data, the results were similar to those observed in the primary efficacy analyses; thereby supporting the robustness of zanamivir efficacy. Importantly, efficacy was demonstrated irrespective of vaccination status, current smoking status, age, gender or underlying medical conditions. Protective efficacy was demonstrated for both influenza A and B.

In the household settings, efficacy was demonstrated whether or not the index was treated with zanamivir. In the Biometrics review, Dr. Smith suggests the effect of prophylaxing the contacts with placebo or zanamivir in the household study NAI30010 was confounded by the effect of giving the same treatment to the index cases. He further states the following: "Index Cases did not receive randomized treatment in the second household study. Therefore one would have expected to observe a smaller zanamivir treatment effect in the second household study since zanamivir has already been labeled to be effective in the treatment of influenza and to reduce the duration of illness by 1 to 1.5 days. It is possible to explain the observed results in the first household study as being due to the shorter and less severe illness in the index cases treated with zanamivir and not at all from a prophylactic effect on the contact cases." We address this issue in the paragraph below.

As described in the clinical studies section of the Tamiflu product labeling for studies of prophylaxis of influenza in the household setting; efficacy was demonstrated whether or not the index case was treated with antiviral medication. This finding is not surprising as we would not expect treating the index case would have a dramatic impact on a prophylaxis intervention. Index cases receive treatment with zanamivir within 36 hours of symptom onset. It is assumed that index cases were already infected with influenza virus and shedding virus prior to the onset of symptoms and initiation of treatment. Therefore, contacts were already exposed to influenza virus prior to treating symptoms in the index cases. Thus, zanamivir is effective for the prophylaxis of influenza in the household setting and the two household studies support this conclusion.

Another noteworthy finding is the statistically significant treatment difference observed in the community study NAI30034 in subjects at high risk for complications from influenza. Efficacy was demonstrated in this older (56% $\geq$ 65 years of age), high risk, vaccinated population (67%). Despite a year with a low influenza attack rate, zanamivir was associated with a reduction in symptomatic, laboratory-confirmed influenza.

Additionally, in the statistical review, Dr. Smith comments on the percentages of subjects in the high risk community study with signs and symptoms of influenza (irrespective of laboratory results). The percentages were similar in the placebo group (10%) and the zanamivir group (9%). An explanation for this finding is subjects are infected with other viral infections during the year and the respective symptoms may be similar to those of an influenza-like illness. Zanamivir is not expected to have an effect on influenza-like illness not caused by influenza viruses. Therefore, the clinically relevant observation is the effectiveness of zanamivir on the reduction of symptomatic, laboratory-confirmed influenza, which is also the primary endpoint of the study.

Safety:

GSK submitted six, double-blind, randomized trials to support the safety of zanamivir in a broad patient population. The six studies include the four studies as described in the efficacy section above and the two previously submitted studies in the nursing home setting. The clinical safety database is adequate to evaluate the relative safety of zanamivir in subject's $\geq$ 5years of age. No notable differences were observed with respect to adverse events between zanamivir and placebo in pediatric subgroups, smoking status or underlying medical condition.

After the original approval of zanamivir for treatment of influenza A and B, postmarketing reports of bronchospasm and decline in lung function were reported. Serious cases of bronchospasm, including fatalities were reported postmarketing in patients with and without underlying airways

disease. As a result of these cases, updated information was included in the WARNINGS section of the package insert and FDA issued a Public Health Advisory. Prior to the submission of this NDA, the Division requested GSK to evaluate the postmarketing reports with zanamivir with an emphasis on respiratory-like reactions. Likewise, the Division consulted the Office of Drug Safety to independently review the postmarketing reports submitted to AERS database. Given the concerns of bronchospasm, and the expanded patient population for the prophylaxis indication, GSK proposed the following statement in the INDICATION AND USAGE section:

- RELENZA is not recommended for treatment or prophylaxis of influenza in individuals with underlying airways disease (such as asthma or chronic obstructive pulmonary disease) (see WARNINGS)

Although efficacy and safety were established in subjects with underlying airways disease during prophylaxis for influenza, we agreed with GSKs conservative approach to not recommend the use of zanamivir in this setting. Of note, the clinical trials did not specifically exclude subjects with underlying airways disease; however, few subjects with severe airways disease were enrolled.

The ODS consult recommended the Division consider a Box Warning regarding the risk of bronchospasm, including fatalities, for treatment and prophylaxis of influenza in individuals with underlying airways disease. After consultation with Dr. Robert Meyer, a pulmonologist and Director of ODE II, we concluded the following. (Please also refer to the memorandum prepared by Dr. Meyer for further details).

At this time a Box Warning is not warranted based on the clinical trial experience in approximately 8,000 subjects for prophylaxis of influenza. The safety of zanamivir versus placebo was similar in subjects with and without underlying respiratory disease such as asthma and COPD. Dr. Meyer commented the anticipated pulmonary safety experience in the prophylaxis setting may be better due to the absence of an active severe upper respiratory infection as seen in the influenza treatment setting. Additionally, we have consolidated the WARNINGS and PRECAUTIONS statements on the use and safety of zanamivir in subjects with underlying airways disease to the WARNING section. We intend to encourage GSK to voluntarily use the new Physician's Labeling Rule format for the package insert before the next influenza season. The highlight portion of the new labeling format will help highlight the pertinent safety and efficacy issues for treatment and prophylaxis settings.

Division of Scientific Investigations Inspections:

As part of the NDA review process, the Division of Scientific Investigations conducted clinical inspections to review the data quality and integrity. Four sites in the United States were investigated. These sites enrolled the greatest number of subjects in Studies NAI30031 and NAI30034. No major deficiencies were observed at these sites that would compromise the integrity of the studies.

3.0 OVERALL CONCLUSIONS AND RECOMMENDATION

Based on the totality of the data and considerations of the multidisciplinary review team's review for NDA 21-036 SE1-008, approval is recommended for this application for zanamivir for prophylaxis of influenza. In the two post-exposure prophylaxis studies, zanamivir dosing of two inhalations (one 5 mg blister per inhalation for a total dose of 10 mg) once daily for 10 days was safe and effective in reducing household transmission of influenza whether or not the index cases received treatment with zanamivir. In the two seasonal prophylaxis studies, zanamivir dosing of two inhalations (one 5 mg blister per inhalation for a total dose of 10 mg) once daily for 28 days was safe and effective in reducing the incidence of symptomatic, laboratory-confirmed influenza during community outbreaks. Efficacy has not been established for the prophylaxis of influenza in the nursing home setting, and this information is included in the Indications and Usage section.

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Kimberly Struble
3/28/2006 01:53:26 PM
MEDICAL OFFICER

Debra Birnkrant
3/28/2006 02:20:16 PM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021036/S-008

CHEMISTRY REVIEW(S)

Efficacy Supplement
Evaluation of Chemistry, Manufacturing and Controls

NDA 21-036 / SE1-008

Letter Date: 4-Nov-2005
CDER Stamp Date: 4-Nov-2005

Planned Action Date: 22-Nov-2005

1) Check all categories of CMC-related changes that are proposed in this efficacy supplement:

New Environmental Assessment data, or a change in exemption status, related to increased use or expanded patient population (e.g., SE6: Rx-to-OTC switch)	☐
Manipulation of drug product, or active control drug, or placebo, either for PK studies or for marketing (e.g., grinding tablets to make unmarked capsules; change in tablet scoring; repackaging of clinical supplies except for solid oral products)	☐
Changes in "Description," or "How Supplied" sections of Package Insert that are relevant to CMC (e.g., change in container/closure; change in amount of fill)	☐
Changes in the "Dosage and Administration" section of Package Insert that involve preparation of the product or delivery to the patient (e.g., preparation or storage of a reconstituted liquid, dilution prior to injection, scoring, syringe calibration, extemporaneous compounding)	☐
Changes in Container or Carton Text or Artwork	☐
Change to, or introduction of, a professional sample	☐
Changes in Patient Package Insert that are relevant to CMC	☐
Other changes needing a CMC evaluation. Specify in Section 2, below	☐

2) Evaluation of issues noted in Part 1.

This supplement provides for a prohylaxis indication for Relenza (zanamivir for inhasla-tion). To trigger an Environmental Assessment sales would need to exceed 400 million courses per year in the US. Therefore an Environmental Assessment is not required. This efficacy supplement has been evaluated from the CMC perspective and there are no issues that need to be documented.

3) Recommendation from CMC perspective:

Recommended for approval from the CMC perspective.

{signed electronically in DFS} 22-Nov-2005
George Lunn, Ph.D. Date

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/s/

George Lunn
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Efficacy supplement with no CMC issues
Resubmitted as PDF. Word document would not distil

Norman Schmuff
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Hasmukh Patel
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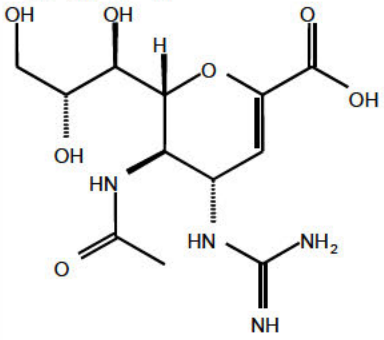
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021036/S-008

PHARMACOLOGY REVIEW(S)

PHARMACOLOGY/TOXICOLOGY COVER SHEET

NDA NUMBER:	**21-036**
SEQUENCE NO./DATE/TYPE:	SE1-008/Nov-4-2005
INFORMATION TO SPONSOR:	Yes () No (x)
SPONSOR:	GlaxoWellcome Inc. Research Triangle Park, NC
MANUFACTURER:	Same as above
DIVISION NAME:	DAVDP
HFD NO.:	HFD-530
REVIEW COMPLETION:	7/6/2004
DRUG:	Zanamivir, GG167; GR121167; Relenza® (zanamivir for inhalation)
CHEMICAL NAME:	5-(Acetylamino)-4-[(aminoiminomethyl)amino]-2,6-anhydro-3,4,5-trideoxy-D-glycero-D-galacto-non-2-enonic acid
CLINICAL FORMULATION & FORMULA/MW:	Oral Inhalation (solubility: 18 mg Zanamivir off-white powder/ml water); pK_a1 (guanidine group)=13; pK_a2 (carboxyl group)=2.4; administered to the respiratory tract by ROTADISK® which contains four regularly spaced double-foil blisters with each blister containing a powder mixture of 5 mg of Zanamivir and 20 mg of lactose. The contents of each blister are inhaled through the mouthpiece of DISKHALER, a breath-activated plastic device. $C_{12}H_{20}N_4O_7$; MW: 332.3
STRUCTURE:	
RELATED INDS/NDAS:	None
DRUG CLASS:	Antivirals
INDICATION:	Anti-Influenza A and B
ROUTE OF ADMINISTRATION	Inhalation

DISCLAIMER: TABULAR AND GRAPHICAL INFORMATION IS FROM SPONSOR'S SUBMISSION UNLESS STATED OTHERWISE.

COMMENTS:

Zanamivir is a competitive inhibitor of influenza A and B virus neuraminidase. The current NDA supplement provides new clinical data and is seeking for indications as follows:

> "Prophylaxis of influenza A and B, in adults and pediatric patients 5 years of age and older, (b) (4)

All preclinical information are cross-referenced to IND 43,776 and the original NDA (Oct., 1998), and no Pharm/Tox information was included in this new submission (see \\Cdsesub1\n21036\S_008\2005-11-04\pharmtox). A summary of animal target organ of toxicity and toxicity profile, especially in regard to local effects on the respiratory tract, are included in the APPENDIX. No Pharm/Tox regulatory comments are needed for this new supplement.

Kuei-Meng Wu, Ph.D.
Reviewing Pharmacologist
DAVDP

Concurrences:
HFD-530/PTL/JFarrelly

cc:
HFD-530 NDA 21-036(008)
HFD-530/Division File
HFN-340
HFD-530/CSO/
HFD-530/MO/

APPENDIX

EXPLORATION OF TOXICITY PROFILE: ***Key Issues.***

Toxicologically, the full toxicity profile and true target organ/system of toxicity of zanamivir have been difficult to identify because of the short half-life and comparably low clinical exposure of the drug. In addition to the inhalation route of administration used in the animal toxicity testings, the sponsor has employed iv bolus and iv infusion to increase drug exposure to explore the toxicity profile. However, the attempts had not been fruitful since none of the chronic, repeat-dose toxicity studies showed a steady-state exposure to zanamivir (i.e., Cmin, trough drug levels or pre-dose drug concentrations were often non-detectable). This is the case even for the iv infusion studies because of the limitation of methodology (duration of the iv infusion in the dog was limited and rather short.) With the issue of drug exposure in mind, systemic and local toxicity findings and key target organ/system of toxicity are highlighted below.

KIDNEY: ***Renal Tubule Necrosis in Rats.***

Continuous iv infusion of zanamivir in rats at dosages of 864 and 1728 mg/kg/day caused a dose-related, vacuolation of the proximal convoluted tubules in the renal cortex. There was no vacuolation in the renal cortex following the 7-day recovery period. The no-effect level was 432 mg/kg/day. In a higher iv (bolus) study in rats (912 and 13,824 mg/kg/day), similar renal toxicity findings were also reported (cortical tubular vacuolation/glomerular sclerosis with eosinophilic material or adhesions in the Bowman's space). This renal toxicity was not reported in any inhalational studies or iv bolus studies. At the no-effect dose of 432 mg/kg, the systemic exposure was 1000 times higher than proposed for the clinical use of zanamivir.

There has been no parallel evidence of zanamivir-related nephrotoxicity reported humans at lower doses studied.

RESPIRATORY SYSTEM: ***Epithelial Hyperplasia and Loss of Ciliated Cells in the Trachea (see table below).***

An increase in incidence and degree of epithelial hyperplasia at the carina (with or without loss of cilia) was seen in all zanamivir-treated groups in the 26-week dog inhalation study. In the 52-week dog inhalation study, there was an increase in loss of cilia at the carina in females in the intermediate and high dose groups. The incidence of this lesion in the 52-week dog inhalation study is shown in the Table below. An increased incidence of loss of ciliated cells at the carina was also recorded in rats following 104 weeks administration. There were statistically significant trends of hyperplasia and loss of cilia hyperplasia in the trachea and bifurcation of the female dogs.

Effects of Lactose.

The histopathologic changes produced by lactose vehicle alone are considered adaptive phenomena due to a prolonged inhalation exposure to high aerosol concentration and the high lung burden.

Table 1.
Overall Incidence of Histopathological Changes in the Respiratory Epithelium (52-Week Dog Inhalational Study)

Histopathology Findings:	Air (M)	Air (F)	Veh. (M)	Veh. (F)	Low dose (M)	Low dose (F)	Mid-dose (M)	Mid-dose (F)	High dose (M)	High dose (F)
Trachea and bifurcation, epithelial hyperplasia at carnia:										
Trace -	1/4	2/4	1/4	2/4	3/4	0/4	2/4	1/4	1/4	1/4
minimal -	1/4	0/4	0/4	1/4	0/4	0/4	0/4	2/4	1/4	3/4
Trachea and bifurcation, loss of cilia at carnia	1/4	0/4	1/4	0/4	1/4	0/4	1/4	3/4	2/4	4/4
Following Recovery Trachea and bifurcation, epithelial hyperplasia at carnia:										
Trace -		1/2		1/2						1/2
minimal -		1/2		1/2						0/2
Trachea and bifurcation, loss of cilia at carnia		2/2		2/2						0/2

M: Male; F: Female; Low, Mid and High Dose: 0.93, 4.31 or 11.2 mg/kg/day

Table 2.
Overall Incidence of Focal Loss of Ciliated Cells In the Respiratory and Olfactory Epithelium (Rat Carcinogenicity Study)

	Male					Female				
Group	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**
Dosage level	**0**	**Lac.**	**Low**	**Middle**	**High**	**0**	**Lac.**	**Low**	**Middle**	**High**
Focal loss of ciliated cells (bifurcation)	4	10	16**	18**	14**	9	14	26**#	14	18*
Number carina examined	55	55	55	55	55	55	55	55	55	55

*Fisher's Exact Test; Air Control (*) or Vehicle Control (#) compared with all other Groups ** p<0.01 one-sided; # or * p<0.05 one-sided*
Low, Middle and High Doses: 7.6, 15.1 and 30.2 mg/kg/day (Weeks 1-17); 14.2, 27.4 and 53.1 mg/kg/day (Weeks 17-104).

RESPIRATORY SYSTEM: ***Increased Number in Enlarged and Foamy***

Increased numbers of enlarged, diffusely distributed (prominent) alveolar macrophages were seen in the alveoli of a small number of rats exposed chronically to zanamivir. In the 26 weeks study, this was present at the higher dose of 44.5mg/kg/day. This finding was also observed in the 104-week rat carcinogenicity study. Incidences of this finding are summarized in the Table below.

Alveolar Macrophages in the Lung. Increased numbers and size of alveolar macrophages are a reflection of the clearance of particulate matter from the lung. Clinical relevance of this finding is uncertain; however, the sponsor estimated the concentration of particulate matter in the lung (high dose) of the rat to be approximately 34mg/m^2, whereas the inhaled dose in man is approximately 0.22mg/m^2; with a 150 fold difference.

Table 3.
Overall Incidence of Enlarged or Foamy Alveolar Macrophages (Rat Carcinogenicity Study)

	Male					Female				
Group	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**
Dosage level	**0**	**Lac.**	**Low**	**Middle**	**High**	**0**	**Lac.**	**Low**	**Middle**	**High**
Prominent numbers of alveolar macrophages	3	1	2	8*	8*	1	1	1	2	5
Foamy alveolar macrophages										
Total	16	8	5	8	20**	12	8	10	12	13
Trace	8	4	2	4	3	8	6	7	6	5
Minimal	8	3	3	4	13**	3	2	3	6	5
Moderate	0	0	0	0	4	1	0	0	0	3
Severe	0	1	0	0	0	0	0	0	0	0
Subpleural aggregations of foamy alveolar macrophages										
Total	23	22	22	16	25	19	27	22	19	26
Trace	14	16	12	9	6	8	16	8	8	6
Minimal	9	5	10	7	14*	11	10	13	11	15
Moderate	0	1	0	0	5[#]	0	1	1	0	4
Marked	0	0	0	0	0	0	0	0	0	1
Number lungs examined	55	55	55	55	55	55	55	55	55	55

*Fisher's Exact Test; Air Control (#) or Vehicle Control (*) compared with all other GG167 treated Groups ** $p<0.01$; [#] or * $p<0.05$ one-sided. Low, Middle and High Doses: 7.6, 15.1 and 30.2 mg/kg/day (Weeks 1-17); 14.2, 27.4 and 53.1 mg/kg/day (Weeks 17-104).*

RESPIRATORY SYSTEM: ***Nasal Passage.*** Increased incidences of eosinophilic inclusions were noted in nasal and respiratory epithelium in both rat and mouse carcinogenicity (inhalational) studies. The eosinophilic material is contained within endoplasmic reticula (by electron microscopy) and again, was considered by the sponsor to be a non-specific defense response.

The increased incidence of goblet cell hyperplasia seen in the rat carcinogenicity study was statistically significant. The toxicity was dose-related in incidence and severity, and a no-effect level was not determined (see Table below). The change was not accompanied by any degeneration or inflammatory changes. The sponsor indicated that goblet cells produce mucus and its proliferation is adaptive response to high concentrations of particulate matter.

Table 4.
Overall Incidence of Eosinophilic Inclusions in the Respiratory and Olfactory Epithelium (Rat Carcinogenicity Study)

STATISTICAL COMPARISON WITH THE AIR CONTROL (GROUP 1)										
	Male					Female				
Group	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**
Dosage level	**0**	**Lac.**	**Low**	**Mid**	**High**	**0**	**Lac.**	**Low**	**Mid**	**High**
Goblet cell hyperplasia										
Total	1	0	4	4	12**	0	3	6*	9**	8**
Trace	0	0	4	4	5*	0	3	6*	9**	8**
Minimal	1	0	0	0	7*	0	0	0	0	0
Eosinophilic inclusions-respiratory epithelium										
Total	15	29**	51**	54**	52**	11	38**	54**	50**	52**
Trace	13	29**	26**	19	9	10	36**	17	12	17
Minimal	2	0	24**	32**	37**	1	2	37**	38**	34**
Moderate	0	0	1	3	6*	0	0	0	0	1
Eosinophilic inclusions-olfactory epithelium										
Total	15	17	52**	55**	52**	7	20**	51**	50**	51**
Trace	7	10	11	5	2	4	17**	8	7	7
Minimal	4	6	21**	13*	8	1	2	20**	16**	19**
Moderate	4	1	18**	35**	30**	2	1	18**	18**	24**
Marked	0	0	2	2	12**	0	0	5*	9**	1

STATISTICAL COMPARISON WITH THE VEHICLE CONTROL (GROUP 2)										
	Male					**Female**				
Group	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**
Dosage level	**0**	**Lac.**	**Low**	**Mid**	**High**	**0**	**Lac.**	**Low**	**Mid**	**High**
Goblet cell hyperplasia										
Total	1	0	4	4	12**	0	3	6	9	8
Trace	0	0	4	4	5*	0	3	6	9	8
Minimal	1	0	0	0	7**	0	0	0	0	0
Eosinophilic inclusions-respiratory epithelium										
Total	15	29	51**	54**	52**	11	38	54**	50**	52**
Trace	13	29	26	19	9	10	36	17	12	17
Minimal	2	0	24**	32**	37**	1	2	37**	38**	34**
Moderate	0	0	1	3	6*	0	0	0	0	1
Eosinophilic inclusions-olfactory epithelium										
Total	15	17	52**	55**	52**	7	20	51**	50**	51**
Trace	7	10	11	5	2	4	17	8	7	7
Minimal	4	6	21**	13	8	1	2	20**	16**	19**
Moderate	4	1	18**	35**	30**	2	1	18**	18**	24**
Marked	0	0	2	2	12**	0	0	5*	9**	1
Number nasal passages examined	55	55	55	55	55	55	55	55	55	55

*Fisher's Exact Test; * p<0.05 ** p<0.01 one-sided. Low, Middle and High Doses: 7.6, 15.1 and 30.2 mg/kg/day (Weeks 1-17); 14.2, 27.4 and 53.1 mg/kg/day (Weeks 17-104).*

Overall Respiratory Tract Pathology:

NOAEL, Margin of Safety & Relevance During Prophylactic Use

The NOAEL dose for histopathology findings in the respiratory tract (e.g., epithelial hyperplasia and loss of cilia) in the dog may be set at the low dose (0.93 mg/kg/day), which had a daily drug exposure of 1.28-2.22 ug.h/ml. In the rat, the NOAEL for these effects could also be set approximately at the low dose (14.2 mg/kg/day) that had exposure levels around 4.23 - 4.98 ug.h/ml. In comparison with human daily exposure (0.4 ug.h/ml), a margin of safety of 3.2-5.6 (dog vs. human) or 10.6-12.5 (rat vs. human) existed for these effects.

Clinical significance of the information on non-neoplastic hyperplasia and other cellular changes in the respiratory tract may become more relevant when the drug is given for long term (e.g., for prophylactic indications) than it is for short-term use (e.g., for treatment indications).

REPRODUCTIVE SYSTEM:

Since original NDA's approval, the Pregnancy category was changed from B to C, as of 1999 (IND 43,776 Submission 82). Please see current drug labeling for the update.

TOXICOLOGY OF IMPURITIES

The impurity profile for batches of zanamivir used in the toxicity studies demonstrates that animals received total doses of these impurities far in excess of clinical exposure.

TOXICOKINETICS

Because of zanavimir's short half-life and its straightforward urinary clearance, the drug exposure as measured by the toxicokinetics in all the repeat-dose toxicity studies (including the reprotoxicity studies and those using iv infusion techniques) did not show any accumulation. The drug accumulation as reflected by the successful maintenance of a significant trough level over the entire study period is important for eliciting meaningful toxicities, and is often achieved in other drug studies in which the toxicity profile and target organ of toxicity have been fully explored.

JUVENILE TOXICOLOGY

A Phase IV commitment juvenile dog study was completed in 2004. Daily inhalation administration of zanamivir to juvenile beagle dogs for 13 weeks at mean dose levels of 0.90, 3.47 and 9.76 mg/kg/day for males and 1.03, 5.48 and 11.03 mg/kg/day for females produced no treatment-related toxicity. The AUCt values ranged from undetected to 544 ng.h/ml at 1 mg/kg, 1204 to 5034 ng.h/ml at 4 mg/kg and 783 to 9245 ng.h/ml at 10 mg/kg.

DNA AND CHROMOSOME SYSTEMS

Zanamivir tested negative in the following genotoxic testing systems: AMES test, fluctuation test, yeast gene conversion assay, mouse lymphoma assay, in vitro chromosome aberration assay in human peripheral lymphocytes, and a micronucleus assay in mouse bone marrow.

CARCINO-

Carcinogenicity studies of lifetime duration (104 weeks) were performed by the

GENICITY

inhaled route in the B6C3F1 mouse (male: 26.6, 47.8 and 102 mg/kg/day; female: 28.0, 50.9 or 108 mg/kg/day) and Han Wistar rat (7.6, 15.1 and 30.2 mg/kg/day, Weeks 1-17; 14.2, 27.4 and 53.1 mg/kg/day, Weeks 17-104). An increase in lymphoblastic/lymphocytic lymphomas was observed in male rats exposed to 53.1mg/kg/day. The lymphomas were found wide-spread in various lymph nodes (e.g., cervical, tracheobronchial, mesenteric, axillary), and organs (e.g., lungs, liver, spleen). The distribution pattern suggests a highly metastatic nature of this tumor. The increase in lymphoma incidence was statistically significant when comparison was made with lactose controls ($p<0.017$), instead of with air controls ($p<0.084$). According to the FDA guidance document, for a common tumor (incidence≅1%) such as this one, the outcome was not considered to be significant and thus zanamivir is not considered carcinogenic.

ADME:

General PK Parameters.

Following iv administration to the rat, plasma clearance of zanamivir is rapid, showing a monophasic elimination with a half-life of approximately 15 minutes. In the dog, the half-life of zanamivir after intravenous administration is approximately 50 minutes. In both species, almost all of the drug is eliminated unchanged in the urine (≅95%) and therefore, renal clearance accounts for almost the total clearance of zanamivir. The renal clearance in the rat and dog is consistent with the fact that the drug has low protein binding. Low volumes of distribution in the rat and dog indicate that zanamivir distributes poorly and is unlikely to penetrate cell membranes to a significant extent. Human pharmacokinetics shared similar clearance and distribution profiles with the rat and dog.

Gender Difference in Exposure and Bioavailability.

No difference in the pharmacokinetics of zanamivir between male and female rat or dog following a single dose was seen (following repeat iv dose in the dog, exposure appeared to be higher in females than males at all dosages, but there were no gender-related differences in toxicity.) Following oral administration, zanamivir is poorly absorbed with a bioavailability of 3% in the rat and 10% in the dog (human=3%). Data from studies with radiolabelled zanamivir (iv) in the rat and dog show that plasma drug levels account for all of the radioactivity in the plasma, indicating that zanamivir does not undergo metabolism.

Distribution.

Radiolabelled zanamivir is widely distributed throughout the tissues with levels in the blood, kidney and bladder being the highest. Radioactive material is cleared rapidly from most tissues, although very low levels persist in the gastrointestinal tract contents. Low levels also appeared to persist in the eyes of pigmented animals. Chromatographic profiling of urine samples indicated that drug-related material consists entirely of unchanged zanamivir, with no evidence of any metabolites.

Placenta Transfer.

In pregnant rabbits, ^{14}C-zanamivir and drug-related material crossed the placental barrier and widely distributed throughout fetal tissues. Drug-related levels in the fetus were higher on day 12 of pregnancy that on day 20, indicating that the placental barrier is more permeable to drug-related material on day 12 than on day 20. The percentage of the administered dose recovered in the fetus was small,

ranging from 0.0006-0.0032%.

Excretion in Milk. Following iv ^{14}C- zanamivir (10mg/kg) to lactating rats, limited amounts of drug-related material partition into milk (Cmax in milk= 1ug equiv/mL at 0.5 hours post-dose, Cmax in maternal plasma= 10.1ug/equiv/ml).

Plasma Protein Binding and Metabolism. Zanamivir has low plasma proteins binding in rats, dogs and human. Plasma protein binding and the association with red blood cells in these species are also negligible. Zanamivir has no effect on metabolic pathways mediated by isozymes CYP1A1, CYP1A2, CYP2A6, CYP2C8/9/10, CYP2C18/19, CYP2D6, CYP2E1 or CYP3A4, and no significant changes in the levels of hepatic cytochrome P-450 isozymes at the end of a 5-week intravenous toxicity study in the rat were reported.

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/s/

Kuei Meng Wu
3/2/2006 09:57:51 AM
PHARMACOLOGIST

James Farrelly
3/2/2006 10:47:02 AM
PHARMACOLOGIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021036/S-008

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	21-036 / SE1-008
Drug Name:	RELENZA® (Inhaled zanamivir) 10 mg
Indication(s):	Prevention of Transmission of Symptomatic Influenza A and B Infections within Household and Community Dwellings
Applicant:	The GlaxoSmithKline group of companies
Dates:	Submitted: November 4, 2005 Received: November 30, 2005 Draft Review Completed: February 3, 2006 Final Review Completed: March 27, 2006
Review Priority:	Priority review
Biometrics Division:	Division of Biometrics III
Statistics Reviewer:	Fraser Smith, Ph.D., Mathematical Statistician
Concurring Reviewers:	Greg Soon, Ph.D., Statistics Team Leader
Medical Division:	Division of Antiviral Products
Clinical Team:	Andreas Pikis, M.D., Medical Reviewer Kimberly Struble, Pharm.D., Medical Team Leader
Project Manager:	David Araojo, Pharm.D., Regulatory Project Manager

Keywords: Influenza, Family/Household, Index Cases, Control Cases, Community, Nursing Home

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

There were four pivotal phase III clinical studies included in this application to support the use of inhaled zanamivir in both household and community settings for the prophylaxis of influenza. Of the four studies, two studies (NAI30010 and NAI30031) were conducted in household settings, and two studies (NAIA3005 and NAI30034) were conducted in community settings.

Overall, based on the data submitted, the following results were observed:

- In the two household studies (NAI30010 and NAI30031), 19.0% of the placebo households and 4.1% of the zanamivir households had at least one contact case that developed symptomatic, laboratory-confirmed influenza. The odds ratios representing the prophylactic effect of zanamivir vs. placebo were 0.18 in study NAI30010 and 0.17 in study NAI30031, both statistically significant with p-values <0.001.

- In the first community study (NAIA3005), 6% of subjects treated with zanamivir and 2% of the subjects in placebo arm developed symptomatic, laboratory-confirmed influenza; the odds ratio was 0.38 with p-value equal to 0.009.

- In the second community study (NAI30034), 1.4% of subjects treated with zanamivir and 0.2% in placebo arm developed symptomatic, laboratory-confirmed influenza; the odds ratio was 0.17 with p-value <0.001.

The effect of treating the contact cases with placebo or zanamivir in the first household study was confounded by the effect of giving the same treatment to the index cases. Index Cases did not receive randomized treatment in the second household study and the study results were not confounded.

Overall the two studies NAI30031 and NAI30010 together appear to have demonstrated the prophylactic effect of zanamivir on influenza in household settings and the two studies NAI30034 and NAIA3005 together appear to have demonstrated the prophylactic effect of zanamivir on influenza in community settings.

The following issues were raised by the statistical review team:

- Nearly identical rates were observed for the primary efficacy endpoint of laboratory-confirmed symptomatic influenza in the two household studies. Such a high degree of coincidence is rare. Similar trends were also apparent in the two studies for many of the secondary endpoints.

- The odds ratio obtained for the prophlyactic effect of zanamivir vs. placebo in the second community study was the same as the odds ratios in the two household studies (0.17 vs. 0.18 and 0.17) and much smaller than the odds ratio that was observed in the first community study (0.38).

- The results of the second community study were highly dependent on a small number of events (there were only 27 symptomatic, laboratory-confirmed cases of influenza). Therefore any kind of mistake or transcription error in the coding of patient identifiers or treatment codes can significantly alter the results.

Therefore on February 17, 2006 the review team requested copies of original source documents for serology in studies NAI30031 and NAI30034. We identified 149 patients with influenza-like illness (ILI) for this request. Among these 149 subjects, we identified placebo subjects with positive laboratory confirmation of influenza and zanamivir subjects without laboratory confirmation of influenza.

GlaxoSmithKline photocopied the original serology documents from the (b) (4) for the two new studies (NAI30031 and NAI30034) and provided copies to the Division of Antiviral Products (DAVP) on March 15, 2006. We examined the photocopies of the serology source documents and found them to be consistent with our data listings.

According to the minutes of a DAVP teleconference call with GlaxoSmithKline on March 9, 2006, the applicant stated that serology source documents were not available at the clinical investigator sites. Therefore the Division of Scientific Investigation (DSI) inspectors could not have checked the original source documents for serology when they inspected the clinical investigator sites. Therefore the results of the primary efficacy analyses and any secondary efficacy analyses of laboratory data could not have been verified and should be interpreted with caution.

1.2 Brief Overview of Clinical Studies

(b) (4)

Since that time, the applicant has conducted one further Phase III household study (NAI30031) and one further Phase III community study (NAI30034) evaluating zanamivir for safety and efficacy for prophylaxis.

Efficacy results will not be reviewed for the nursing home population since the current sNDA submission is not seeking an efficacy claim for nursing home patients and no new studies have been submitted for this population. (b) (4)

Phase III Prophylaxis Studies

Study	Number of Subjects (Intent-to-Treat Population)			Duration of Prophylaxis
	Placebo	Zanamivir	Rimantadine	
Primary Phase III Studies				
Family/Household				
NAI30010	168 (423)[1]	169 (414)[1]	N/A	10 days[2]
NAI30031	242 (630)[1]	245 (661)[1]	N/A	10 days[2]
Community				
NAIA3005	554	553	N/A	28 days[2]
NAI30034	1685	1678	N/A	28 days[2]
Secondary Phase III Studies				
Nursing Home				
NAIA3003	13[3]	238[3]	231[3]	14 days[2]
NAIA3004	252[3]	242[3]	N/A	14 days[2]

Source: Summary of Clinical Efficacy Table 1, Section 6.3 of the Clinical Study Reports for Studies NAI30010 and NAI30031
N/A = not applicable
1. Households (Contact cases)
2. 10mg of inhaled zanamivir, once daily
3. Includes all randomizations

1.3 Statistical Issues and Findings

The primary efficacy endpoint for the two phase III household studies was the proportion of randomized households in which at least one randomized contact case developed symptomatic, laboratory-confirmed influenza A or B infection.

The primary efficacy endpoint for the two phase III community studies was the proportion of subjects who developed symptomatic, laboratory-confirmed influenza A or B infection.

Symptomatic influenza was defined as the presence of at least two of the following influenza symptoms: fever (temperature ≥37.8º C)/feverishness (counted as two separate symptoms in studies NAIA3005 and NAI30010 and as one symptom in studies NAI30031 and NAI30034), cough, headache, sore throat, myalgia (studies NAIA3005 and NAI30010 only) or muscle/joint aches and pains (studies NAI30031 and NAI30034 only).

At least two symptoms must have been present concurrently for three consecutive Diary Card entries during Days 1-11 inclusive, but these did not need to be the same symptoms.

Laboratory confirmation of influenza infection in studies NAI30010 and NAI30031 was a positive result by any of the following methods: culture, seroconversion or polymerase chain reaction (PCR). Laboratory confirmation of influenza infection in studies NAIA3005 and NAI30034 was a positive result by either culture or seroconversion. Polymerase chain reaction (PCR) tests were not performed in study NAIA3005 and were only included as part of a secondary composite endpoint in study NAI30034.

The table below summarizes the results of the primary efficacy analyses for each of the four pivotal phase III clinical trials.

		Placebo	Zanamivir	p-value[4]	Odds Ratio[4] (95% CI)	Approximate Relative Risk[4] (95% CI)
Household	**Study NAI30010[1]**	N=168	N=169			
	Number (%) of households	32 (19.0%)	7 (4.1%)	<0.001	0.18 (0.06, 0.43)	0.21 (0.11, 0.43)
	Study NAI30031[1]	N=242	N=245			
	Number (%) of households	46 (19.0%)	10 (4.1%)	<0.001	0.17 (0.07, 0.37)	0.19 (0.10, 0.36)
Community	**Study NAIA3005[2]**	N=475	N=473			
	Number (%) of subjects	28 (6%)	11 (2%)	0.009	0.38 (0.1, 0.80)	0.40 (0.20, 0.76)
	Study NAI30034[3]	N=1685	N=1678			
	Number (%) of subjects	23 (1.4%)	4 (0.2%)	<0.001	0.17 (0.04, 0.50)	0.17 (0.07, 0.44)

[1] ITT Population
[2] Non-vaccinated population
[3] Excludes subjects vaccinated within 21 days of randomization or during the study
[4] Analyses were stratified by center for all study populations, except the ITT Population in Study NAIA3005 in which stratification was by vaccination status and center.

Based on our review of the collective data we conclude the following.

1. In the first household study (NAI30010), where the index case as well as contact cases in the household received study medication for influenza, 19.0% (32/168) of the placebo households had at least one contact case that developed symptomatic, laboratory-confirmed influenza compared to 4.1% (4/169) of the zanamivir households. This treatment difference was statistically significant ($p<0.001$).

2. In the second household study (NAI30031), where only the contact cases in the household received study medication for influenza, 19.0% (46/242) of the placebo households had at least one contact case that developed symptomatic, laboratory-confirmed influenza compared to 4.1% (10/245) of the zanamivir households. This treatment difference was statistically significant ($p<0.001$).

3. It was highly unusual to observe almost exactly the same percentage of placebo patients and almost exactly the same percentage of zanamivir patients with laboratory-confirmed influenza in the two household studies. Similar trends were also apparent in the two studies for many of the secondary endpoints.

4. The effect of treating the contact cases with placebo or zanamivir in the first household study was confounded by the effect of giving the same treatment to the index cases. Index Cases did not receive randomized treatment in the second household study.

5. (b) (4)

6. In the first community study (NAIA3005), consisting of subjects 18 years of age or older, living in a university community setting, 6% (34/554) of the placebo subjects developed symptomatic, laboratory-confirmed influenza compared to 2% (11/553) of the zanamivir subjects. This treatment difference was statistically significant ($p=0.009$).

7. Unlike the first community study, the second community study (NAI30034) consisted of subjects who were at high risk of complications from influenza. High risk was defined as subjects age 65 or older, subjects with diabetes mellitus and subjects with chronic disorders of the pulmonary or cardiovascular systems. In this study, 1.4% (23/1685) of the placebo subjects developed symptomatic, laboratory-confirmed influenza compared to 0.2% (4/1678) of the zanamivir subjects. This treatment difference was statistically significant ($p<0.001$).

8. Similar trends were observed in the two community studies for non-vaccinated subjects and for the per protocol population.

9. In contrast to the three other pivotal phase III trials, there was no significant difference between the percentage of placebo and zanamivir patients with signs and symptoms of influenza in the second community study (NAI30034). The percentage of subjects with signs and symptoms of influenza (irrespective of laboratory results) was nearly the same in both treatment groups (10% of the subjects in the placebo treatment group and 9% of the subjects in the zanamivir treatment group had signs and symptoms of influenza).

10. Once laboratory data were utilized, the observed prophylactic effect of zanamivir in the second community study was more significant than it was in the first community study. In addition the odds ratio from the second community study was the same as the odds ratios in the two household studies and much smaller than the odds ratio in the first community study. (The odds ratio was 0.38 in the first community study compared to only 0.17-0.18 in the other three studies.)

11. The results of the second community study were highly dependent on a small number of events (there were only 27 symptomatic, laboratory-confirmed cases of influenza). Therefore any kind of mistake or transcription error in the coding of patient identifiers or treatment codes could have significantly altered the results.

12. Therefore on February 17, 2006 we requested copies of original source documents for serology in studies NAI30031 and NAI30034. We identified 149 patients with influenza-like illness (ILI) for this request. Among these 149 subjects, we identified placebo subjects with positive laboratory confirmation of influenza and zanamivir subjects without laboratory confirmation of influenza.

13. GlaxoSmithKline photocopied the original serology documents from the (b) (4) for the two new studies (NAI30031 and NAI30034) and provided copies to the DAVP on March 16, 2006. We examined the photocopies of the serology source documents and found them to be consistent with our data listings.

14. According to the minutes of a DAVP teleconference call with GlaxoSmithKline on March 9, 2006, the applicant stated that serology source documents were not available at the clinical investigator sites. Therefore the Division of Scientific Investigation (DSI) inspectors could not have checked the original source documents for serology when they inspected the clinical investigator sites. Therefore the results of the primary efficacy analyses and any secondary efficacy analyses of laboratory data could not have been verified and should be interpreted with caution.

15. In each of the four pivotal studies, treatment differences in the proportion of contact cases/subjects that developed symptomatic laboratory-confirmed influenza were consistently lower in the zanimivir treatment group than in the placebo treatment group for whites, blacks and other races and different age groups.

2. INTRODUCTION

2.1 Overview

Three Phase III studies (NAIA3002, NAIB3002, and NAIB3001) provided the basis for the original New Drug Application (NDA 21-036) for the treatment of influenza A and B. This NDA was submitted on October 26, 1998 and was designated for a priority review. A meeting of the Antiviral Drug Products Advisory Committee to review the data from NDA 21-036 took place on February 24, 1999. As a result of an unfavorable vote on the data presented at the Advisory Committee, the applicant requested to provide further information, mainly statistical reanalyses, in order to complete the review. After a three month extension to the review, Relenza (zanamivir for inhalation) was approved on July 26, 1999.

A Supplemental NDA 21-036/S-001 was submitted on October 25, 1999 for an indication of zanamivir treatment of pediatric patients with influenza A and B. A single clinical trial (NAI30009) was provided for the basis of this indication. This supplement was given a priority review designation and was approved on April 26, 2000 for the treatment of pediatric patients 7 years or older.

On November 4, 2005 the current Supplemental NDA 21-036/S-008 was submitted to the FDA. sNDA 21-036/S-008 included the Phase III trials from the previous submission plus two additional Phase III trials (NAI30031 and NAI30034) to address the DAVDP's concerns about sNDA 21-036/S-002.

2.2 Data Sources

This statistical review is based on data submitted for Studies NAIA3005, NAI30010, NAI30031 and NAI30034.

The electronic submission of the NDA can be found in the FDA, Center for Drug Evaluation and Research (CDER) internal network directory of

\\Cdsesub1\n21036\S_008\2005-11-04\N021036.

The electronic datasets and programs can be found in the FDA, CDER, internal network directory \\Cdsesub1\n21036\S_008\2005-11-21.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

The applicant's phase III clinical trials were evaluated in family/household settings (NAI30010, NAI30031), community settings (NAIA3005, NAI30034) and in nursing homes (NAIA3003, NAIA3004).

The six phase III studies were randomized, double-blind controlled studies to evaluate the safety and efficacy of zanamivir 10mg inhalation once daily in the prevention of influenza. With the exception of study NAIA3003, all phase III studies were placebo-controlled. Standard of care was used as the control for study NAIA3003. Rimantadine was considered as the standard of care for influenza A outbreaks while placebo was considered as the standard of care for influenza B outbreaks.

The duration of prophylaxis varied among studies between 10 and 28 days and was determined by the expected duration of risk, which is shorter in contacts of a single case or in a closed community, and longer where influenza is spreading through a relatively large community.

Symptoms, temperature, study/relief medication taken and ability to perform normal activities were recorded in a diary card.

Efficacy results will be reviewed for the two family/household studies and for the two community setting studies.

Efficacy results will not be reviewed for the nursing home population since the current sNDA submission is not seeking an efficacy claim for nursing home patients and no new studies have been submitted for this population. (b) (4)

3.1.1 Study Design

Phase III Prophylaxis Studies

Study	Number of Subjects (Intent-to-Treat Population)			Duration of Prophylaxis
	Placebo	Zanamivir	Rimantadine	
Primary Phase III Studies				
Family/Household				
NAI30010	168 (423)[1]	169 (414)[1]	N/A	10 days[2]
NAI30031	242 (630)[1]	245 (661)[1]	N/A	10 days[2]
Community				
NAIA3005	554	553	N/A	28 days[2]
NAI30034	1685	1678	N/A	28 days[2]
Secondary Phase III Studies				
Nursing Home				
NAIA3003	13[3]	238[3]	231[3]	14 days[2]
NAIA3004	252[3]	242[3]	N/A	14 days[2]

Source: Summary of Clinical Efficacy Table 1, Section 6.3 of the Clinical Study Reports for Studies NAI30010 and NAI30031
N/A = not applicable
1. Households (Contact cases)
2. 10mg of inhaled zanamivir, once daily
3. Includes all randomizations

Family/Household Prophylaxis Studies:

Two phase III studies were conducted in the family/household setting to assess the efficacy and safety of a 10-day course of once-daily inhaled zanamivir 10mg versus

placebo in the prevention of influenza A and B.

NAI30010 was conducted predominantly in the United States, while over half of the subjects recruited to study NAI30031 were from other countries. Families must have been comprised of two to five members with at least one adult and one child 5-17 years old. The first subject to be identified as having influenza-like-illness ILI) was designated as the index case.

Once the index case was identified, the other healthy contacts in the household were randomized (within 1.5 days of symptom onset in the index case) to inhaled zanamivir 10mg or placebo once daily for 10 days. All randomized contacts in the family/household were allocated to the same treatment group. Children <5 years of age were enrolled but did not receive study drug.

Index cases in NAI30010 were allocated to the same treatment group as the other family contacts, and received the standard treatment regimen (inhaled zanamivir 10mg or placebo twice daily for 5 days). Unlike study NAI30010, index cases in study NAI30031 were not treated with zanamivir or placebo, but received relief medications for supportive care (acetaminophen and cough syrup).

Subjects completed diary cards for 14 days (or 28 days if symptoms were still present on Day 14) to record study drug administration, symptom assessments, temperature and relief medication use.

Community Prophylaxis Studies:

NAIA3005 and NAI30034 were both Phase III phophylaxis studies that evaluated the efficacy and safety of inhaled zanamivir 10 mg administered once a day for 28 days in the prevention of influenza in contacts living in the same community.

Study NAIA3005 was conducted in subjects ≥17 years of age a college/community setting at two centers in the United States. Less than 15% of the subjects in this study were vaccinated for the current influenza season.

Study NAI30034 was conducted in high risk subjects in the US during the 2000-2001 influenza season. The majority of the subjects in this study were ≥ 65 years of age and 2/3 of the subjects in study NAI30034 had been vaccinated. This study was conducted during a season with low influenza activity, so large numbers of high-risk subjects were required to be enrolled to obtain relatively few influenza cases.

3.1.2 Methods for Statistical Analysis of Efficacy Data

The **Intent-to-Treat (ITT)** population was defined as all randomized subjects, regardless of whether study drug was received or whether the subject completed the planned duration of the study. In studies NAI30010 and NAI30031 subjects who were <5 years of age were excluded from this population because they did not take the study drug.

The **Non-Vaccinated** population was defined only for Study NAIA3005 and included all randomized subjects who had not received vaccine for the current season and who took at least one dose of study medication. Non-vaccinated, randomized subjects were excluded if there was clear evidence of failure to take study medication.

In studies NAI30010 and NAI30031, the **Index Influenza Positive** population included all randomized family members in families/households where the index case had laboratory confirmation of influenza infection. This was a secondary population for the assessment of efficacy.

Populations Used in Efficacy Analyses in the Phase III Prophylaxis Studies

	Intent-to-Treat	Non-Vaccinated	Index Influenza Positive
Primary Phase III Studies			
Family/Household			
NAI30010	Primary	n/a	Secondary
NAI30031	Primary	n/a	Secondary
Community			
NAIA3005	Secondary	Primary	n/a
NAI30034	Primary	n/a	n/a
Secondary Phase III Studies			
Nursing Home			
NAIA3003	Primary	n/a	n/a
NAIA3004	Primary	n/a	n/a

Source: Summary of Clinical Efficacy Table 2

The primary population was prospectively defined to be the Intent-to-Treat (ITT) population in all but one of the six phase III studies. The non-vaccinated population was designated as the primary population in the first community study (NAIA3005). The protocol for the second community study (NAI30034) was amended to exclude serology results for the primary endpoint

if the subject had been vaccinated either within 21 days prior to randomization or during the study.

Influenza-like Symptoms (at least two) Required for the Primary Endpoint: Family/Household and Community Studies

ILI Symptoms	Family/Household Studies		Community Studies	
	NAI30010	NAI30031	NAIA3005	NAI30034
Fever ≥37.8°C	X		X	
Feverishness	X		X	
Fever ≥37.8°C or feverishness		X		X
Cough	X	X	X	X
Headache	X	X	X	X
Sore throat	X	X	X	X
Myalgia	X		X	
Muscle/joint aches and pains		X		X

Source: Summary of Clinical Efficacy Table 3

The primary efficacy endpoint for the two phase III household studies was the proportion of randomized households in which at least one randomized contact case developed symptomatic, laboratory-confirmed influenza A or B infection.

The primary efficacy endpoint for the two phase III community studies was the proportion of subjects who developed symptomatic, laboratory-confirmed influenza A or B infection.

Symptomatic influenza was defined as the presence of at least two of the following influenza symptoms: fever (temperature ≥37.8º C)/feverishness (counted as two separate symptoms in studies NAIA3005 and NAI30010 and as one symptom in studies NAI30031 and NAI30034), cough, headache, sore throat, myalgia (studies NAIA3005 and NAI30010 only) or muscle/joint aches and pains (studies NAI30031 and NAI30034 only).

At least two symptoms must have been present concurrently for three consecutive Diary Card entries during Days 1-11 inclusive, but these did not need to be the same symptoms.

Laboratory confirmation of influenza infection in studies NAI30010 and NAI30031 was a positive result by any of the following methods: culture, seroconversion or polymerase chain reaction (PCR). Laboratory confirmation of influenza infection in studies NAIA3005 and NAI30034 was a positive result by either culture or seroconversion. Polymerase chain reaction (PCR) tests were not performed in study NAIA3005 and were only included as part of a secondary composite endpoint in study NAI30034.

Serology samples were supposed to be collected for all patients on day 1 and on day 30 for patients with no ILI. For patients with ILI between Day 8 and Day 35, serology samples were supposed to have been collected 21 days from the day on which patients first presented with ILI or on Day 49 (whichever day occurred first).

Serology seroconversion tests were performed for [redacted] (b) (4)

Virus culture and PCR samples were obtained from a throat swab, throat/nasal swab, nasopharyngeal swab, nasal wash or nasal aspirate. These samples were supposed to be collected from all subjects within 48 hours of any ILI.

PCR seroconversion tests were performed by [redacted] (b) (4) while culture seroconversion tests were performed by [redacted] (b) (4)

3.1.3 Patient Disposition

**Summary of Contact Cases Who Discontinued Study NAI30010:
Intent-to-Treat Population**

n (%)	Placebo N=423	Zanamivir N=414
Discontinued the Study Prematurely	5 (1%)	3 (<1%)
Completed Study	418 (99%)	411 (99%)
Reason for Premature Discontinuation:		
Adverse event	0	1 (<1%)
Consent Withdrawn	1 (<1%)	0
Lost to follow-up	2 (<1%)	1 (<1%)
Protocol Violation	2 (<1%)	1 (<1%)

Source: Section 6.1 of the Clinical Study Report

Only 1% of the contact cases and index cases discontinued prematurely from study NAI30010.

**Summary of Index Cases Who Discontinued Study NAI30010:
Intent-to-Treat Population**

n (%)	Placebo N=158	Zanamivir N=163
Discontinued the Study Prematurely	2 (1%)	1 (<1%)
Completed Study	156 (99%)	162 (99%)
Reason for Premature Discontinuation:		
Adverse event	0	0
Consent Withdrawn	0	0
Lost to follow-up	1 (<1%)	1 (<1%)
Protocol Violation	1 (<1%)	0

Source: Section 6.1 of the Clinical Study Report

Summary of Contact Cases Who Discontinued Study Medication in Study NAI30010: Intent-to-Treat Population

n (%)	Placebo N=423	Zanamivir N=414
No. who Discontinued Trial Medication Prematurely	7 (2%)	9 (2%)
Completed Study Medication	416 (98%)	405 (98%)
Reason for Premature Discontinuation:		
Adverse event	1 (<1%)	2 (<1%)
Consent Withdrawn	1 (<1%)	0
Lost to follow-up	2 (<1%)	0
Protocol Violation	2 (<1%)	1 (<1%)
Other	1 (<1%)	6 (1%)

Source: Section 6.1 of the Clinical Study Report

Only 2% of the contact cases and <1% of the index cases discontinued trial medication in study NAI30010.

Summary of Index Cases Who Discontinued Study Medication in Study NAI30010: Intent-to-Treat Population

n (%)	Placebo N=158	Zanamivir N=163
No. who Discontinued Trial Medication Prematurely	1 (<1%)	1 (<1%)
Completed Study Medication	157 (99%)	162 (99%)
Reason for Premature Discontinuation:		
Adverse event	0	0
Consent Withdrawn	0	0
Lost to follow-up	1 (<1%)	0
Protocol Violation	0	0
Other	0	1 (<1%)

Source: Section 6.1 of the Clinical Study Report

Summary of Contact Cases Who Discontinued Study NAI30031: Intent-to-Treat Population

n (%)	Placebo N=630	Zanamivir N=661
Discontinued the Study Prematurely	11 (2%)	6 (<1%)
Completed Study	619 (98%)	655 (99%)
Reason for Premature Discontinuation:		
Adverse event	0	0
Consent Withdrawn	6 (<1%)	2 (<1%)
Lost to follow-up	2 (<1%)	2 (<1%)
Protocol Violation	2 (<1%)	1 (<1%)
Other	1 (<1%)	1 (<1%)

Source: Section 6.1.1 of the Clinical Study Report

Only 2% of the placebo contact and index cases and <1% of the zanamivir contact cases and 1% of the zanamivir index cases discontinued prematurely from study NAI30031.

Summary of Index Cases Who Discontinued Study NAI30031: Intent-to-Treat Population

n (%)	Placebo N=242	Zanamivir N=245
Discontinued the Study Prematurely	4 (2%)	3 (1%)
Completed Study	238 (98%)	242 (99%)
Reason for Premature Discontinuation:		
Adverse event	0	0
Consent Withdrawn	3 (1%)	1 (<1%)
Lost to follow-up	1 (<1%)	1 (<1%)
Protocol Violation	0	1 (<1%)

Source: Supporting Table 27 of the Clinical Study Report

Summary of Contact Cases Who Discontinued Study Medication in Study NAI30031: Intent-to-Treat Population

N (%)	Placebo N=630	Zanamivir N=661
No. who Discontinued Trial Medication Prematurely	18 (3%)	8 (1%)
Completed Study Medication	612 (97%)	653 (99%)
Reason for Premature Discontinuation:		
Adverse event	4 (<1%)	1 (<1%)
Consent Withdrawn	5 (<1%)	2 (<1%)
Lost to follow-up	1 (<1%)	0
Protocol Violation	2 (<1%)	2 (<1%)
Other	6 (<1%)	3 (<1%)

Source: Section 6.1.2 of the Clinical Study Report

Only 3% of the contact cases and 1% of the index cases discontinued trial medication in study NAI30031.

Summary of Subjects Who Discontinued Study NAIA3005: Intent-to-Treat Population

n (%)	Placebo N=554	Zanamivir N=553
Discontinued the Study Prematurely	17 (3%)	10 (2%)
Completed Study	537 (97%)	543 (98%)
Reason for Premature Discontinuation:		
Adverse event	6 (1%)	4 (<1%)
Consent Withdrawn	3 (<1%)	1 (<1%)
Lost to follow-up	7 (1%)	5 (<1%)
Other	1 (<1%)	0

Source: Section 6.1 of the Clinical Study Report

In study NAIA3005, 3% of the placebo subjects and 2% of the zanamivir subjects discontinued from the study prematurely.

The main reasons for discontinuation from the study were adverse events and lost to follow-up.

Summary of Subjects Who Discontinued Study Medication in Study NAIA3005: Intent-to-Treat Population

N (%)	Placebo N=554	Zanamivir N=553
No. who Discontinued the Trial Medication Prematurely	73 (13%)	60 (11%)
Completed Study Medication	481 (87%)	493 (89%)
Reason for Premature Discontinuation:		
Adverse event	7 (1%)	4 (<1%)
Consent Withdrawn	4 (<1%)	2 (<1%)
Lost to follow-up	6 (<1%)	4 (<1%)
Other	56 (10%)	50 (9%)

Source: Section 6.1 of the Clinical Study Report

In study NAIA3005, 13% of the placebo subjects and 11% of the zanamivir subjects discontinued trial medication prematurely.

The majority of subjects who discontinued study medication did so for other reasons. The majority of subjects who discontinued for other reasons ran out of study medication on the last day because an additional dose was inadvertently taken on a previous study day.

Summary of Subjects Who Discontinued Study NAI30034: Intent-to-Treat Population

	Placebo (N=1685) n (%)	**Zanamivir** (N=1678) n (%)
Completed study:	1594 (95%)	1595 (95%)
Discontinued study prematurely:	91 (5%)	83 (5%)
Reason for premature discontinuation:		
Adverse event	36 (2%)	32 (2%)
Consent withdrawn	34 (2%)	29 (2%)
Lost to follow-up	5 (<1%)	4 (<1%)
Protocol Violation	7 (<1%)	6 (<1%)
Other	9 (<1%)	11 (<1%)
Missing	0	1 (<1%)

Source: Table 4 of the Clinical Study Report

In study NAI30034, 5% of the placebo and zanamivir subjects discontinued from the study prematurely.

The main reasons for discontinuation from the study were adverse events and withdrawal of consent. The main reasons for discontinuation of study medication were adverse events, protocol violations and other reasons.

Summary of Subjects Who Discontinued Study Medication in Study NAI30034: Intent-to-Treat Population

	Placebo (N=1685) n (%)	**Zanamivir** (N=1678) n (%)
Completed study drug:	1493 (89%)	1495 (89%)
Discontinued study drug prematurely:	192 (11%)	183 (11%)
Reason for premature discontinuation of study drug:		
Adverse event	46 (3%)	41 (2%)
Consent withdrawn	30 (2%)	27 (2%)
Lost to follow-up	4 (<1%)	3 (<1%)
Protocol Violation	51 (3%)	51 (3%)
Other	61 (4%)	61 (4%)

Source: Table 5 of the Clinical Study Report

Eleven percent (11%) of the placebo and zanamivir subjects discontinued study medication prematurely. The main reasons for discontinuation of study medication were adverse events, protocol violations, withdrawal of consent and other reasons. The majority of patients who discontinued study medication prematurely due to other reasons did so because they used the medication twice a day or took too many doses at one time.

Summary of Populations for Study NAI30010

	n	Placebo	Zanamivir
Intent-to-Treat Population (subjects ≥ 5 years of age)	Families	168	169
	Index Cases	158	163
	Contact Cases	423	414
Index Influenza Positive Population (subjects ≥ 5 years of age)	Families	87	78
	Index Cases	81	76
	Contact Cases	215	195
Per Protocol Population (subjects ≥ 5 years of age)	Families	164	165
	Index Cases	152	157
	Contact Cases	402	384
Safety Population (subjects ≥ 5 years of age)	Index Cases	160	161
	Contact Cases	430	407
Non-Treated Subjects (subjects < 5 years of age)	Index Cases	10	6
	Contact Cases	7	8

Source: Section 6.3 of the Clinical Study Report

The **Intent-to-Treat (ITT)** population was defined as all randomized subjects, regardless of whether study drug was received or whether the subject completed the planned duration of the study. In studies NAI30010 and NAI30031 subjects who were <5 years of age were excluded from this population because they did not take the study drug.

The **Index Influenza Positive** population included all randomized family members in families/households where the index case had laboratory confirmation of influenza infection. This was a secondary population for the assessment of efficacy.

The **Per-Protocol** population included all randomized contact cases who had no major protocol deviations. A household was excluded from the Per-Protocol population if all the randomized household members had a protocol deviation or if the index case had a protocol deviation. This was a secondary population for the assessment of efficacy.

The **Safety** population included all contact cases randomized to treatment who took at least one dose of study medication. Randomized subjects were only excluded if there was clear evidence of failure to take study medication.

Non-Treated Subjects consisted of all subjects <5 years of age. In study NAI30010 none of the index cases or contact cases <5 years of age were to be treated. In study NAI30031, none of the contact cases <5 years of age and none of the index cases were to be treated. The Non-Treated Subjects were not included in any of the other populations in studies NAI30010 and NAI30031.

Summary of Populations for Study NAI30031

	n	Placebo	Zanamivir
Intent-to-Treat Population	Total Households Contact Cases	242 630	245 661
Index Influenza Positive Population	Total households Contact Cases	153 398	129 368
Per Protocol Population	Total Households Contact Cases	228 568	232 603
Safety Population	Contact Cases	629	661
Non-Treated Subjects	Index Cases	242	245

Source: Section 6.3 of the Clinical Study Report

Summary of Populations for Study NAIA3005

	Placebo n	Zanamivir n
Intent-to-Treat Population	554	554
Safety Population	554	553
Non-Vaccinated Population	475 (86%)	473 (86%)
Per Protocol Population	439 (79%)	452 (82%)

Source: Section 6.3 of the Clinical Study Report

The **Non-Vaccinated** population was defined only for Study NAIA3005 and included all randomized subjects who had not received vaccine for the current season and who took at least one dose of study medication. Non-vaccinated, randomized subjects were excluded if there was clear evidence of failure to take study medication.

Summary of Populations in Study NAI30034

	Placebo n	Zanamivir n
Intent-to-Treat Population	1685	1678
Safety Population	1685	1678
Per Protocol Population	1417	1440

Source: Table 2 of the Clinical Study Report

3.1.4 Demographics and Baseline Characteristics

Summary of Baseline Demography and Vaccination Status: Family/Household Studies (Contact Cases, ITT Population)

	NAI30010	NAI30031
Sex - males, n (%) - females, n (%)	 376 (45) 461 (55)	 592 (46) 699 (54)
Age - mean (years)	26.2	27.3
Vaccinated prior to randomization, n (%)	135 (16)	132 (10)
Race - White, n (%) - Black, n (%) - Asian, n (%) - American Hispanic, n (%) - Other, n (%)	 749 (89) 45 (5) 9 (1) 13 (2) 21 (3)	 1210 (94) 26 (2) 31 (2) 12 (<1) 12 (<1)

Source: Summary of Clinical Efficacy Table 7

Approximately 45% of the subjects in each of the two household studies were male. The mean age was 26 years in study NAI30010 and 27 years in study NAI30031.

Sixteen percent (16%) of the subjects in study NAI30010 and 10% of the subjects in study NAI30031 were vaccinated prior to randomization.

Approximately 90% of the subjects in study NAI30010 were white, while 5% were black, 2% were American Hispanic, 1% were Asian and the remaining 3% were other races.

Approximately 95% of the subjects in study NAI30031 were white, while 2% were black and 2% were Asian.

Summary of Baseline Demography and Vaccination Status: Community Studies (ITT Population)

	NAIA3005	NAI30034
Sex - males, n (%) - females, n (%)	 449 (41) 658 (59)	 1417 (42) 1946 (58)
Age - mean (years)	28.8	60.4
Vaccinated prior to randomization, n (%)	159 (14)	1819 (54)
Race - White, n (%) - Black, n (%) - Asian, n (%) - American Hispanic, n (%) - Other, n (%)	 915 (83) 80 (7) 59 (5) 17 (2) 36 (3)	 3135 (93) 122 (4) 19 (<1) 76 (2) 11 (<1)

Source: Summary of Clinical Efficacy Table 11

Approximately 40% of the subjects in each of the two household studies were male. The mean age in the first community study (NAIA3005) was 29 years of age while the mean age in the second community study (NAI30034) was 60 years of age.

Fourteen percent (14%) of the subjects in study NAIA3005 were vaccinated prior to randomization while 54% of the subjects in NAI30034 were vaccinated at least 21 days prior to randomization. An additional 13% of the subjects in study NAI30034 were vaccinated within 21 days of randomization or post-randomization. (Source: Table 13 of the CSR.)

Eighty-three percent (83%) of the subjects in study NAIA3005 were white while 7% were black, 5% were Asian, 2% were American Hispanic and 3% were other races.

Ninety-three percent (93%) of the subjects in study NAI30034 were white while 4% were black and 2% were American Hispanic.

Summary of Households/Contact Cases Randomised by Country for Study NAI30031

	Country	Placebo (N)	Zanamivir (N)	Total (N)
Total	Households	242	245	487
	Contact Cases	630	661	1291
Canada	Households	8	8	16
	Contact Cases	22	25	47
USA	Households	116	119	235
	Contact Cases	280	303	583
Czech Republic	Households	9	9	18
	Contact Cases	26	25	51
Finland	Households	19	18	37
	Contact Cases	48	52	100
France	Households	22	25	47
	Contact Cases	71	74	145
Latvia	Households	3	1	4
	Contact Cases	6	2	8
Sweden	Households	17	15	32
	Contact Cases	42	36	78
United Kingdom	Households	2	2	4
	Contact Cases	7	6	13
Australia	Households	13	15	28
	Contact Cases	33	36	69
New Zealand	Households	2	1	3
	Contact Cases	3	1	4
South Africa	Households	31	32	63
	Contact Cases	92	101	193

Source: Section 6.1 of the Clinical Study Report

The first household study (NAI30010) enrolled subjects from the United States, Canada, the UK and Finland.

The second household study (NAI30031) enrolled subjects from 11 countries; the majority of subjects came from the United States, South Africa, France and Finland.

The first community study (NAIA3005) only enrolled patients from two sites in the United States while the second community study (NAI30034) was conducted in the United States, Canada, France, the Czech Republic, Germany and Latvia.

Summary of High-Risk Conditions and Severity for Subjects in Study NAI30034 (ITT Population)

	Placebo (N=1685)	**Zanamivir** (N=1678)	**Total** (N=3363)
Elderly (aged ≥65 years), n (%)	950 (56%)	946 (56%)	1896 (56%)
Respiratory Disease, n (%)	695 (41%)	684 (41%)	1379 (41%)
Asthma, n (%)	582 (35%)	564 (34%)	1146 (34%)
Mild, n (%)	329 (57%)	306 (54%)	635 (55%)
Moderate, n (%)	252 (43%)	258 (46%)	510 (45%)
Severe[a], n (%)	1 (<1%)	0	1 (<1%)
COPD, n (%)	139 (8%)	147 (9%)	286 (9%)
Mild, n (%)	62 (45%)	63 (43%)	125 (44%)
Moderate, n (%)	51 (37%)	52 (35%)	103 (36%)
Severe, n (%)	26 (19%)	32 (22%)	58 (20%)
Cardiovascular Disease, n (%)	307 (18%)	331 (20%)	638 (19%)
Mild, n (%)	164 (53%)	182 (55%)	346 (54%)
Moderate, n (%)	132 (43%)	133 (40%)	265 (42%)
Severe, n (%)	11 (4%)	16 (5%)	27 (4%)
Diabetes, n (%)	370 (22%)	359 (21%)	729 (22%)
Insulin dependent, n (%)	108 (29%)	127 (35%)	235 (32%)
Non-insulin dependent[b], n (%)	261 (71%)	232 (65%)	493 (68%)

Source: Table 9 and 10 of the Clinical Study Report
a Subject had severe asthma condition, but was not considered sufficiently severe at baseline to be a protocol violator.
b Subjects receiving oral medication for diabetes.

Fifty-six percent (56%) of the high-risk subjects in study NAI30034 were elderly (aged ≥ 65 years), 41% had respiratory disease, 34% had asthma, 9% had COPD, 19% had cardiovascular disease, and 22% had diabetes.

Summary of Other Medical Conditions For Subjects in Study NAI30034 (ITT Population)

	Placebo (N=1685)	Zanamivir (N=1678)	Total (N=3363)
Other Medical Conditions, n (%)	1685 (100%)	1678 (100%)	3363 (100%)
Endocrine Disease, n (%)	101 (6%)	93 (6%)	194 (6%)
Hepatic Disease, n (%)	19 (1%)	21 (1%)	40 (1%)
Neurological Disease, n (%)	73 (4%)	81 (5%)	154 (5%)
Renal Disease, n (%)	28 (2%)	35 (2%)	63 (2%)
Other, n (%)	869 (52%)	904 (54%)	1773 (53%)

Source: Table 11 of the Clinical Study Report

In addition, 6% of the high-risk subjects in study NAI30034 had endocrine disease, 5% had neurological disease, 2% had renal disease, 1% had hepatic disease and 53% had other diseases.

3.1.5 Applicant's Results and Statistical Reviewer's Findings

3.1.5.1 Primary Efficacy Analyses of Relative Risk of Laboratory-Confirmed, Symptomatic Influenza

Placebo and Zanamivir treatment groups were compared using stratified relative odds ratios and corresponding p-values and exact 95% confidence intervals with proc stratify in (b) (4) Approximate stratified relative risks were computed using proc freq.

Analyses were stratified by center for all study populations, except the ITT Population in Study NAIA3005 in which stratification was by vaccination status and center.

The applicant used proc freq in version 6 of SAS to compute approximate CMH confidence intervals for the relative risk. Results were similar to those computed by the statistical reviewer using proc freq in version 8 of SAS with only slight differences in the 95% confidence intervals for the approximate relative risk [e.g., (0.10, 0.47) instead of (0.11, 0.43) for study NAI30010 and (0.09, 0.39) instead of (0.10, 0.36) for study NAI30031].

Summary of Primary Efficacy Analysis - Relative Risk of Laboratory-Confirmed, Symptomatic Influenza: NAI30010 (ITT Population)

	Placebo N=168	Zanamivir N=169
Families/households with symptomatic, laboratory-confirmed influenza; symptoms any time from Day 1 to Day 11		
Present in at least one contact case, n (%)	32 (19.0)	7 (4.1)
Not present, n (%)	136 (81.0)	162 (95.9)
Treatment comparison		
Relative odds (95% CI)	0.18	(0.06, 0.43)
p-value		<0.001
Approximate relative risk[1] (95% CI)	0.21	(0.11, 0.43)

Source: Summary of Clinical Efficacy Table 8
1. Approximate relative risk = risk on zanamivir/risk on placebo

Nineteen percent (19.0%) of the households in the placebo treatment group in studies NAI30010 and NAI30031 had symptomatic, laboratory-confirmed influenza in at least one contact case while 4.1% of the households in the zanamivir treatment group in studies NAI30010 and NAI30031 had symptomatic, laboratory-confirmed influenza in at least one contact case.

The zanamivir treatment effect was highly significant ($p<0.001$, odds ratios and relative risks were approximately 0.20) in both studies.

Summary of Primary Efficacy Analysis - Relative Risk of Laboratory-Confirmed, Symptomatic Influenza: NAI30031 (ITT Population)

	Placebo N=242	Zanamivir N=245
Families/households with symptomatic, laboratory-confirmed influenza; symptoms any time from Day 1 to Day 11		
Present in at least one contact case, n (%)	46 (19.0)	10 (4.1)
Not present, n (%)	196 (81.0)	235 (95.9)
Treatment comparison		
Relative odds (95% CI)	0.17	(0.07, 0.37)
p-value		<0.001
Approximate relative risk[1] (95% CI)	0.19	(0.10, 0.36)

Source: Summary of Clinical Efficacy Table 9
1. Approximate relative risk = risk on zanamivir/risk on placebo

Summary of Primary Efficacy Analysis - Relative Risk of Laboratory-Confirmed, Symptomatic Influenza: NAIA3005

	ITT Population		Non-Vaccinated Population	
	Placebo N=554	**Zanamivir** N=553	**Placebo** N=475	**Zanamivir** N=473
Symptomatic, laboratory-confirmed influenza (any days)				
Present, n (%)	34 (6)	11 (2)	28 (6)	11 (2)
Not identified, n (%)	520 (94)	542 (98)	447 (94)	462 (98)
Treatment comparison				
Relative odds (95% CI)	0.31 (0.14, 0.64)		0.38 (0.17, 0.80)	
p-value	<0.001		0.009	
Approximate relative risk[1] (95% CI)	0.33 (0.17, 0.61)		0.40 (0.20, 0.76)	

Source: Summary of Clinical Efficacy Table 12
1. Approximate relative risk = risk on zanamivir/risk on placebo

In study NAIA3005, 6% of the placebo subjects developed laboratory-confirmed, symptomatic influenza compared to only 2% of the zanamivir subjects ($p<0.001$ in the ITT population and $p=0.009$ in the primary non-vaccinated population).

Summary of Primary Efficacy Analysis - Relative Risk of Laboratory-Confirmed, Symptomatic Influenza: NAI30034 (ITT Population)

	Placebo N=1685	**Zanamivir** N=1678
Symptomatic influenza confirmed by culture/serology (Days 1 to 28)		
Present, n (%)	23 (1.4)	4 (0.2)
Not identified, n (%)	1662 (98.6)	1674 (99.8)
Treatment comparison		
Relative odds (95% CI)	0.17 (0.04, 0.50)	
p-value	<0.001	
Approximate relative risk[1] (95% CI)	0.17 (0.07, 0.44)	

Source: Summary of Clinical Efficacy Table 13
1. Approximate relative risk = risk on zanamivir/risk on placebo

In the second community study NAIA3034, 1.4% of the placebo subjects developed laboratory-confirmed, symptomatic influenza compared to only 0.2% of the zanamivir subjects ($p<0.001$).

3.1.5.2 Robustness of Primary Efficacy Analyses

Summary of Applicant's Sensitivity Analysis Data for Households/Subjects in which at Least One Contact Case Developed Laboratory-Confirmed Influenza (ITT Population)

Study	Number of Households / Subjects with Influenza, Including Imputed Events			Approximate Relative Risk[1] (95% CI)
	Placebo n (%)	Zanamivir n (%)	p-value	
NAI30010[2]	33 (20)	8 (5)	<0.001	0.24 (0.12, 0.46)
NAI30031[2]	48 (20)	11 (4)	<0.001	0.20 (0.11, 0.37)
NAIA3005[3]	36 (6)	12 (2)	<0.001	0.34 (0.18, 0.62)
NAI30034[3]	25 (1)	6 (<1)	<0.001	0.24 (0.11, 0.54)

Source: Summary of Clinical Efficacy Table 20
1. Approximate relative risk = risk on zanamivir/risk on placebo
2. Events for families/households with missing data were imputed at the placebo rate for both treatment groups, rounding up to the nearest integer, if necessary.
3. Events for subjects who withdrew without developing influenza are imputed at the placebo rate for both treatment groups, rounding up to the nearest integer, if necessary

The applicant performed sensitivity analyses for missing data assuming events for families/households/subjects with missing data could be imputed using the placebo rate for both treatment groups.

The reviewer performed additional sensitivity analyses assuming 1, 2 and 3 times the placebo incidence rates for contact cases / subjects who discontinued from the study. The zanamivir treatment effect remained highly significant using these assumptions.

The results of the applicant's and reviewer's analyses demonstrated that the primary efficacy analyses are robust to reasonable assumptions regarding missing data.

Summary of Reviewer's Sensitivity Analysis Data for Contact Cases/Subjects in which at Least One Contact Case Developed Laboratory-Confirmed Influenza (ITT Population)

Events for contact cases / subjects who discontinued with missing data were imputed at 1 × the placebo rate for both treatment groups, rounding up to the nearest integer.

Study	Number of Contact Cases/Subjects with Influenza, Including Imputed Events			Approximate Relative Risk[1] (95% CI)
	Placebo n / N (%)	Zanamivir n / N (%)	p-value	
NAI30010	41 / 423 (10)	8 / 414 (2)	<0.001	0.20 (0.09, 0.42)
NAI30031	56 / 630 (9)	13 / 661 (2)	<0.001	0.22 (0.12, 0.40)
NAIA3005	36 / 554 (6)	12 / 553 (2)	<0.001	0.33 (0.18, 0.64)
NAI30034	25 / 1685 (1.5)	6 / 1678 (0.4)	<0.001	0.24 (0.10, 0.59)

Source: Reviewer's Analysis
1. Approximate relative risk = risk on zanamivir/risk on placebo

Events for contact cases / subjects who discontinued with missing data were imputed at 2 × the placebo rate for both treatment groups, rounding up to the nearest integer.

Study	Number of Contact Cases/Subjects with Influenza, Including Imputed Events			Approximate Relative Risk[1] (95% CI)
	Placebo n / N (%)	Zanamivir n / N (%)	p-value	
NAI30010	42 / 423 (10)	9 / 414 (2)	<0.001	0.22 (0.11, 0.44)
NAI30031	57 / 630 (9)	14 / 661 (2)	<0.001	0.23 (0.13, 0.42)
NAIA3005	37 / 554 (7)	13 / 553 (2)	<0.001	0.35 (0.19, 0.65)
NAI30034	26 / 1685 (1.5)	7 / 1678 (0.4)	<0.001	0.27 (0.12, 0.62)

Source: Reviewer's Analysis
1. Approximate relative risk = risk on zanamivir/risk on placebo

Events for contact cases / subjects who discontinued with missing data were imputed at 3 × the placebo rate for both treatment groups, rounding up to the nearest integer.

Study	Number of Contact Cases/Subjects with Influenza, Including Imputed Events			Approximate Relative Risk[1] (95% CI)
	Placebo n / N (%)	Zanamivir n / N (%)	p-value	
NAI30010	42 / 423 (10)	10 / 414 (2)	<0.001	0.24 (0.12, 0.48)
NAI30031	58 / 630 (9)	14 / 661 (2)	<0.001	0.23 (0.13, 0.41)
NAIA3005	38 / 554 (7)	13 / 553 (2)	<0.001	0.34 (0.18, 0.64)
NAI30034	27 / 1685 (1.6)	8 / 1678 (0.5)	0.001	0.30 (0.14, 0.65)

Source: Reviewer's Analysis
1. Approximate relative risk = risk on zanamivir/risk on placebo

Summary of Families in Which at Least One Contact Case Developed Symptomatic, Laboratory-Confirmed Influenza Infection in Study NAI30010 (excluding non-treated contact cases <5 years of age)

	Placebo	Zanamivir	p-value	Relative Odds (95% CI)	Approximate Relative Risk (95% CI)
Intent-to-Treat Number (%) of families	N=168 32 (19%)	N=169 7 (4%)	<0.001	0.18 (0.06, 0.43)	0.21 (0.11, 0.43)
Index Influenza Positive Number (%) of families	N=87 25 (29%)	N=78 6 (8%)	<0.001	0.21 (0.06, 0.56)	0.28 (0.13, 0.58)
Per Protocol Number (%) of families	N=164 31 (19%)	N=165 6 (4%)	<0.001	0.16 (0.05, 0.41)	0.19 (0.09, 0.40)

Source: Section 7.1 of the Clinical Study Report

The treatment effect of zanamivir for study NAI30010 was highly significant in the ITT, Index Influenza Positive and Per Protocol Populations.

Summary of Families in Which at Least One Contact Case Developed Symptomatic, Laboratory-Confirmed Influenza Infection in Study NAI30010 (including non-treated contact cases <5 years of age)

	Placebo	Zanamivir	p-value	Relative Odds (95% CI)	Approximate Relative Risk (95% CI)
Intent-to-Treat Number (%) of families	N=168 32 (19%)	N=169 8 (5%)	<0.001	0.21 (0.08, 0.48)	0.24 (0.12, 0.48)
Index Influenza Positive Number (%) of families	N=87 25 (29%)	N=78 7 (9%)	0.002	0.24 (0.08, 0.64)	0.33 (0.16, 0.65)
Per Protocol Number (%) of families	N=164 31 (19%)	N=165 7 (4%)	<0.001	0.19 (0.07, 0.46)	0.22 (0.11, 0.45)

Source: Section 7.1.2 of the Clinical Study Report

Unlike the primary analysis, these analyses included a non-treated contact case <5 years of age so there was an additional zanamivir case. The results were still highly significant.

Summary of Households in Which at Least One Contact Case Developed Symptomatic, Laboratory-Confirmed Influenza at Any Time From Day 1 to Day 11 in Study NAI30031

	Placebo	Zanamivir	p-value	Relative Odds (95% CI)	Approximate Relative Risk (95% CI)
Intent-to-Treat Number (%) of households	N=242 46 (19%)	N=245 10 (4%)	<0.001	0.17 (0.07, 0.37)	0.19 (0.10, 0.36)
Index Influenza Positive Number (%) of households	N=153 44 (29%)	N=129 8 (6%)	<0.001	0.18 (0.07, 0.43)	0.21 (0.11, 0.43)
Per Protocol Number (%) of households	N=228 41 (18%)	N=232 9 (4%)	<0.001	0.17 (0.07, 0.38)	0.19 (0.10, 0.36)

Source: Section 7.1 of the Clinical Study Report

The treatment effect of zanamivir for study NAI30031 was highly significant in the ITT, Index Influenza Positive and Per Protocol Populations.

Summary of Symptomatic, Laboratory Confirmed Influenza on Any Day in Study NAIA3005

	Placebo	Zanamivir	p-value	Relative Odds (95% CI)
Non-Vaccinated Population	N=475	N=473		
Influenza confirmed on any Day	28 (6%)	11 (2%)	0.009	0.38 (0.1, 0.80)
Per Protocol Population	N=439	N=452		
Influenza confirmed on any Day	26 (6%)	10 (2%)	0.008	0.36 (0.15, 0.78)
Intent-to treat Population	N=554	N=553		
Influenza confirmed on any Day	34 (6%)	11 (2%)	<0.001	0.31 (0.14, 0.64)

Source: Section 7.1.1 of the Clinical Study Report

The treatment effect of zanamivir for study NAIA3005 was highly significant in the non-vaccinated, per protocol and ITT populations.

Summary of Subjects with Symptomatic Influenza Confirmed by Culture/Serology in Study NAI30034

	Placebo	Zanamivir	p-value	Relative odds	Approximate Relative Risk
Intent-to-Treat Population	N=1685	N=1678			
Number (%) of subjects	23 (1.4%)	4 (0.2%)	<0.001	0.17 (0.04, 0.50)	0.17 (0.07, 0.44)
Per Protocol Population	N=1417	N=1440			
Number (%) of subjects	15 (1.1%)	4 (0.3%)	0.014	0.25 (0.06, 0.79)	0.25 (0.09, 0.70)

Source: Tables 20 and 21 of the Clinical Study Report

The treatment effect of zanamivir for study NAI30034 was highly significant in the ITT population and was also significant in the per protocol population.

Summary of Subjects with Symptomatic Influenza Confirmed by Culture/Serology in Study NAI30034

	Placebo	Zanamivir	p-value	Relative odds	Approximate Relative Risk
Non-Vaccinated Population[1]	N=1460	N=1465			
Number (%) of subjects	21 (1.4%)	4 (0.3%)	<0.001	0.18 (0.06, 0.53)	0.18 (0.06, 0.54)

Source: Reviewer's Analyses
[1] Excludes subjects vaccinated within 21 days of randomization or post-randomization

The treatment effect of zanamivir for study NAI30034 was also highly significant after excluding subjects who were vaccinated within 21 days of randomization or post-randomization.

3.1.5.3 Secondary Efficacy Analyses

Summary of Subjects with Symptomatic Influenza Confirmed by Culture/Serology or PCR in Study NAI30034.

	Placebo	Zanamivir	p-value	Relative odds	Approximate Relative Risk
Intent-to-Treat Population Number (%) of subjects	N=1685 23 (1.4%)	N=1678 4 (0.2%)	<0.001	0.17 (0.04, 0.50)	0.17 (0.07, 0.44)

Source: Table 25 of the Clinical Study Report
This secondary efficacy analysis was pre-specified in the amended protocol

The results of the primary efficacy analysis for study NAI30034 remained unchanged using PCR laboratory confirmation in addition to culture/serology tests.

Summary of Households in Which at Least One Contact Case Developed Laboratory-Confirmed (Symptomatic or Asymptomatic) Influenza in Study NAI30010

	Placebo	Zanamivir	p-value	Relative Odds (95% CI)	Approximate Relative Risk (95% CI)
Intent-to-Treat Number (%) of households	N=168 47 (28)	N=169 22 (13)	0.001	0.39 (0.21, 0.70)	0.47 (0.30, 0.73)
Index Influenza Positive Number (%) of households	N=87 33 (38)	N=78 15 (19)	0.014	0.39 (0.18, 0.85)	0.52 (0.32, 0.85)
Per Protocol Number (%) of households	N=164 45 (27)	N=165 19 (12)	<0.001	0.35 (0.19, 0.65)	0.43 (0.27, 0.68)

Source: Section 7.1.3 of the Clinical Study Report
These secondary efficacy analyses were pre-specified in the protocol

In each of the three populations in study NAI30010, the percentage of zanamivir households in which at least one contact case developed laboratory-confirmed (symptomatic or asymptomatic) influenza was significantly lower than the corresponding percentage of placebo households.

Summary of Households in Which at Least One Contact Case Developed Laboratory-Confirmed (Symptomatic or Asymptomatic) Influenza in Study NAI30031

	Placebo	Zanamivir	p-value	Relative Odds (95% CI)	Approximate Relative Risk (95% CI)
Intent-to-Treat Number (%) of households	N=242 75 (31)	N=245 35 (14)	<0.001	0.34 (0.20, 0.55)	0.44 (0.31, 0.62)
Index Influenza Positive Number (%) of households	N=153 67 (44)	N=129 27 (21)	<0.001	0.31 (0.17, 0.57)	0.46 (0.32, 0.67)
Per Protocol Number (%) of households	N=228 72 (32)	N=232 34 (15)	<0.001	0.32 (0.19, 0.54)	0.43 (0.30, 0.61)

Source: Section 7.2.1 of the Clinical Study Report
These secondary efficacy analyses were pre-specified in the protocol

In each of the three populations in study NAI30031, the percentage of zanamivir households in which at least one contact case developed laboratory-confirmed (symptomatic or asymptomatic) influenza was significantly lower than the corresponding percentage of placebo households ($p<0.001$).

Summary of Laboratory-Confirmed (Symptomatic or Asymptomatic) Influenza in Study NAIA3005

	Placebo	Zanamivir	p-value	Relative Odds (95% CI)
Non-Vaccinated Population	N=475	N=473		
Number (%) of subjects	64 (13)	50 (11)	0.203	0.76 (0.50, 1.15)
Per Protocol Population	N=439	N=452		
Number (%) of subjects	59 (13)	47 (10)	0.195	0.75 (0.49, 1.15)
Intent-to-Treat Population	N=554	N=553		
Number (%) of subjects	77 (14)	53 (10)	0.034	0.66 (0.44, 0.97)

Source: Section 7.2.2 of the Clinical Study Report
These secondary efficacy analyses were pre-specified in the protocol

In study NAIA3005, the percentage of zanamivir subjects who developed laboratory-confirmed (symptomatic or asymptomatic) influenza was significantly lower than the corresponding percentage of placebo subjects in the ITT population (p=0.034) but there were no statistically significant treatment differences in the primary non-vaccinated or in the per-protocol populations.

Summary of Subjects with Influenza (Symptomatic or Asymptomtic) Confirmed by Culture/Serology in Study NAI30034.

	Placebo	Zanamivir	p-value	Relative odds	Approximate Relative Risk
Intent-to-Treat Population	N=1685	N=1678			
Number (%) of subjects	52 (3%)	39 (2%)	0.228	0.75 (0.48, 1.17)	0.76 (0.50, 1.15)

Source: Section 7.2.2 of the Clinical Study Report
This secondary efficacy analysis was pre-specified in the protocol but the amended protocol changed the secondary analysis to include PCR results

In the ITT population of the second community study (NAI30034), there was no statistically significant difference between the percentage of zanamivir subjects with laboratory-confirmed (symptomatic or asymptomatic) influenza and the corresponding percentage of placebo subjects (p=0.228).

Study	**Placebo n/N (%)**	**Zanamivir n/N (%)**
NAI30034[1]	103 / 1685 (6)	90 / 1678 (6)
NAI30034[2]	54 / 1685 (3)	39 / 1678 (2)
NAI30034[3]	52 / 1685 (3)	39 / 1678 (2)

Source: Reviewer's analyses
1. Includes results from all serology, viral culture and PCR data.
2. Excludes serology results for subjects vaccinated less than 21 days before the start of the study. This secondary analysis was pre-specified in the amended protocol (to include PCR data).
3. Excludes PCR results (corresponding to what was done for the primary endpoint for study NAI30034) and excludes serology results for subjects vaccinated less than 21 days before the start of the study.

The reviewer also compared results in study NAI30034 using all serology results, excluding serology results for subjects vaccinated less than 21 days before the start of the study, and excluding both PCR results and serology results for subjects vaccinated less than 21 days before the start of the study. There were no statistically significant differences between treatment groups using any of these approaches.

Serology Data for Study NAI30034

Serum samples were to be collected at Day 1 from all participating subjects for influenza antibody detection. At Day 30 (the end of prophylaxis visit) serum samples were to be collected from all participating subjects who, during prophylaxis, did not develop influenza-like illness (ILI) or developed ILI prior to Day 8.

Subjects who presented with ILI from Day 8 to Day 35 attended an ILI Convalescent Visit (up to Day 49). This visit took place 3 weeks (21 days) from the day that they first presented with ILI symptoms or on Day 49, whichever occurred first, but no later than Day 49. At this visit , a serum sample was to be taken for influenza antibody detection.

Zanamivir Serology Results

Signs and Symptoms of Influenza	Negative n/N (%)	Type A n/N (%)	Type B n/N (%)	Positive to both A and B n/N (%)	Missing n/N (%)
Asymptomatic	1393 / 1523 (91)	66 / 1523 (4)	4 / 1523 (<1)	10 / 1523 (1)	50 / 1523 (3)
Symptomatic	137 / 151 (91)	6 / 151 (4)	0 / 151	2 / 151 (1)	6 / 151 (4)
Missing	0 / 4	0 / 4	0 / 4	0 / 4	4 / 4

Source: Reviewer's analyses

Placebo Serology Results

Signs and Symptoms of Influenza	Negative n/N (%)	Type A n/N (%)	Type B n/N (%)	Positive to both A and B n/N (%)	Missing n/N (%)
Asymptomatic	1387 / 1509 (92)	52 / 1509 (3)	12 / 1509 (1)	8 / 1509 (1)	50 / 1509 (3)
Symptomatic	140 / 169 (83)	13 / 169 (8)	8 / 169 (5)	3 / 169 (2)	5 / 169 (3)
Missing	1 / 7 (14)	0 / 7	0 / 7	0 / 7	6 / 7 (86)

Source: Reviewer's analyses

Serology data were missing for 3% of the subjects with symptomatic and asymptomatic influenza.

Zanamivir Serology Results for Patients vaccinated within 21 days of randomization or post-randomization

Signs and Symptoms of Influenza	Negative n/N (%)	Type A n/N (%)	Type B n/N (%)	Positive to both A and B n/N (%)	Missing n/N (%)
Asymptomatic	145 / 195 (74)	38 / 195 (19)	1 / 195 (1)	7 / 1953 (4)	4 / 195 (2)
Symptomatic	12 / 18 (67)	4 / 18 (22)	0 / 18	1 / 18 (6)	1 / 18 (6)
Missing	0 / 0	0 / 0	0 / 0	0 / 0	0 / 0

Source: Reviewer's analyses

Placebo Serology Results for Patients vaccinated within 21 days of randomization or post-randomization

Signs and Symptoms of Influenza	Negative n/N (%)	Type A n/N (%)	Type B n/N (%)	Positive to both A and B n/N (%)	Missing n/N (%)
Asymptomatic	159 / 206 (77)	35 / 206 (17)	2 / 206 (1)	6 / 206 (3)	4 / 206 (2)
Symptomatic	11 / 18 (61)	3 / 18 (17)	1 / 18 (6)	3 / 18 (17)	0 / 18
Missing	0 / 1	0 / 1	0 / 1	0 / 1	1 / 1

Source: Reviewer's analyses

Among patients who were vaccinated within 21 days of randomization or post-randomization, serology data were missing for only one of the 18 zanamivir and none of the 18 placebo subjects with symptomatic influenza and were missing for 2% of zanamivir and placebo subjects with asymptomatic influenza.

Summary of Subjects in Study NAI30034 with Symptomatic Influenza that was Confirmed using Serology data, including serology results for subjects vaccinated within 21 days of randomization or post-randomization

	Placebo n/N (%)	Zanamivir n/N (%)
Intent-to-Treat Number (%) of Households	24 / 1685 (1.4%)	8 / 1678 (0.5%)

Source: Reviewer's analyses

Using serology data for laboratory confirmation, 1.4% of the placebo patients had symptomatic laboratory-confirmed influenza compared to only 0.5% of the zanamivir subjects.

Serology data was not used for patients vaccinated within 21 days of randomization or post-randomization in the primary analysis. Therefore compared to the primary analysis, a few additional patients had symptomatic influenza that was confirmed using all of the available serology data.

Summary of Subjects in Study NAI30034 with Symptomatic Influenza that was Confirmed using Serology data, excluding serology results from subjects vaccinated within 21 days of randomization or post-randomization

	Placebo n/N (%)	Zanamivir n/N (%)
Intent-to-Treat Number (%) of Households	17 / 1685 (1.0%)	3 / 1678 (0.2%)

Source: Reviewer's analyses

One percent (1.0%) of the placebo patients had symptomatic influenza that was confirmed using serology data compared to only 0.2% of the zanamivir subjects.

Summary of Subjects in Study NAI30034 with Symptomatic Influenza that was Confirmed using Serology, PCR or Culture (Primary Analysis), excluding serology results for subjects vaccinated within 21 days of randomization or post-randomization

	Placebo n/N (%)	Zanamivir n/N (%)
Intent-to-Treat Number (%) of Households	23 / 1685 (1.4%)	4 / 1678 (0.2%)

Source: Reviewer's analyses

When serology results for subjects vaccinated within 21 days of randomization or post-randomization were not used, event rates were slightly higher in the primary analysis since PCR and culture data confirmed a few additional cases.

PCR data for Study NAI30034

A sample (i.e., throat swab, throat/nasal swab, nasopharyngeal swab, nasal wash or nasal aspirate) for diagnosis of influenza was to be collected from subjects within 48 hours of onset of any ILI. Virus culture and PCR (a secondary endpoint) were to be performed on this sample.

Zanamivir PCR Results

Signs and Symptoms of Influenza	Negative PCR n/N (%)	Positive PCR n/N (%)	Missing PCR n/N (%)
Asymptomatic	23 / 1523 (2)	1 / 1523 (<1)	1499 / 1523 (98)
Symptomatic	84 / 151 (56)	1 / 151 (1)	66 / 151 (44)
Missing	0 / 4	0 / 4	4 / 4

Source: Reviewer's analyses

Placebo PCR Results

Signs and Symptoms of Influenza	Negative PCR n/N (%)	Positive PCR n/N (%)	Missing PCR n/N (%)
Asymptomatic	22 / 1509 (1)	2 / 1509 (<1)	1485 / 1509 (98)
Symptomatic	85 / 169 (50)	15 / 169 (9)	69 / 169 (41)
Missing	0 / 7	0 / 7	7 / 7

Source: Reviewer's analyses

In reality, PCR data were missing for approximately 40% of the subjects with symptomatic influenza and approximately 98% of subjects with asymptomatic influenza.

Zanamivir PCR Results for Patients vaccinated within 21 days of randomization or post-randomization

Signs and Symptoms of Influenza	Negative PCR n/N (%)	Positive PCR n/N (%)	Missing PCR n/N (%)
Asymptomatic	3 / 195 (2)	0 / 195 (0)	192 / 195 (98)
Symptomatic	12 / 18 (67)	0 / 18 (0)	6 / 18 (33)
Missing	0 / 0	0 / 0	0 / 0

Source: Reviewer's analyses

Placebo PCR Results for Patients vaccinated within 21 days of randomization or post-randomization

Signs and Symptoms of Influenza	Negative PCR n/N (%)	Positive PCR n/N (%)	Missing PCR n/N (%)
Asymptomatic	4 / 206 (2)	1 / 206 (<1)	201 / 206 (98)
Symptomatic	12 / 18 (67)	2 / 18 (11)	4 / 18 (22)
Missing	0 / 1	0 / 1	1 / 1

Source: Reviewer's analyses

Among patients who were vaccinated within 21 days of randomization or post-randomization, PCR data were missing for 33% of the zanamivir and 22% of the placebo subjects with symptomatic influenza and were missing for 98% of zanamivir and placebo subjects with asymptomatic influenza.

Among subjects vaccinated within 21 days of randomization or post-randomization, only 2 placebo patients had symptomatic influenza that was confirmed using PCR data.

Cross-tabulation of Serology and PCR Data for subjects with signs and symptoms of influenza (counting serology results for subjects vaccinated within 21 days of randomization or post-randomization as negative)

	Missing PCR	Negative PCR	Positive PCR
Negative Serology	132	163	5
Positive Serology	3	6	11

Source: Reviewer's analyses

Three (3) patients with missing PCR data had positive serology data while 6 patients with negative PCR data had positive serology data. None of the patients with missing serology had PCR samples.

Summary of Subjects in Study NAI30034 with Symptomatic Influenza that was Confirmed using PCR data

	Placebo n/N (%)	**Zanamivir n/N (%)**
Intent-to-Treat Number (%) of Households	15 / 1685 (0.9%)	1 / 1678 (0.1%)

Source: Reviewer's analyses

0.9% of the placebo patients had symptomatic influenza that was confirmed using PCR data compared to only 0.1% of the zanamivir subjects.

Seventeen (17) zanamivir cases of influenza were detected using serology data (for patients vaccinated more than 21 days prior to randomization) compared to 15 using PCR data. Three (3) placebo cases were detected using serology data (for patients vaccinated more than 21 days prior to randomization) compared to 1 using PCR data.

Virus Culture data for Study NAI30034

Zanamivir Culture Results

Signs and Symptoms of Influenza	Negative n/N (%)	Type A n/N (%)	Type B n/N (%)	Other / Indeterminant n/N (%)	Missing / Not Done n/N (%)
Asymptomatic	21 / 1523 (1)	1 / 1523 (<1)	0 / 1523	0 / 1523	1500 / 1523 (98)
Symptomatic	82 / 151 (54)	1 / 151 (<1)	0 / 151	2 / 151 (1)	65 / 151 (43)
Missing	0 / 4	0 / 4	0 / 4	0 / 4	4 / 4

Source: Reviewer's analyses

Placebo Culture Results

Signs and Symptoms of Influenza	Negative n/N (%)	Type A n/N (%)	Type B n/N (%)	Other / Indeterminant n/N (%)	Missing / Not Done n/N (%)
Asymptomatic	25 / 1509 (2)	0 / 1509	0 / 1509	1 / 1509 (<1)	1483 / 1509 (98)
Symptomatic	81 / 169 (48)	9 / 169 (5)	9 / 169 (5)	3 / 169 (2)	66 / 169 (39)
Missing	0 / 7	0 / 7	0 / 7	0 / 7	7 / 7

Source: Reviewer's analyses

Culture data were missing for approximately 40% of the subjects with symptomatic influenza and approximately 98% of subjects with asymptomatic influenza.

Zanamivir Culture Results for Patients vaccinated within 21 days of randomization or post-randomization

Signs and Symptoms of Influenza	Negative n/N (%)	Type A n/N (%)	Type B n/N (%)	Other / Indeterminant n/N (%)	Missing / Not Done n/N (%)
Asymptomatic	3 / 195 (2)	0 / 195 (0)	0 / 195 (0)	0 / 195 (0)	192 / 195 (98)
Symptomatic	12 / 18 (67)	0 / 18 (0)	0 / 18 (0)	0 / 18 (0)	6 / 18 (33)
Missing	0 / 0	0 / 0	0 / 0	0 / 0	0 / 0

Source: Reviewer's analyses

Placebo Culture Results for Patients vaccinated within 21 days of randomization or post-randomization

Signs and Symptoms of Influenza	Negative n/N (%)	Type A n/N (%)	Type B n/N (%)	Other / Indeterminant n/N (%)	Missing / Not Done n/N (%)
Asymptomatic	4 / 206 (2)	0 / 206 (0)	0 / 206 (0)	1 / 206 (<1)	201 / 206 (98)
Symptomatic	11 / 18 (61)	1 / 18 (6)	1 / 18 (6)	1 / 18 (6)	4 / 18 (22)
Missing	0 / 1	0 / 1	0 / 1	0 / 1	1 / 1

Source: Reviewer's analyses

Among patients who were vaccinated within 21 days of randomization or post-randomization, culture data were missing for 27% of the zanamivir and 21% of the placebo subjects with symptomatic influenza and were missing for 98% of zanamivir and placebo subjects with asymptomatic influenza.

Among subjects vaccinated within 21 days of randomization or post-randomization, only 2 placebo patients had symptomatic influenza that was confirmed using culture data.

Cross-tabulation of Serology and Culture Data for subjects with signs and symptoms of influenza (counting serology results for subjects vaccinated within 21 days of randomization or post-randomization as negative)

	Missing Culture / Culture Not Done	Negative Culture	Positive Culture	Indeterminate / Other Culture Result
Negative Serology	130	157	7	6
Positive Serology	2	6	12	0

Source: Reviewer's analyses

Two (2) patients with missing culture data / culture not done had positive serology data while 6 patients with negative culture data had positive serology data. None of the patients with missing serology had culture samples.

Cross-tabulation of Culture and PCR Data for subjects who had Negative serology data with signs and symptoms of influenza (counting serology results for subjects vaccinated within 21 days of randomization or post-randomization as negative)

	Missing PCR	Negative PCR	Positive PCR
Missing Culture / Culture Not Done	128	2	0
Negative Culture	3	154	0
Positive Culture	0	2	5
Indeterminate / Other Culture Result	0	3	5

Source: Reviewer's analyses

Since the primary analysis did not use PCR results, there were 7 additional laboratory-confirmed influenza cases detected using culture samples in addition to serology data (after counting patients with positive serology results as negative if they were vaccinated within 21 days of randomization or post-randomization).

A total of 12 additional cases of laboratory-confirmed influenza were detected using culture and PCR when serology data were negative or when serology results were positive within 21 days of randomization or post-randomization (2 negative PCR / positive culture + 5 positive PCR / positive culture + 5 indeterminate / other culture result / positive PCR).

Cross-tabulation of Culture and PCR Data for subjects who had Positive Serology data with signs and symptoms of influenza (counting serology results for subjects vaccinated within 21 days of randomization or post-randomization as negative)

	Missing PCR	Negative PCR	Positive PCR
Missing Culture / Culture Not Done	2	0	0
Negative Culture	0	5	1
Positive Culture	1	1	10
Indeterminate / Other Culture Result	0	0	0

Source: Reviewer's analyses

The majority of subjects who had positive serology data also had positive PCR and positive culture results.

Summary of Subjects in Study NAI30034 with Symptomatic Influenza that was Confirmed using Culture Data

	Placebo n/N (%)	**Zanamivir n/N (%)**
Intent-to-Treat Number (%) of Households	18 / 1685 (1.1%)	1 / 1678 (0.06%)

Source: Reviewer's analyses

1.1% of the placebo patients had symptomatic influenza that was confirmed using culture data compared to only 0.06 % of the zanamivir subjects.

Seventeen (17) zanamivir cases of influenza were detected using serology data (for patients vaccinated more than 21 days prior to randomization) compared to 18 using culture data. Three (3) placebo cases were detected using serology data (for patients vaccinated more than 21 days prior to randomization) compared to 1 using culture data.

Summary of Households in Which at Least One Contact Case Developed a Febrile Illness in Study NAI30010

	Placebo	Zanamivir	p-value	Relative Odds (95% CI)	Approximate Relative Risk (95% CI)
Intent-to-Treat	N=168	N=169			
Febrile Illness and Lab Confirmed Influenza[1]	30 (18%)	12 (7%)	0.005	0.36 (0.16, 0.75)	0.40 (0.22, 0.73)
Febrile Illness +/- Lab Confirmed Influenza[2]	79 (47%)	77 (46%)	0.827	0.93 (0.59, 1.47)	0.96 (0.77, 1.21)
Index Influenza Positive	N=87	N=78			
Febrile Illness and Lab Confirmed Influenza[1]	26 (30%)	7 (9%)	0.003	0.25 (0.09, 0.65)	0.34 (0.17, 0.66)
Febrile Illness +/- Lab Confirmed Influenza[2]	45 (52%)	39 (50%)	1.000	1.00 (0.51, 1.98)	1.00 (0.74, 1.35)
Per Protocol	N=164	N=165			
Febrile Illness and Lab Confirmed Influenza[1]	30 (18%)	10 (6%)	0.001	0.30 (0.13, 0.65)	0.34 (0.18, 0.64)
Febrile Illness +/- Lab Confirmed Influenza[2]	78 (48%)	73 (44%)	0.557	0.86 (0.54, 1.36)	0.92 (0.73, 1.16)

Source: Tables 26, 27 and 28 of the Clinical Study Report
[1] This secondary efficacy analysis was not pre-specified in the protocol
[2] This secondary efficacy analysis was pre-specified in the protocol

In study NAI30010, the treatment effect of zanamivir in preventing the transmission of laboratory-confirmed influenza and a febrile illness was statistically significant.

There were no statistically significant differences between treatment groups in the incidence of a febrile illness with or without laboratory confirmation.

Summary of Households in Which at Least One Contact Case Developed a Febrile Illness in Study NAI30031

	Placebo	Zanamivir	p-value	Relative Odds (95% CI)	Approximate Relative Risk (95% CI)
Intent-to-Treat	N=242	N=245			
Febrile Illness and Lab Confirmed Influenza[1]	50 (21%)	23 (9%)	<0.001	0.35 (0.19, 0.63)	0.41 (0.26, 0.65)
Febrile Illness +/- Lab Confirmed Influenza[2]	130 (54%)	127 (52%)	1.000	1.00 (0.68, 1.46)	1.00 (0.84, 1.19)
Index Influenza Positive	N=153	N=129			
Febrile Illness and Lab Confirmed Influenza[1]	46 (30%)	18 (14%)	0.004	0.38 (0.18, 0.76)	0.48 (0.29, 0.78)
Febrile Illness +/- Lab Confirmed Influenza[2]	94 (61%)	69 (53%)	0.183	0.70 (0.41, 1.17)	0.85 (0.68, 1.06)
Per Protocol	N=228	N=232			
Febrile Illness and Lab Confirmed Influenza[1]	47 (21%)	22 (9%)	<0.001	0.35 (0.18, 0.64)	0.41 (0.26, 0.66)
Febrile Illness +/- Lab Confirmed Influenza[2]	116 (51%)	113 (49%)	0.933	0.97 (0.66, 1.42)	0.98 (0.81, 1.19)

Source: Tables 34, 35 and 36 of the Clinical Study Report
[1] This secondary efficacy analysis was pre-specified in the protocol
[2] This secondary efficacy analysis was not pre-specified in the protocol

The treatment effect of zanamivir in preventing the transmission of laboratory-confirmed influenza and a febrile illness was also statistically significant in the second household study.

There were no statistically significant differences between treatment groups in the incidence of a febrile illness with or without laboratory confirmation.

Summary of Presence of Febrile Illness in Study NAIA3005

	Placebo	Zanamivir	p-value
Non-Vaccinated Population	N=475	N=473	
Febrile Illness and Lab Confirmed Influenza	16 (3%)	3 (<1%)	0.004
Febrile Illness +/- Lab Confirmed Influenza	51 (11%)	27 (6%)	0.007
Per Protocol Population	N=439	N=452	
Febrile Illness and Lab Confirmed Influenza	16 (4%)	3 (<1%)	0.003
Febrile Illness +/- Lab Confirmed Influenza	47 (11%)	27 (6%)	0.014
Intent-to-Treat	N=554	N=553	
Febrile Illness and Lab Confirmed Influenza	19 (3%)	3 (<1%)	0.001
Febrile Illness +/- Lab Confirmed Influenza	58 (10%)	33 (6%)	0.009

Source: Tables 14, 23, 32 of the Clinical Study Report
Lab confirmation was by culture / serology
None of these secondary efficacy analyses were pre-specified in the protocol. (The protocol only prespecified febrile illness with confirmation using serology, viral culture and PCR as a secondary endpoint.)

The treatment effect of zanamivir in preventing the transmission of laboratory-confirmed influenza and a febrile illness was statistically significant in study NAIA3005 and of borderline statistical significance in study NAI30034.

In addition, the treatment effect of zanamivir in preventing the transmission of febrile illness with or without laboratory confirmation was statistically significant in both studies.

Summary of Subjects with a Febrile Illness in Study NAI30034.

Intent-to-Treat Population	Placebo	Zanamivir	p-value	Relative odds	Approximate Relative Risk
	N=1685	N=1678			
Febrile Illness and Lab Confirmed Influenza	16 (0.9%)	6 (0.4%)	0.050	0.37 (0.12, 1.00)	0.37 (0.15, 0.92)
Febrile Illness +/- Lab Confirmed Influenza	109 (6%)	81 (5%)	0.023	0.70 (0.51, 0.95)	0.71 (0.54, 0.95)

Source: Table 28 of the Clinical Study Report
Lab confirmation was by culture / serology
These secondary efficacy analyses were not pre-specified in the protocol. (The protocol only prespecified febrile illness with confirmation and +/- confirmation, using serology, viral culture and PCR as a secondary endpoint.)

Summary of Relative Risk of Laboratory-Confirmed, Symptomatic

Influenza A and B in Household Studies (ITT Population)

Study	Influenza Type	Household Cases of Influenza			Approximate Relative Risk[1] (95% CI)
		Placebo n (%)	Zanamivir n (%)	p-value	
NAI30010	A	20 (12)	4 (2)	<0.001	0.19 (0.08, 0.49)
NAI30010	B	13 (8)	3 (2)	0.016	0.23 (0.07, 0.69)
NAI30031	A	27 (11)	6 (2)	<0.001	0.22 (0.10, 0.49)
NAI30031	B	20 (8)	4 (2)	<0.001	0.15 (0.06, 0.41)

Source: Summary of Clinical Efficacy Table 21
1. Approximate relative risk = risk on zanamivir/risk on placebo
These secondary efficacy analyses were not pre-specified in the protocol

The endpoint for these analyses was the presence of laboratory-confirmed, symptomatic Influenza Types A and B in at least one contact case per household, regardless of the type of influenza the index case had.

In both household studies, 11-12% of the placebo households had at least one contact case with laboratory-confirmed, symptomatic type A influenza compared to only 2% of the zanamivir households ($p<0.001$ in both studies) while 8% of the placebo households in both studies had at least one contact case with laboratory-confirmed, symptomatic type B influenza compared to only 2% of the zanamivir households ($p=0.016$ in study NAI30010 and $p<0.001$ in study NAI30031).

Summary of Relative Risk of Laboratory-Confirmed, Symptomatic Influenza by Contact Case (ITT Population)

Study	Contact Cases of Influenza			Approximate Relative Risk[1] (95% CI)
	Placebo n/N (%)	Zanamivir n/N (%)	p-value	
NAI30010	40 / 423 (9.5)	7 / 414 (1.7)	<0.001	0.19 (0.09, 0.37)
NAI30031	55 / 630 (8.7)	12 / 661 (1.8)	<0.001	0.18 (0.10, 0.32)

Source: Summary of Clinical Efficacy Table 22
1. Approximate relative risk = risk on zanamivir/risk on placebo
These secondary efficacy analyses were not pre-specified in the protocol

The zanamivir treatment effect was also highly significant when the percentage of contact cases developing laboratory-confirmed, symptomatic influenza were compared in each treatment group.

In study NAI30010, 9.5% of the placebo contact cases had laboratory-confirmed, symptomatic influenza compared to only 1.7% of the zanamivir contact cases ($p<0.001$).

In study NAI30031, 8.7% of the placebo contact cases had laboratory-confirmed, symptomatic influenza compared to only 1.8% of the zanamivir contact cases ($p<0.001$).

Summary of Days to Alleviation For Contact Cases with Symptomatic, Laboratory-Confirmed Influenza During Prophylaxis in Study NAI30010

	Placebo	Zanamivir
Intent-to-Treat Population	N=423	N=414
CCs with symptomatic lab-confirmed influenza	40	7
Median number of days to alleviation	6.25	3.5
Index Influenza Positive Population	N=215	N=195
CCs with symptomatic lab-confirmed influenza	33	6
Median number of days to alleviation	6.5	3.0
Per Protocol population	N=402	N=384
CCs with symptomatic lab-confirmed influenza	38	6
Median number of days to alleviation	6.5	3.0

Source: Section 7.1.7 of the Clinical Study Report
These secondary efficacy analyses were pre-specified in the protocol

In the ITT population, the zanamivir contact cases who developed laboratory-confirmed, symptomatic influenza had a median time of 3.5 days to alleviation of clinically significant symptoms while the placebo contact cases had a median time of 6.25 days.

The times to alleviation of clinically significant symptoms of influenza in the other populations were similar to those obtained in the ITT population.

Summary of Days to Alleviation For Contact Cases with Symptomatic, Laboratory-Confirmed Influenza During Prophylaxis in Study NAI30031

	Placebo	Zanamivir
Intent-to-Treat Population	N=630	N=661
CCs with symptomatic lab-confirmed influenza	55	12
Median number of days to alleviation	6.5	5.0
Index Influenza Positive Population	N=398	N=368
CCs with symptomatic lab-confirmed influenza	51	9
Median number of days to alleviation	6.5	5.0
Per Protocol population	N=568	N=603
CCs with symptomatic lab-confirmed influenza	47	10
Median number of days to alleviation	6.5	5.0

Source: Section 7.3.2 and Supporting Tables 3, 4 and 5 of the Clinical Study Report
These secondary efficacy analyses were pre-specified in the protocol

In the ITT, index influenza positive and per protocol populations, the zanamivir contact cases that developed laboratory-confirmed, symptomatic influenza had a median time of 5.0 days to alleviation of clinically significant symptoms while the placebo contact cases had a median time of 6.5 days.

Summary of Relative Risk of Laboratory-Confirmed, Symptomatic Influenza by Influenza Type and by Contact Case (ITT Population)

Study	Influenza Type	Contact Cases of Influenza			Approximate Relative Risk[1] (95% CI)
		Placebo n/N (%)	Zanamivir n/N (%)	p-value	
NAI30010	A	26 / 423 (6)	4 / 414 (<1)	<0.001	0.17 (0.07, 0.41)
NAI30010	B	14 / 423 (3)	3 / 414 (<1)	0.014	0.23 (0.07, 0.68)
NAI30031	A	32 / 630 (5)	7 / 661 (1)	<0.001	0.21 (0.10, 0.45)
NAI30031	B	23 / 630 (4)	5 / 661 (<1)	<0.001	0.13 (0.05, 0.36)

Source: Summary of Clinical Efficacy Table 23
1. Approximate relative risk = risk on zanamivir/risk on placebo
These secondary efficacy analyses were not pre-specified in the protocol

The endpoint for these analyses was the presence of laboratory-confirmed, symptomatic Influenza Types A and B in contact cases, regardless of the type of influenza the index case had.

In study NAI30010, 6% of the placebo contact cases had laboratory-confirmed, symptomatic type A influenza compared to <1% of the zanamivir contact cases ($p<0.001$) while 3% of the placebo contact cases had laboratory-confirmed, symptomatic type B influenza compared to <1% of the zanamivir contact cases ($p=0.014$).

In study NAI30031, 5% of the placebo contact cases had laboratory-confirmed, symptomatic type A influenza compared to 1% of the zanamivir contact cases ($p<0.001$) while 4% of the placebo contact cases had laboratory-confirmed, symptomatic type B influenza compared to <1% of the zanamivir contact cases ($p<0.001$).

Summary of Relative Risk of Laboratory-Confirmed, Symptomatic Influenza by Contact Case According to Whether Influenza Types of IC and CC Match (ITT Population)

Study	Influenza Type Match[1]	Placebo n/N (%)	Zanamivir n/N (%)	p-value	Approximate Relative Risk[2]
NAI30010	Yes	29 / 423 (7)	5 / 414 (1)	<0.001	0.18
NAI30010	No	11 / 423 (3)	2 / 414 (<1)	0.036	0.21
NAI30031	Yes	46 / 630 (7)	9 / 661 (1)	<0.001	0.19
NAI30031	No	9 / 630 (1)	3 / 661 (<1)	0.021	0.11

Source: Summary of Clinical Efficacy Table 24
1. A match is considered to be an index case with influenza type A plus a contact case with influenza type A, or an index case with influenza type B plus a contact case with influenza type B. All other combinations were considered to be not a match (including those cases where the index case was negative).
2. Approximate relative risk = risk on zanamivir/risk on placebo
These secondary efficacy analyses were not pre-specified in the protocol

In both household studies, 7% of the placebo contact cases had laboratory-confirmed, symptomatic influenza types that matched compared to only 1% of the zanamivir contact cases ($p<0.001$).

Three percent (3%) of the placebo contact cases in study NAI30010 and 1% of the placebo contact cases in study NAI30031 had laboratory-confirmed, symptomatic influenza types that did not match compared to <1% of the zanamivir contact cases in both studies ($p=0.036$ in study NAI30010 and $p=0.021$ in study NAI30031).

The proportion of unmatched symptomatic laboratory-confirmed cases of influenza in contact cases was significantly lower in the zanamivir treatment group than in the placebo treatment group ($p=0.036$ for study NAI30010 and $p=0.021$ for study NAI30031). Influenza types that didn't match included index cases that had different strains of influenza than contact cases (index cases with type A influenza and contact cases with type B influenza or vice versa) and contact cases from households where index cases who had negative laboratory tests (unconfirmed signs and symptoms). Influenza was most likely transmitted to the contact case from a source outside the household if influenza types didn't match.

(b) (4)

(b) (4)

Summary of Contact Cases / Subjects with (Symptomatic or Asymptomatic) Influenza Confirmed by Culture/Serology/PCR (ITT Population)

Study	Placebo n/N (%)	Zanamivir n/N (%)
NAI30010	66 / 423 (16)	26 / 414 (6)
NAI30031	105 / 630 (17)	48 / 661 (7)

Source: Reviewer's analyses

The statistical reviewer computed the percentage of contact cases / subjects with laboratory confirmed (symptomatic or asymptomatic) influenza in each study. The results for contact cases were consistent with the results obtained by the applicant for households in which at least one contact case had laboratory confirmed (symptomatic or asymptomatic) influenza.

Summary of Families / Households with Symptomatic Influenza Irrespective of results of Laboratory Confirmation (ITT Population)

Study	Placebo	Zanamivir
	n/N (%)	n/N (%)
NAI30010	68 / 168 (40)	41 / 169 (24)
NAI30031	93 / 242 (38)	67 / 245 (27)

Source: Reviewer's Analysis
This is the only reviewer analysis that was also pre-specified in the protocol.

The statistical reviewer computed the percentage of households with symptomatic influenza (regardless of laboratory confirmation) in each study. In both studies, approximately 40% of the placebo households had symptomatic influenza compared to approximately 25% of the zanamivir households.

Summary of Contact Cases / Subjects with Symptomatic Influenza Irrespective of results of Laboratory Confirmation (ITT Population)

Study	Placebo	Zanamivir
	n/N (%)	n/N (%)
NAI30010	95 / 423 (22)	46 / 414 (11)
NAI30031	122 / 630 (19)	93 / 661 (14)
NAIA3005	127 / 554 (23)	94 / 553 (17)
NAI30034	169 / 1685 (10)	151 / 1678 (9)

Source: Reviewer's Analysis

The statistical reviewer computed the percentage of contact cases / subjects with symptomatic influenza (regardless of laboratory confirmation) in each study. The percentage of zanimivir contact cases / subjects with symptomatic influenza were generally lower than the corresponding placebo percentages with the possible exception being the second community study where the percentage of subjects with symptomatic influenza was approximately 10% in both treatment groups.

NAI30034 Placebo

23 Confirmed Symptomatic Cases	52-23=29 Confirmed Asymptomatic Cases	52 Confirmed Symptomatic or Asymptomatic Cases
169 Symptomatic Cases	1516 Asympotomatic	1685 Total

Source: Reviewer's Analysis

23/169 = 14% of the symptomatic placebo cases were confirmed
29/1516 = 2% of the asymptomatic placebo cases were confirmed

NAI30034 Zanamivir

4 Confirmed Symptomatic Cases	39-4=35 Confirmed Asymptomatic Cases	39 Confirmed Symptomatic or Asymptomatic Cases
151 Symptomatic Cases	1527 Asympotomatic	1678 Total

Source: Reviewer's Analysis

4/151 = 3% of the symptomatic zanamivir cases were confirmed
35/1527 = 2% of the asymptomatic zanamivir cases were confirmed

Although the percentage of symptomatic influenza cases were nearly the same in both treatment groups in study NAI30034, the percentage of symptomatic, laboratory-confirmed zanamivir

cases was much lower than the percentage of symptomatic, laboratory-confirmed placebo cases (only 3% for zanamivir subjects compared to 14% for placebo subjects).

The same percentage (2%) of asymptomatic placebo and zanamivir cases were confirmed.

In study NAI30010, 47% (n=32) of the 68 placebo households with ILI had symptomatic, laboratory-confirmed influenza compared to 17% (7 / 41) of the zanamivir households.

In study NAI30031, 49% (n=46) of the 93 placebo households with ILI had symptomatic, laboratory-confirmed influenza compared to 15% (10 / 67) of the zanamivir households.

In study NAIA3005, 27% (n=34) of the 127 placebo households with ILI had symptomatic, laboratory-confirmed influenza compared to 12% (11 / 94) of the zanamivir households.

3.2 Evaluation of Safety

The Statistical Reviewer did not examine any specific safety issues in the submission. For details on review of the safety data for Relenza please refer to the medical review by Dr. Andreas Pikis.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Summary of Efficacy Analyses by Age (ITT Population)

Study	Age group (years)	Contact Cases/Subjects with Symptomatic, Laboratory-confirmed Influenza	
		Placebo n/N (%)	Zanamivir n/N (%)
Family/Household Studies			
NAI30010	5-7	4/48 (8)	1/47 (2)
	8-16	9/140 (6)	4/135 (3)
	17-34	4/53 (8)	1/58 (2)
	35-49	21/160 (13)	1/151 (<1)
	50+	2/22 (9)	0/23
NAI30031	5-7	5/43 (12)	1/45 (2)
	8-16	23/211 (11)	6/237 (3)
	17-34	6/100 (6)	3/91 (3)
	35-49	20/240 (8)	2/250 (<1)
	50+	1/36 (3)	0/38
Community Studies			
NAIA3005	18-34	27/416 (6)	9/416 (2)
	35-49	5/116 (4)	2/105 (2)
	50+	2/22 (9)	0/32
NAI30034	12-16	3/55 (5)	1/51 (2)
	17-34	4/114 (4)	1/123 (<1)
	35-49	7/246 (3)	1/228 (<1)
	50-64	4/320 (1)	0/330
	65-79	4/829 (<1)	0/818
	80+	1/121 (1)	1/128 (1)

Source: Reviewer's Analysis

Compared to the zanimavir treatment group, the percentage of contact cases/subjects with symptomatic, laboratory-confirmed influenza appeared to be consistently higher in the placebo treatment group in each age group with the possible exception of subjects 80 years of age and older.

Summary of Efficacy Analyses by Race (ITT Population)

Study	Race	Contact Cases/Subjects with Symptomatic, Laboratory-confirmed Influenza	
		Placebo n/N (%)	Zanamivir n/N (%)
Family/Household Studies			
NAI30010	Whites	38/372 (10)	7/377 (2)
	Blacks	2/22 (9)	0/23
	Others	0/29	0/14
NAI30031	Whites	51/596 (19)	11/614 (2)
	Blacks	1/9 (11)	0/17
	Others	3/25 (12)	1/29 (3)
Community Studies			
NAIA3005	Whites	27/462 (6)	9/453 (2)
	Blacks	4/37 (11)	0/43
	Others	3/55 (5)	2/57 (4)
NAI30034	Whites	21/1563 (1)	4/1572 (<1)
	Blacks	1/70 (1)	0/52
	Others	1/52 (2)	0/54

Source: Reviewer's Analysis

Compared to the zanimavir treatment group, the percentage of contact cases/subjects with symptomatic, laboratory-confirmed influenza appeared to be consistently higher in the placebo treatment group for whites, blacks and other races.

4.1 Other Special/Subgroup Populations

Summary of Efficacy Analyses by Vaccination Status (ITT Population)

Study	Vaccination Status	Contact Cases/Subjects with Symptomatic, Laboratory-confirmed Influenza	
		Placebo n/N (%)	Zanamivir n/N (%)
NAI30010	Yes	5/78 (6)	0/57
NAI30010	No	35/345 (10)	7/357 (2)
NAI30031	Yes	7/60 (12)	1/72 (1)
NAI30031	No	48/570 (8)	11/589 (2)
NAIA3005	Yes	6/79 (8)	0/80
NAIA3005	No	28/475 (6)	11/473 (2)
NAI30034	Yes[1]	4/916 (<1)	1/903 (<1)
NAI30034	No	19/768 (2)	3/775 (<1)

Source: Summary of Clinical Efficacy Table 29

1. Excludes subjects vaccinated less than 21 days before the start of the study.

Compared to the zanimavir treatment group, the percentage of contact cases/subjects with symptomatic, laboratory-confirmed influenza appeared to be consistently higher in the placebo treatment group regardless of vaccination status or whether or not subjects vaccinated less than 21 days before the start of the study were included in the analysis.

In primary analysis for study NAI30034, subjects who were vaccinated less than 21 days before the start of the study were included in the denominator of the non-vaccinated subgroup. Serology results were not used in the non-vaccinated subgroup if subjects were vaccinated less than 21 days before the start of the study.

Study	Vaccination Status	Contact Cases/Subjects with Symptomatic, Laboratory-confirmed Influenza	
		Placebo n/N (%)	Zanamivir n/N (%)
NAI30034	Yes[1]	12/1141 (1)	6/1116 (1)
NAI30034	No	17/544 (3)	3/562 (1)

Source: Reviewer's Analysis
1. Including subjects vaccinated less than 21 days before the start of the study

In an alternative analysis for study NAI30034, subjects who were vaccinated less than 21 days before the start of the study were included in the denominator of the vaccinated subgroup. Serology results were used in the vaccinated subgroup even if subjects were vaccinated less than 21 days before the start of the study.

Summary of Efficacy Analyses by Vaccination Status
(ITT Population, excluding subjects vaccinated less than 21 days before the start of the study in both treatment groups)

Study	Vaccination Status	Contact Cases/Subjects with Symptomatic, Laboratory-confirmed Influenza	
		Placebo n/N (%)	Zanamivir n/N (%)
NAI30034	Yes[1]	4/916 (<1)	1/903 (<1)
NAI30034	No[1]	17/544 (3)	3/562 (1)

Source: Reviewer's Analysis
1. Excludes subjects vaccinated less than 21 days before the start of the study

In an alternative analysis for study NAI30034, subjects who were vaccinated less than 21 days before the start of the study were excluded from both vaccination subgroups.

Summary of Efficacy Analyses by Age (ITT Population, Not Vaccinated)

Study	Age group (years)	Contact Cases/Subjects with Symptomatic, Laboratory-confirmed Influenza	
		Placebo n/N (%)	Zanamivir n/N (%)
Family/Household Studies			
NAI30010	5-7	4/47 (9)	1/45 (2)
	8-16	9/128 (7)	4/127 (3)
	17-34	4/48 (8)	1/50 (2)
	35-49	17/110 (15)	1/120 (1)
	50+	1/12 (8)	0/15
NAI30031	5-7	5/41 (12)	1/43 (2)
	8-16	22/204 (11)	6/219 (3)
	17-34	4/91 (4)	4/83 (4)
	35-49	16/205 (8)	1/216 (<1)
	50+	1/29 (3)	0/28
Community Studies			
NAIA3005	18-34	24/369 (7)	9/369 (2)
	35-49	4/94 (4)	2/81 (2)
	50+	0/12	0/23
NAI30034	12-16	3/35 (9)	1/35 (3)
	17-34	4/88 (5)	1/89 (1)
	35-49	7/147 (5)	1/157 (<1)
	50-64	3/147 (2)	0/165
	65-79	1/307 (<1)	0/299
	80+	1/45 (2)	0/30

Source: Reviewer's Analysis

Compared to the zanimavir treatment group, the percentage of contact cases/subjects in non-vaccinated contact cases/subjects with symptomatic, laboratory-confirmed influenza appeared to be consistently higher in the placebo treatment group in each age group.

Summary of Efficacy Analyses by Age (ITT Population, Vaccinated)

Study	Age group (years)	Contact Cases/Subjects with Symptomatic, Laboratory-confirmed Influenza	
		Placebo n/N (%)	Zanamivir n/N (%)
Family/Household Studies			
NAI30010	5-7	0/1	0/2
	8-16	0/12	0/8
	17-34	0/5	0/8
	35-49	4/50 (8)	0/31
	50+	1/10 (10)	0/8
NAI30031	5-7	0/2	0/2
	8-16	1/7 (14)	0/18
	17-34	2/9 (22)	0/8
	35-49	4/35 (11)	1/34 (3)
	50+	0/7	0/10
Community Studies			
NAIA3005	18-34	3/47 (6)	0/47
	35-49	1/22 (5)	0/24
	50+	2/10 (20)	0/9
NAI30034	12-16	0/20	0/16
	17-34	0/26	0/34
	35-49	0/99	0/71
	50-64	1/173 (1)	0/165
	65-79	3/522 (1)	0/519
	80+	0/76	1/98 (1)

Source: Reviewer's Analysis

Compared to the zanimavir treatment group, the percentage of contact cases/subjects who were vaccinated with symptomatic, laboratory-confirmed influenza appeared to be the same or higher in the placebo treatment group in each age group.

Summary of Efficacy Analyses by Smoking Status (ITT Population)

Study	Current Smoker	Contact Cases/Subjects with Symptomatic, Laboratory-confirmed Influenza	
		Placebo n/N (%)	Zanamivir n/N (%)
NAI30010	Yes	0/30	0/38
NAI30010	No	40/393 (10)	7/376 (2)
NAI30031	Yes	2/70 (3)	0/73
NAI30031	No	53/560 (9)	12/588 (2)
NAIA3005	Yes	11/96 (11)	1/80 (1)
NAIA3005	No	23/457 (5)	10/470 (2)
NAI30034	Yes	4/153 (3)	0/151
NAI30034	No	191531 (1)	4/1526 (<1)

Source: Summary of Clinical Efficacy Table 28

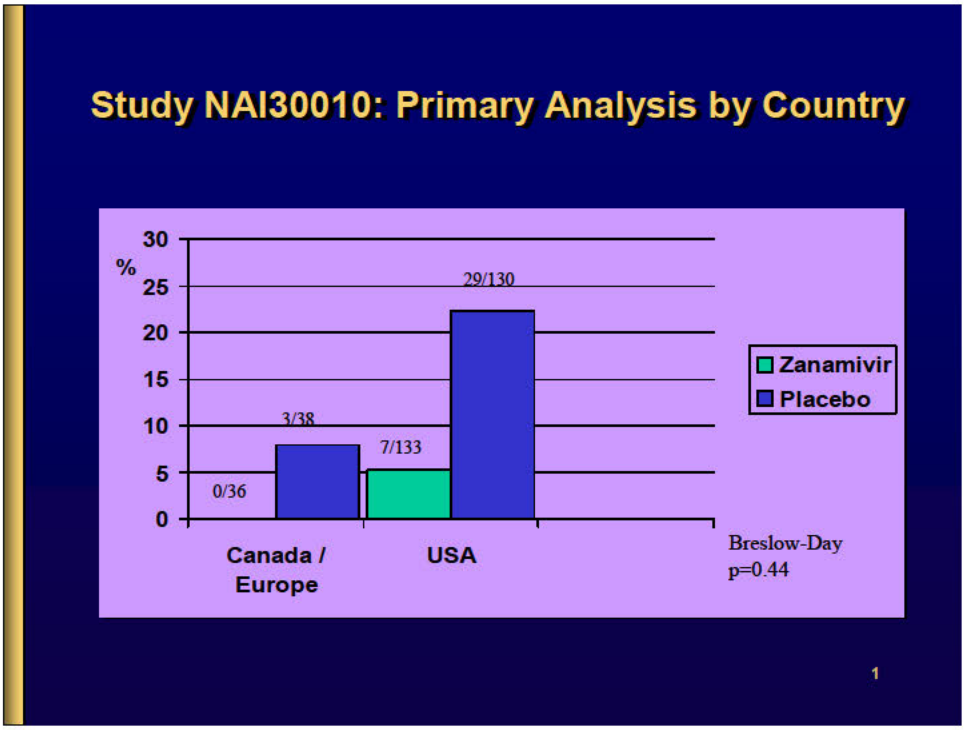
Compared to the zanimavir treatment group, the percentage of contact cases/subjects with symptomatic, laboratory-confirmed influenza appeared to be consistently higher in the placebo treatment group for subjects who were not current smokers and in all the studies except NAI30010 for current smokers.

Summary of Efficacy Analyses by High-Risk Category (ITT Population)

Study	High-Risk Category	Subjects with Symptomatic, Laboratory-confirmed Influenza	
		Placebo n/N (%)	Zanamivir n/N (%)
NAI30034	All subjects	23/1685 (1)	4/1678 (<1)
	Subjects aged ≥65 years	5/950 (<1)	1/946 (<1)
	Subjects with respiratory disease	17/695 (2)	3/684 (<1)
	Subjects with cardiovascular disease	1/307 (<1)	0/331
	Subjects with diabetes mellitus	3/370 (<1)	0/359

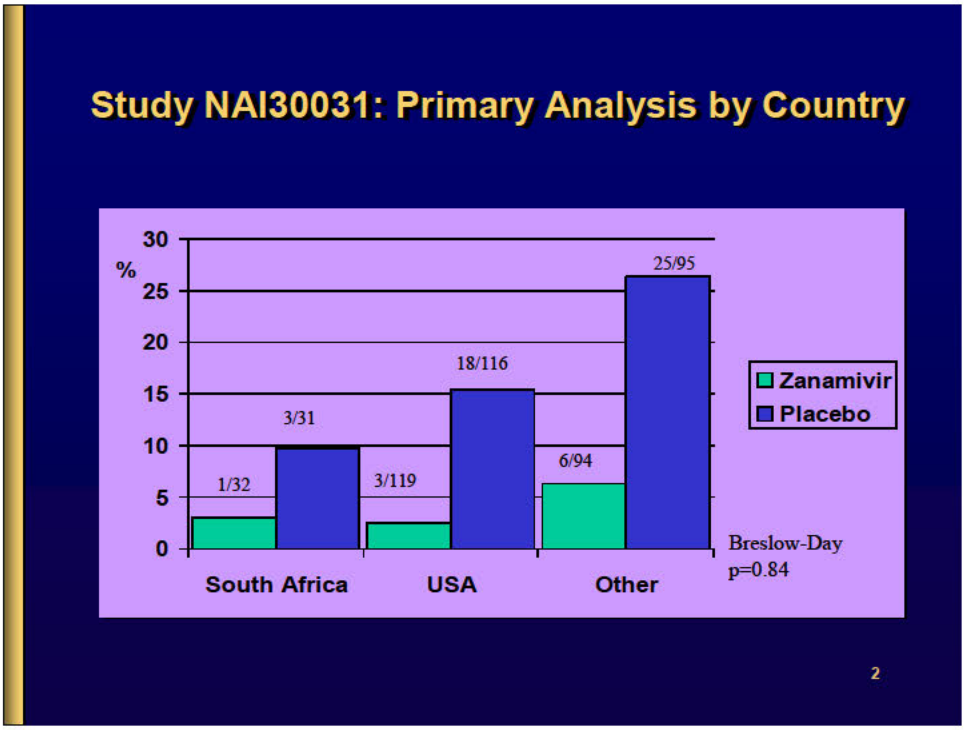
Source: Summary of Clinical Efficacy Table 30

Compared to the zanimavir treatment group, the percentage of contact cases/subjects with symptomatic, laboratory-confirmed influenza appeared to be consistently higher in high risk patients in study NAI30034.

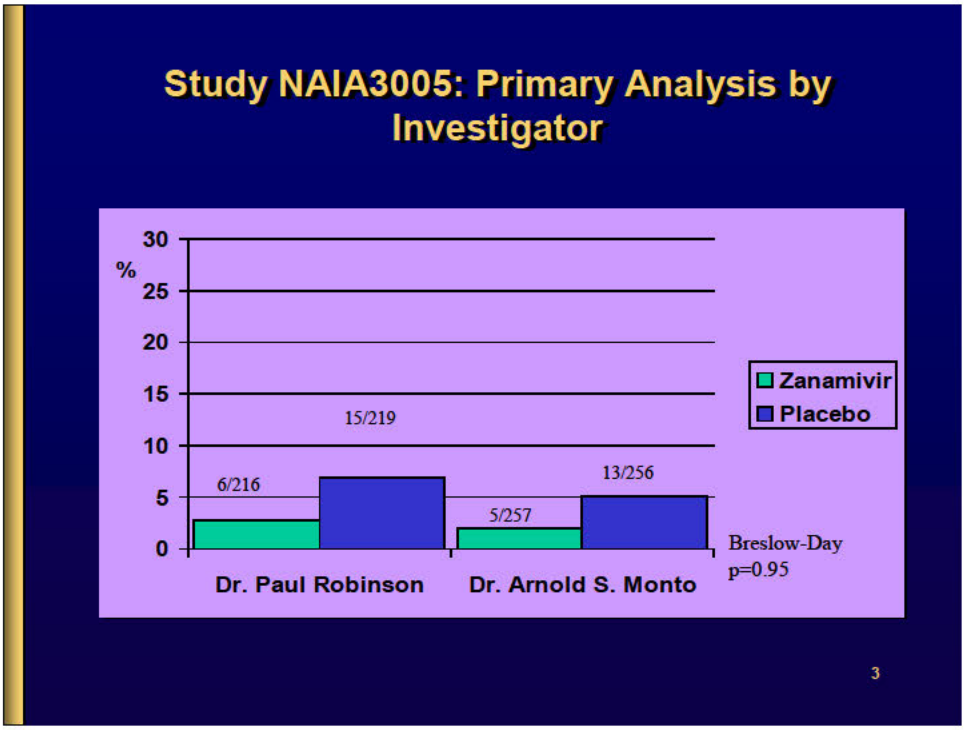


Source: Reviewer's Analysis

There were no statistically significant treatment by country interactions in either household study.

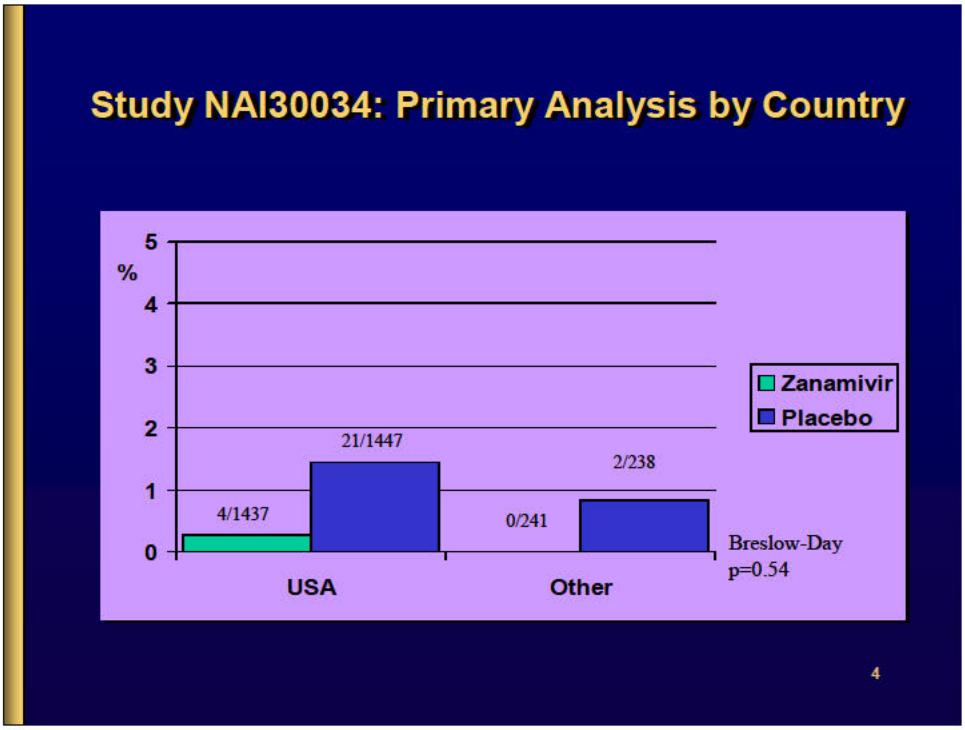


Source: Reviewer's Analysis



Source: Reviewer's Analysis

Study NAIA3005 was only conducted in the United States where the treatment effect of zanamivir relative to placebo was comparable in both centers.



Source: Reviewer's Analysis

The treatment by country interaction was not statistically significant in study NAI30034.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

Based on our review of the collective data we conclude the following.

1. In the first household study (NAI30010), where the index case as well as contact cases in the household received study medication for influenza, 19.0% (32/168) of the placebo households had at least one contact case that developed symptomatic, laboratory-confirmed influenza compared to 4.1% (4/169) of the zanamivir households. This treatment difference was statistically significant ($p<0.001$).

2. In the second household study (NAI30031), where only the contact cases in the household received study medication for influenza, 19.0% (46/242) of the placebo households had at least one contact case that developed symptomatic, laboratory-confirmed influenza compared to 4.1% (10/245) of the zanamivir households. This treatment difference was statistically significant ($p<0.001$).

3. It was highly unusual to observe almost exactly the same percentage of placebo patients and almost exactly the same percentage of zanamivir patients with laboratory-confirmed influenza in the two household studies. Similar trends were also apparent in the two studies for many of the secondary endpoints.

4. The effect of treating the contact cases with placebo or zanamivir in the first household study was confounded by the effect of giving the same treatment to the index cases. Index Cases did not receive randomized treatment in the second household study.

5. (b) (4)

6. In the first community study (NAIA3005), consisting of subjects 18 years of age or older, living in a university community setting, 6% (34/554) of the placebo subjects developed symptomatic, laboratory-confirmed influenza compared to 2% (11/553) of the zanamivir subjects. This treatment difference was statistically significant (p=0.009).

7. Unlike the first community study, the second community study (NAI30034) consisted of subjects who were at high risk of complications from influenza. High risk was defined as subjects age 65 or older, subjects with diabetes mellitus and subjects with chronic disorders of the pulmonary or cardiovascular systems. In this study, 1.4% (23/1685) of the placebo subjects developed symptomatic, laboratory-confirmed influenza compared to 0.2% (4/1678) of the zanamivir subjects. This treatment difference was statistically significant (p<0.001).

8. Similar trends were observed in the two community studies for non-vaccinated subjects and for the per protocol population.

9. In contrast to the three other pivotal phase III trials, there was no significant difference between the percentage of placebo and zanamivir patients with signs and symptoms of influenza in the second community study (NAI30034). The percentage of subjects with signs and symptoms of influenza (irrespective of laboratory results) was nearly the same in both treatment groups (10% of the subjects in the placebo treatment group and 9% of the subjects in the zanamivir treatment group had signs and symptoms of influenza).

10. Once laboratory data were utilized, the observed prophylactic effect of zanamivir in the second community study was more significant than it was in the first community study. In addition the odds ratio from the second community study was the same as the odds ratios in the two household studies and much smaller than the odds ratio in the first community study. (The odds ratio was 0.38 in the first community study compared to only 0.17-0.l8 in the other three studies.)

11. The results of the second community study were highly dependent on a small number of events (there were only 27 symptomatic, laboratory-confirmed cases of influenza). Therefore any kind of mistake or transcription error in the coding of patient identifiers or treatment codes could have significantly altered the results.

12. Therefore on February 17, 2006 we requested copies of original source documents for serology in studies NAI30031 and NAI30034. We identified 149 patients with influenza-like illness (ILI) for this request. Among these 149 subjects, we identified placebo subjects with positive laboratory confirmation of influenza and zanamivir subjects without laboratory confirmation of influenza.

13. GlaxoSmithKline photocopied the original serology documents from the (b) (4) for the two

new studies (NAI30031 and NAI30034) and provided copies to the DAVP on March 16, 2006. We examined the photocopies of the serology source documents and found them to be consistent with our data listings.

14. According to the minutes of a DAVP teleconference call with GlaxoSmithKline on March 9, 2006, the applicant stated that serology source documents were not available at the clinical investigator sites. Therefore the Division of Scientific Investigation (DSI) inspectors could not have checked the original source documents for serology when they inspected the clinical investigator sites. Therefore the results of the primary efficacy analyses and any secondary efficacy analyses of laboratory data could not have been verified and should be interpreted with caution.

15. In each of the four pivotal studies, treatment differences in the proportion of contact cases/subjects that developed symptomatic laboratory-confirmed influenza were consistently lower in the zanimivir treatment group than in the placebo treatment group for whites, blacks and other races and different age groups.

5.2 Conclusions and Recommendations

There were four pivotal phase III clinical studies included in this application to support the use of inhaled zanamivir in both household and community settings for the prophylaxis of influenza. Of the four studies, two studies (NAI30010 and NAI30031) were conducted in household settings, and two studies (NAIA3005 and NAI30034) were conducted in community settings.

Overall, based on the data submitted, the following results were observed:

- In the two household studies (NAI30010 and NAI30031), 19.0% of the placebo households and 4.1% of the zanamivir households had at least one contact case that developed symptomatic, laboratory-confirmed influenza. The odds ratios representing the prophylactic effect of zanamivir vs. placebo were 0.18 in study NAI30010 and 0.17 in study NAI30031, both statistically significant with p-values <0.001.

- In the first community study (NAIA3005), 6% of subjects treated with zanamivir and 2% of the subjects in placebo arm developed symptomatic, laboratory-confirmed influenza; the odds ratio was 0.38 with p-value equal to 0.009.

- In the second community study (NAI30034), 1.4% of subjects treated with zanamivir and 0.2% in placebo arm developed symptomatic, laboratory-

confirmed influenza; the odds ratio was 0.17 with p-value <0.001.

The effect of treating the contact cases with placebo or zanamivir in the first household study was confounded by the effect of giving the same treatment to the index cases. Index Cases did not receive randomized treatment in the second household study and the study results were not confounded.

Overall the two studies NAI30031 and NAI30010 together appear to have demonstrated the prophylactic effect of zanamivir on influenza in household settings and the two studies NAI30034 and NAIA3005 together appear to have demonstrated the prophylactic effect of zanamivir on influenza in community settings.

The following issues were raised by the statistical review team:

- Nearly identical rates were observed for the primary efficacy endpoint of laboratory-confirmed symptomatic influenza in the two household studies. Such a high degree of coincidence is rare. Similar trends were also apparent in the two studies for many of the secondary endpoints.

- The odds ratio obtained for the prophlyactic effect of zanamivir vs. placebo in the second community study was the same as the odds ratios in the two household studies (0.17 vs. 0.18 and 0.17) and much smaller than the odds ratio that was observed in the first community study (0.38).

- The results of the second community study were highly dependent on a small number of events (there were only 27 symptomatic, laboratory-confirmed cases of influenza). Therefore any kind of mistake or transcription error in the coding of patient identifiers or treatment codes can significantly alter the results.

Therefore on February 17, 2006 the review team requested copies of original source documents for serology in studies NAI30031 and NAI30034. We identified 149 patients with influenza-like illness (ILI) for this request. Among these 149 subjects, we identified placebo subjects with positive laboratory confirmation of influenza and zanamivir subjects without laboratory confirmation of influenza.

GlaxoSmithKline photocopied the original serology documents from the (b) (4) for the two new studies (NAI30031 and NAI30034) and provided copies to the Division of Antiviral Products (DAVP) on March 15, 2006. We examined the photocopies of the serology source documents and found them to be consistent with our data listings.

According to the minutes of a DAVP teleconference call with GlaxoSmithKline on March 9, 2006, the applicant stated that serology source documents were not available at the clinical investigator sites. Therefore the Division of Scientific Investigation (DSI) inspectors could not have checked the original source documents for serology when they inspected the clinical investigator sites. Therefore the results of the primary efficacy analyses and any secondary efficacy analyses of laboratory data could not have been verified and should be interpreted with caution.

Fraser Smith, Ph.D.

Mathematical Statistician

Concur: Greg Soon, Ph.D.

Biometrics Team Leader

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Fraser Smith
3/27/2006 06:23:12 PM
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Greg Soon
3/28/2006 09:54:12 AM
BIOMETRICS

Mohammad Huque
3/28/2006 10:29:28 AM
BIOMETRICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021036/S-008

MICROBIOLOGY REVIEW(S)

Microbiology Review
Division of Antiviral Drug Products (HFD-530)

NDA#: 21-036, SE1-008 **Reviewer**: N. Battula
NDA #:21-036, SE1-008-BJ

Date submitted: November 4, 2005 **Date received**: November 5, 2005
Date assigned: November 10, 2005 **Date reviewed**: March 1, 2006,

Sponsor: Glaxo Wellcome Inc.
Five Moore Drive
Research Triangle Park, NC 27709

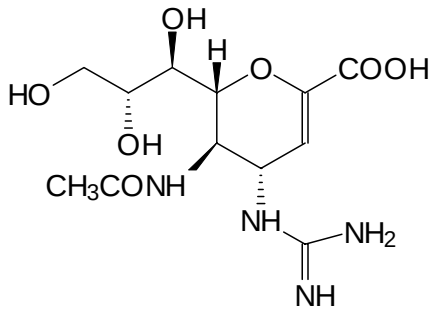
Product Names: Proprietary: Relenza®
Nonproprietary: Zanamivir
Code: GR121167X or GG167

Chemical name: 5-(acetylamino)-4-[(aminoiminomethyl)amino]- 2,6-anhydro-3,4,5-trideoxy-D-glycero-D-galacto-non-2-enoic acid.

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

Molecular Weight: 332.3

Structural Formula:



Dosage form: Inhalation powder (Relenza® Rotadisk)

Indication: Prophylaxis of influenza A and B in adults and pediatric patients 5 years of age and older

Related documents: IND 46,050 and NDA 21-036

Background and Summary: By this Supplemental New Drug Application for Relenza® (Zanamivir for inhalation) the applicant, GlaxoSmithKline, is seeking extension of current treatment indication of Relenza® to prophylaxis of influenza virus A and B in adults and pediatric patients 5 years of age and older. The original NDA # 21-036 for the treatment of uncomplicated acute illness due to influenza virus in adults and adolescents of ≥ 12 years of age who have been symptomatic for no more than 2 days was approved on July 26, 1999. Subsequently, a supplemental NDA #21-036 S-001 for Relenza® was approved for the treatment of acute uncomplicated illness due to influenza virus A and B in pediatric patients 7 years of age or older.

In support of the current request for the prophylaxis indication in adults and pediatric patients ≥5 years of age and older, the applicant submitted data from 6 Phase 3 prophylaxis studies, 4 of which were primary and 2 of which were secondary. Five of the studies were conducted as randomized, double-blind, placebo-controlled studies to evaluate the safety and efficacy of zanamivir 10 mg inhalation once daily in the prevention of influenza. One study, NAIA3003, was conducted with rimantadine as the active control (standard of care) for influenza A infection and placebo for influenza virus B infection. The primary Phase 3 studies include two post-exposure prophylaxis studies in family/household settings (Study NA130010 and Study 130031), and two seasonal prophylaxis studies in community outbreaks (study NAIA3005 and study NAI30034). The secondary phase 3 studies include two studies conducted in nursing home settings (study NAIA3003 and NAIA3004).

The primary efficacy end point for the four primary Phase 3 studies was similar. For the family/household studies it was the proportion of family/households for which at least one randomized contact developed symptomatic, laboratory confirmed influenza virus A or B. For the community studies the primary efficacy endpoint was the proportion of subjects who developed symptomatic, laboratory-confirmed influenza virus A or B during prophylaxis. In the case of the nursing home studies, the primary efficacy endpoint was the proportion of randomized subjects who, during prophylaxis, developed a new sign or symptom and had laboratory confirmation of influenza infection.

In all of the prophylaxis studies, symptomatic influenza was defined as the presence of at least two influenza-like symptoms (fever ≥ 37.8 C and/or feverishness, cough, headache, sore throat, myalgia and muscle/joint aches and pains). Laboratory confirmation of influenza virus infection for family/household studies and nursing home studies was a positive result as determined by virus culture, seroconversion (defined as a 4-fold increase in convalescent antibody titer from baseline) or PCR. In the case of community studies, laboratory confirmation of influenza virus infection determined by viral culture or by seroconversion.

The focus of this microbiology review and evaluation is to determine whether influenza viruses A or B isolated from Relenza® recipients exposed to the drug up to 28 days resulted in the emergence of influenza viruses resistant to Relenza®. The resistance evaluations involved phenotypic assessment of neuraminidase susceptibility of viral isolates before and after treatment with zanamivir and genotypic assessment by sequencing of the neuraminidase gene and sequencing of the HA1 subunit (which contains the binding site for the sialic acid receptor) of the HA gene. The applicant provided virology substudies for 5 out of the 6 phase 3 studies. However, the applicant stated that in the community prophylaxis study, NAIA3005, very few positive influenza virus isolates were obtained and resistance was not evaluated. Therefore, the resistance data submitted for the five virology substudies is evaluated and summarized.

A brief summary of the methods used in theses studies and the list of abbreviations used are presented in appendices 1 and 2, respectively.

Family/household study NAI30010: The purpose of the study was to evaluate the safety and efficacy of inhaled zanamivir 10 mg once daily for 10 days, compared with placebo in the prevention of symptomatic, laboratory confirmed influenza A and B viral infections in family/household settings. As a part of this study a virology substudy was conducted to determine if viruses resistant to zanamivir were transmitted from index cases to their family members when the drug was used for both treatment and post-exposure prophylaxis. Neuraminidase susceptibility to zanamivir was determined for each isolate. In addition, genotyping of NA and HA1 subunit of HA of the virus isolates from matching virus pairs was conducted to see if zanamivir-resistant viruses emerged.

In this study (compared to the 2nd family study, NA130031) both the index cases (10 mg BID for 5 days) and contact cases (10 mg QD for 10 days beginning after influenza was identified for that household) received Relenza® or Placebo. Virus Samples were collected by throat or nasal swabs or washes on day 1 of the index case (before treatment) and day 5 after treatment. Virus samples were also collected from family members (contact cases) who developed symptomatic illness during prophylaxis days. A total of 57 virus isolates from 22 families were assayed for IC_{50} values of neuraminidase (Table1).

Table 1. IC_{50} values of NA in virus isolates in family study NAI30010[+]

Flu Isolates	Flu A	Flu B	Index	Contact	IC_{50} Value
Patient Isolates (n=57)	40	17	20	37	1.1-12.0 nM*
	40				1.1-5.0 nM
		17			3.0-12.0 nM
WT flu A(H4N2) Control					2.15 nM[#]
Resistant Flu A (K292R) Control					81 nM[#]

[+] Summary table constructed from the sponsor provided text and datasets for virology sub-study NAI30010

*In duplicate assays there was a 2-3 fold difference in the IC_{50} value.

Average of duplicate values

The results in Table 1 show that all virus isolates recovered from index cases and contact cases were sensitive to zanamivir in the neuraminidase inhibition assays. The IC_{50} values of the index and contact cases for influenza A fell in the range from 1.1 nM to 5.0 nM, whereas the IC_{50} values for influenza virus B isolates fell in the range from 3.0 nM to 12.0 nM. Furthermore, the IC_{50} values in duplicate assays varied by 2-3 fold. In contrast, the IC_{50} values for the sensitive control influenza virus A and positive control zanamivir resistant mutant K292R was about 40-fold. The results indicate that the NA in these isolates retained sensitivity to zanamivir.

Genotyping of neuraminidase and hemagglutinin: As an additional measure of resistance emergence, the applicant determined the nucleotide sequence of the NA of influenza virus A and B isolates of the study to see if there were any changes in the genotype of NA (NA enzyme assay was done for all isolates, but genotyping of NA and HA1 was not done for all). Nucleotide sequence analysis was conducted on viruses isolated from index and contact cases on day 1 and day 5, and viruses isolated from contact cases where viruses from index cases were not recovered. Nucleotide sequence analysis of 13/15 Influenza A isolates (2 matched index cases of day 1 and 5, four index to contact pairs, one index and 2 contacts, one contact only) and 8 influenza B isolates (2 matched index cases of day 1 and 5, one index and 2 contacts, one contact only) showed no amino acid substitutions in the enzyme active site region, indicating that no influenza virus mutants with NA resistance to zanamivir have emerged or transmitted to the family members.

Nucleotide sequence analysis of HA1 subunit of the HA gene of 15 influenza A viruses (2 pairs of matched index day 1 and day 5, four pairs of index to contact cases, 2 contacts only sequences, one index case only, and 8 influenza B viruses (2 pairs of matched index cases, day 1 and day 5, one index to 2 contact cases, one contact only) showed no differences in the sialic acid binding site of HA1, indicating that no influenza viruses with amino acid substitutions in the active (sialic acid binding) emerged in the study.

Family/household study NAI30031: The purpose of the study was to evaluate the safety and efficacy of inhaled zanamivir 10 mg once daily for 10 days in the prevention of symptomatic laboratory confirmed influenza A and B viral infections in household settings. As a part of this clinical study a virology sub-study was conducted to determine if viruses resistant to zanamivir were transmitted from index cases to contact cases when the drug was used for post-prophylaxis of contact cases only. The phenotype and genotype of virus isolates obtained during prophylaxis was determined to monitor for evidence of reduced susceptibility to zanamivir in contact case isolates.

Table 2. IC_{50} values of NA in virus isolates in family study NAI30031[+]

Flu isolates	Flu A	Flu B	Index	Contact	IC_{50}
80	54	26			0.237-2.337 nM*
Flu A			24	30	0.237-1.52 nM
Flu B		26	12	14	0.903-2.337 nM
WT Flu B control					2.5 nM
Res. Flu B Control					13666 nM

[+] Summary table constructed from the text and datasets of virology sub-study NAI30031

The data in Table 2 show that the IC_{50} values of the index and contact cases for influenza A virus fell in the range from 0.237 to 1.52 nM, whereas the IC_{50} values for influenza virus B isolates fell in the range from 0.502 nM to 1.029 nM. In contrast, the average IC_{50} values for zanamivir-susceptible influenza virus B was 2.5 nM and for the zanamivir-resistant mutant was 13666 nM. The results suggest that in this study no influenza virus mutants with NA resistance to zanamivir have emerged or transmitted to the family members.

Genotyping of neuraminidase and hemagglutinin: The neuraminidase gene was amplified from all of the 80 influenza virus isolates and the nucleotide sequence determined. The neuraminidase amino acid sequences for the index and contact isolates were compared to identify amino acid substitutions. No substitutions were found at the conserved residues of the NA active site.

HA1 encoding region of the HA gene was amplified from all of the 80 influenza virus isolates and the nucleotide sequence determined. The applicant stated that the differences in amino acid sequences between the index and contact isolates of each family were noted in the tables without further comments. The data in the tables show that there were several amino acid substitutions in different isolates but none of them appear to be at the sialic acid binding site of HA1. Frame work mutations besides the active site mutations could alter the binding specificity but the applicant has not discussed the significance of these substitutions.

Evaluation of the sources of influenza virus infection by match/mismatch analysis: (In the "Summary of Clinical Efficacy" section the applicant provided 2 tables regarding the sources of infection). In the family/household studies, there is the potential that the contact cases may get influenza virus infection from the identified index case within the family or from an unidentified infected individuals from communities outside of the family. Therefore, the applicant investigated the potential sources of influenza virus infection by analysis of matched versus mismatched types of influenza virus between the contact case and index case in the same household.

The matching was evaluated by two criteria: (a) Influenza virus infection is considered a match when an index case with influenza virus type A plus contact with influenza virus type A, or an index case with influenza virus type B plus contact with influenza virus type B. All other combinations were considered not to be a match, including cases where the index case was negative.

Table 3. Matched versus mismatched influenza virus infection in index versus contact cases

Study	Influenza virus type match	Cases of influenza		Match (%)
		Placebo, N (%)	Zanamivir, N (%)	
NAI30010	Yes	29/423 (7)	5/414 (1)	34/47 (72)
NAI30010	No	11/423 (3)	2/414 (<1)	
NAI30031	Yes	46/630 (7)	9/661 (1)	55/67 (82)
NAI30031	No	9/630 (1)	3/661 (<1)	

The data in the Table 3 show that the influenza virus in most of the contact cases matches with the index case. In the family study NAI30010, 72% (34/47) of the contact cases match and in study NAI30031, 82% (55/67) of the contact cases match indicating that the transmission predominantly occurred from index cases to contact cases. However, the applicant has not determined the subtype of influenza A virus that was transmitted from index cases to contact cases or used genotyping to confirm true transmission of influenza virus A.

In the family/household studies the applicant also examined matching of viruses by sequencing of the HA1 subunit of HA gene of influenza viruses isolated from contact cases and index cases. The analysis included nucleotide differences between the contact cases and index cases in influenza A virus subtypes and influenza B virus.

Table 4. Match and mismatch between contact cases and index cases by genotyping of HA1 subunit of HA

	NAI30010 contact cases		NAI30031 contact cases	
	Placebo, N	Zanamivir, N	Placebo, N	Zanamivir, N
Subtype, A/H1N1	0	0	21	5
Subtype A/H3N2	15	6	4	1
Subtype B	10	2	13	1
All subtypes	25	8	39*	7
Matched contact and index	22* (88%)	4 (50%)	30 (77%)	6 (86%)
Unmatched contact and index	3 (12%)	4 (50%)	9 (23%)	1 (14%)

*The sponsor presented Table 4 in the section on the "Summary of Clinical Efficacy". The numbers on matches and mismatches presented do not add up to the summary results stated.

The sponsor stated that the data in Table 4 on the family studies regarding matching and mismatching of contact cases and index cases analyzed by genotyping show that matching was more common with 82% (27/33) of the cases in study NAI30010 and 80% (37/46) of the cases in study NAI30031. However, the numbers provided in Table 4 show that matching occurred in 78% (26/33) of the cases in study NAI30010 and also 78% (36/46) of the cases study NA130031. This percentage difference in the transmission has no major impact on the results of the study. The applicant has not included sufficient details to evaluate the viral transmissions and confirm the matches and mismatches.

Seasonal prophylaxis during community outbreaks, Study NA130034: The purpose of the study is to evaluate the safety and efficacy of zanamivir 10 mg once daily for 28 days in the prevention of influenza virus A and B infections in subjects who were at high risk of complications from influenza. High risk was defined as ≥65 years of age, subjects with diabetes mellitus, and subjects with chronic disorders of pulmonary or cardiovascular systems. Included with this study was a virology sub-study to investigate the susceptibility of zanamivir in clinical isolates obtained during prophylaxis of high risk subjects. The phenotype of the clinical isolates was judged by determining the susceptibility of neuraminidase and the genotype by sequencing the neuraminidase and HA1 subunit of HA.

A total of 19 virus samples were recovered in the study. Determination of the IC_{50} values of zanamivir showed that in influenza A (H1N1) isolates (n=10) the IC_{50} values ranged from 0.48 nM to 1.27 nM and for influenza B isolates the IC_{50} values ranged 1.36 nM to 3.66 nM which is within the NA sensitivity range. The results suggest that the NA activity of the virus isolates in this study retained susceptibility to zanamivir.

Genotyping of neuraminidase and hemagglutinin: The gene encoding NA from all 19 NA positive virus samples were amplified and their nucleotide sequence determined. The NA amino acid sequences from the 10 H1N1 viruses and 9 flu B viruses were compared to the consensus NA amino acid sequences of A strains and the conserved sequences of B strains. The 10 H1N1 viruses differed at 13 amino acid positions: 48, 50, 75, 94, 188, 189, 198, 222, 267, 344, 355, 415 and 432. In Flu B there were differences in 8 amino acid positions at 15, 40, 73, 81, 91, 148, 198 and 403. None of the H1N1 or B viruses possessed changes in the NA enzyme active site, consistent with the observation of retention of susceptibility of the NA enzyme activity in the phenotyping assay. However, some of these amino acid substitutions in the frame work of NA could contribute to an alteration of the enzyme activity and/or the antigenicity of the protein as the assays used were not sensitive enough to detect the effect of these amino acid substitutions.

The HA1 encoding region for all of the NA enzyme positive samples were amplified the nucleotide sequence determined. The deduced amino acid HA1 sequences were compared to HA1 amino acid sequences within the trial and to the reference strains. There were differences at 7 amino acid positions among the flu A viruses at 48, 108, 120, 128, 163, 166, and 252. In the flu B viruses there were 7 amino acid differences at positions 58, 126, 136, 164, 175, 230 and 286. Three of these changes have been found in previous isolates due to antigenic drift. None of these changes were at the receptor binding of HA1. However, some of the same amino acid substitutions have occurred in several isolates suggesting the possibility of alterations in receptor binding and/or the antigenic properties of the HA as the methods in the analysis are not adequate to determine the effect of the amino acid substitutions. By the methods used in this analysis the study suggest no evidence of resistance to zanamivir as determined by the susceptibility NA enzymatic activity and by nucleotide sequence analysis of the NA gene and HA1 region of HA.

Nursing home study NAIA3003: The purpose of the study was to evaluate the safety and efficacy of inhaled zanamivir 10 mg once daily for 14 days compared with standard of care in the prevention of influenza A and B virus infections in U.S. nursing homes. Standard of care was 100 mg/day of rimantadine for influenza virus A and placebo for influenza virus B. The study includes a virology sub-study to assess the emergence and transmission of resistant virus during influenza outbreaks. Samples were collected for flu virus detection when there was a new sign or symptom onset during prophylaxis. A repeat sample was collected within 2 or 3 working days.

A total of 92 isolates were obtained for analysis: Seventy from 55 subjects during the 1997/98 season; 14 from 14 subjects during 1998/99 season; and 8 from 8 subjects during the 1999/2000 season. All of the 92 samples were assayed for the susceptibility of NA enzymatic activity. Eight of the isolates had very low NA activity for determining IC_{50} value. Assay of the remaining 84 isolates showed that they were fully susceptible to zanamivir (IC_{50} values in the range of 0.44 nM to 5.86 nM (80 were H3N2 with IC_{50}

range 0.44-2.89 nM and 4 were Flu B with IC_{50} range 0.97 to 5.86 nM). In control experiments, the zanamivir susceptible Flu B virus IC_{50} value was 2.0 nM and the Zanamivir resistant Flu B isolate IC_{50} value was 5142 nM. The NA IC_{50} values for zanamivir fall within the sensitivity range indicating no evidence of resistance to zanamivir in the study. A limitation to this analysis is that isolates were cultured before the analysis possibly selecting for the outgrowth of wild type virus in the isolate.

Genotyping of neuraminidase and hemagglutinin: The NA gene was amplified from 33 selected samples that included zanamivir treated isolates, rimantadine treated isolates and isolates from which no IC_{50} value could be obtained. The NA amino acid sequences generated were compared against the consensus sequences constituted from influenza isolates of 3 influenza seasons as well as a reference strain A/Sydney/5/97. Fourteen out of 33 sequences were identical to the consensus sequence. In others there were 25 amino acid substitutions at 21 positions. These substitutions were not at the enzyme active site and the applicant ascribed the amino acid substitutions to natural variation and/or antigenic drift as they occurred independent of Relenza® treatment.

The HA1 sequences generated for 85 isolates (4/85 were Flu B) were compared for changes in the HA1 receptor binding region that may be associated with reduced susceptibility to zanamivir. There were no pre or post treatment samples for comparison. A consensus sequence was generated from all of the isolates sequenced within each season. In addition, the consensus sequence was also compared to the relevant WHO vaccine strains, A/Sydney/5/97 (H3N2) and B/Beijing/184/93 which represented the viruses circulating during the seasons. The applicant stated that there were no amino acid substitutions in the receptor binding site of HA1. The amino acid differences found were attributed to natural variation and/or genetic drift as they occurred independently of drug treatment.

Genotyping of the matrix (M2) gene: The antiviral target of rimantadine in influenza virus is the matrix protein, M2. The M2 protein of influenza virus A is 97 amino acids long. The transmembrane region encompasses 19 amino acids (25-43), and primarily single amino acid substitutions at positions 27, 30 and 31 confer rimantadine resistance with substitutions at amino acid position 31 predominating.

The applicant sequenced the entire M2 coding region of 87 Flu A isolates to determine if resistance mutations that conferred resistance to rimantadine occurred in the study. Thirty three out of the 87 isolates (38%) had 1 of 3 amino acid substitutions (at positions 27, 30 and 31) associated with development of resistance (1 had a mutation at amino acid position 27, 3 at position 30, and 29 at position 31). The applicant stated that they confirmed the genotypic resistance by phenotypic assay in MDCK cells by ELISA. The combined results suggest that no zanamivir resistance was observed in the 85 isolates examined, whereas rimantadine resistance was frequent with 38% of the treated isolates showing emergence of resistance to rimantadine.

Nursing home study NAIA3004: The purpose of the study was to determine the safety and efficacy of inhaled zanamivir 10 mg once daily for 14 days in controlling influenza outbreaks in nursing homes. In this study rimantadine was not used as the standard of care when flu outbreak was declared in the nursing home. Samples were collected for flu virus detection when there was a new sign or symptom onset during prophylaxis. A repeat sample was collected within 2 or 3 working days. The study was conducted in 3 flu seasons 1997/1998, 1998/1999 and 1999/2000

A total of 107 isolates from 103 subjects were obtained over the 3 influenza seasons. Twenty one had low virus titers with low NA activity for the determination of IC_{50} values. The remainder 86 isolates (21/86 from the 1997/1998 season, 37/86 from the 1998/1999 season and 28/86 from the 1999/2000 season) were tested for susceptibility to zanamivir in the NA enzyme inhibition assay. All of the isolates were reported to be influenza A (H3N2) where subtype information was available. Determination of the IC_{50} values for all of the 86 isolates showed that they were in the range of 0.26 nM to 1.79 nM. For the reference susceptible strain A/Sidney/5/97 (H3N2) the IC_{50} value was 0.64 nM, the IC_{50} for susceptible B strain was 2.0 nM and the IC_{50} for resistant B/Beijing/1/87 was 5142 nM.

Genotyping of neuraminidase and hemagglutinin: The NA gene of 33 influenza virus isolates was amplified and the nucleotide sequence determined. The amino acid sequences were compared to a single consensus sequence that was generated from all 3 influenza seasons. Among 33 NA amino acid sequences there were substitutions at 15 positions. None of the substitutions occurred at the enzyme active site, an observation consistent with the retention of NA sensitivity to zanamivir sensitivity in the phenotypic assay.

HA1 nucleotide sequences were obtained for all of the 103 isolates. The deduced amino acid sequences were examined for changes in the HA1 receptor binding region that may be associated with reduced susceptibility to zanamivir by comparing them to a consensus HA1 sequence generated for each season. In addition, each of the HA1 sequences were compared with the WHO recommended vaccine strain A which represents the prevalent virus circulating during the influenza seasons. There were several amino acid substitutions in isolates from each of the seasons (25/103 from the 1997/1998 season had 4 amino acid changes), 46/103 from the 1998/1999 had 11 amino acid changes 32/103 from the 1999/2000 had 4 amino acid changes). None of the substitutions occurred at the receptor binding site. All of the substitutions were ascribed to natural variation and/or antigenic drift of the virus as they occurred independently of drug treatment.

According to the applicant in all of the prophylaxis studies 45 isolates have been cultured from zanamivir treated subjects and 166 from placebo-treated subjects. In these studies none of the isolates have shown shifts in neuraminidase susceptibility or changes in

amino acids within the NA binding site or within the HA1 receptor binding. The applicant's previous studies on the emergence of resistance to zanamivir in treatment studies also failed to detect the emergence of resistance. However, in published literature treatment of influenza virus infected subjects showed emergence of resistance to zanamivir as determined by shifts in susceptibility in the NA and amino acid changes in the NA and/or HA. The sample size in the prophylaxis studies reported is too small and virus sampling and assay methods available are inadequate to score for resistance.

Conclusions: GlaxoSmithKline conducted 6 controlled phase 3 clinical studies to evaluate the prophylactic effectiveness of Relenza® in the transmission of influenza virus A and B from index cases to contact cases. These prophylaxis studies involved situations of family/household settings, community settings, and nursing home settings, and the study population included children, adolescents, adults and geriatric subjects. The objective of the studies is to evaluate the safety and efficacy of inhaled zanamivir 10 mg once daily up to 28 days in the prevention of transmission of influenza virus A and B.

As a component of antiviral efficacy of Relenza® the applicant conducted virology substudies to evaluate the potential emergence and transmission of influenza viruses resistant to zanamivir. The resistance evaluations involved phenotypic assessment determined by changes in the susceptibility of neuraminidase in viral isolates before, during and after treatment with zanamivir. In addition, genotypic assessment of resistance was conducted by sequencing of the viral neuraminidase and the HA1 subunit of HA which contains the binding site for the sialic acid receptor.

Phenotypic assessment of zanamivir resistance by changes in the susceptibility of neuraminidase enzyme activity has long been considered an inadequate method as the virus can undergo compensatory changes to alter viral entry, replication, assembly or budding with a different spectrum of resistance emergence than that scored by the susceptibility changes in the NA alone. The availability of a cell culture system that measures viral replication is considered more appropriate to evaluate the emergence of drug resistance. However, to date no satisfactory cell culture system that specifically supports the replication of human influenza viruses is available to measure the emergence of resistance to NA inhibitors. In view of the dual deficiency limitation of NA susceptibility assay and lack of specific cell-virus replication system to quantify true resistance, the current measures of resistance and cross-resistance are inadequate. Therefore, for both drug development and evaluation of true resistance rates, it is essential to construct recombinant cell lines that are specific to human influenza virus infection and replication.

Resistance to zanamivir has been recognized to emerge due to genotypic changes in the target NA and or the non-target HA as these two viral molecules serve complementary functions in influenza viral infection and replication. Accordingly, the applicant appropriately evaluated the genotypes of these two components of the virus genome for

the emergence of resistance. In these studies, the applicant focused on the amino acid substitutions in the enzyme active site of the neuraminidase and the sialic acid binding receptor site of HA1 subunit of HA. Framework amino acids beyond the active sites can also alter active site conformations and confer resistance. In the genotyping studies several amino acid substitutions were identified in the frame work amino acids of NA and HA1 all of which the applicant attributed to natural variation and or genetic drift. Some of these substitutions may contribute to resistance to zanamivir. However, determination of the phenotypic susceptibility of neuraminidase showed that the enzyme retained susceptibility during the course of exposure to zanamivir.

Influenza virus is a very successful infectious agent. The remarkable adaptability of influenza virus including the error-prone nature of its replication endows the virus with pre-existence of any conceivable mutant providing opportunities for selection and selective amplification of the mutants under drug pressure. As expected treatment of influenza virus infections with neuraminidase inhibitors showed the emergence of resistance to both of the currently approved drugs (2, 3, 4). The NA inhibitors have a low genetic barrier for resistance in that a single mutation is sufficient to overcome the drug pressure making it facile for the virus to select for the single mutations.

The applicant stated that in the prophylaxis studies that they have conducted there was no evidence for the emergence of resistance to zanamivir as measured by phenotyping of NA activity and by genotyping of NA and HA1 subunit of the HA. The number of samples analyzed in these studies is too small to determine resistance. In addition, the methods applied for delineating the emergence of resistance in influenza viruses against zanamivir are inadequate as discussed earlier. The scientific community eagerly awaits the development of suitable cell-virus combination systems for influenza virus replication to facilitate drug development for the treatment of influenza virus infections as well as to determine the emergence of resistance to anti influenza viral drugs.

Recommendations: In this supplemental NDA requesting Relenza® indication in adults and pediatric patients 5 years of age and older for prophylaxis of influenza, the sponsor provided clinical microbiology data on the emergence of resistance in clinical samples collected from index and contact cases. The submitted data are evaluated and the package insert is revised to reflect the current microbiology information from the submission and that available in published literature. With respect to microbiology the application is recommended for approval.

Package insert: The microbiology portion of the package insert the applicant submitted is revised to incorporate additional information from the applicant's submission and that available in the open literature. The revised package insert agreed upon by the applicant and the FDA is presented below.

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Phase 4 Commitment: Provide an annual update on emergence of resistance to zanamivir, as well as cross-resistance between zanamivir and other neuraminidase inhibitors, as an integrated review of information from NISN (Neuraminidase Inhibitor Surveillance Network), data collected by GSK, and information in the published literature. Each annual update will include information on the methodologies (e.g., culture, PCR) used in studies during that reporting period.
Timeline: Provide this annual update as part of the NDA Annual Reports due within 60 days of the original approval anniversaries in July 2007, July 2008, and July 2009.

References:

1. Gubareva L.V. et al., J Infect Dis (1998) 178: 1257-1262
2. Ison M.G. et al., JID (2006) 193: 760-764
3. Kiso M. et al., Lancet (2004) 364: 759-765
4. De Jong, M.D. et al., N Engl J Med (2005) 353: 2667-2672

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Narayana Battula, Ph.D.
Microbiologist

Concurrence:
HFD 530/ Assoc Dir. _____Date _____

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Narayana Battula
3/28/2006 09:17:52 AM
MICROBIOLOGIST

Julian O Rear
3/28/2006 07:15:45 PM
MICROBIOLOGIST

James Farrelly
3/29/2006 07:27:44 AM
PHARMACOLOGIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021036/S-008

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA:	21-036, SE1-008
Submission Dates:	11/04/2005
Brand Name	RELENZA®
Generic Name:	Zanamivir
Formulation:	(b) (4)
Applicant:	GlaxoSmithKline
Reviewer:	Jenny H. Zheng, Ph.D.
Team Leader:	Kellie Reynolds, Pharm.D.
OCPB Division:	DCPB 4
Clinical Division:	DAVP
Indication :	Prophylaxis of Influenza A and B

Summary of Clinical Pharmacology:

Zanamivir is indicated for the treatment of uncomplicated acute illness due to influenza A and B virus (10 mg twice daily for 5 days). In the current supplement the applicant seeks approval of zanamivir for the prophylaxis of influenza A and B in family/household and community settings. The proposed dose of zanamivir for prophylaxis of influenza in adults and pediatric patients 5 years of age and older in a household setting is 10 mg once daily (2 inhalations) for 10 days. The recommended dose of zanamivir for prophylaxis of influenza in adults and adolescents during a community outbreak is 10 mg once daily for 28 days. The doses proposed for prophylaxis are half the recommended daily dose for treatment of influenza but the duration is longer.

The applicant conducted Phase III clinical trials to support their claim. These trials provide the basis of approval for this supplement and are described in the medical and statistical reviews. No clinical pharmacology information was provided with this supplement because the information from the original NDA and the pediatric efficacy supplement also apply to the new indication.

During review of this supplement, questions were raised regarding the use of zanamivir for a longer duration (greater than 5 days) in patients with renal impairment. The original NDA included an evaluation of zanamivir pharmacokinetics in subjects with renal impairment. Subjects received a single intravenous dose of zanamivir (4 mg or 2 mg). The study showed that the clearance of zanamivir is substantially decreased in subjects with renal impairment as compared to subjects with normal renal function. In subjects with mild to moderate impairment, AUC nearly doubled; while in subjects with severe impairment, AUC increased by almost 7-fold. The elimination half-life was prolonged from 2.9 hours in subjects with normal renal function to 4.4 hours in subjects with mild to moderate impairment and to 15 hours in subjects with severe impairment. Based on an assessment of safety in the original NDA, there was no concern for subjects with mild to moderate renal impairment and no dose adjustment was recommended. Due to the magnitude of the AUC increase for subjects with severe renal impairment, the statement "Safety and efficacy have not been documented in the presence of severe renal insufficiency" was included in the CLINICAL PHARMACOLOGY/Pharmacokinetics/ *Impaired Renal Function* section. For prophylaxis, zanamivir could be used for up to 28 days. Although the daily exposure (AUC) for prophylaxis at steady-state is half of the

daily exposure for treatment, the safety of the longer use of zanamivir in subjects with renal impairment was of potential concern. Therefore, we asked the applicant to provide an integrated summary of all subjects with renal impairment enrolled in zanamivir prophylaxis studies. The data provided by the sponsor indicated that from three prophylaxis studies, 39.1% (822/2076) of subjects had some degree of renal insufficiency, and 2.6% (54/2076) had severe renal impairment. In subjects with renal impairment, changes in laboratory parameters were similar between treatment groups and degrees of renal impairment. Since there was an insufficient number of subjects with renal impairment to fully determine the safe use of zanamivir in this population, the statement in the label regarding subjects with severe renal impairment will not be changed.

There are no other clinical pharmacology issues for this efficacy supplement.

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Jenny H. Zheng
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Kellie Reynolds
3/24/2006 04:45:31 PM
BIOPHARMACEUTICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021036/S-008

OTHER REVIEW(S)

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: February 13, 2006

TO: David Araojo, Regulatory Project Manager
Andreas Pikis, M. D., Medical Officer
Division of Special Pathogen and Transplant Products, HFD-530

THROUGH: Constance Lewin, M.D., M.P.H.
Acting Branch Chief
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations

FROM: Antoine El-Hage, Ph.D.
Regulatory Pharmacologist
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 21-036/SE1-008

APPLICANT: GlaxoSmithKline

DRUG: Relenza (zanamivir inhalation 10 mg powder)

THERAPEUTIC CLASSIFICATION: Priority Review

INDICATION: Prophylaxis of Influenza

CONSULTATION REQUEST DATE: November 10, 2005

DIVISION ACTION GOAL DATE: March 3, 2006

PDUFA DATE: May 4, 2006

I. BACKGROUND:

Relenza (zanamivir) is approved for the treatment of influenza in adults and adolescents aged 12 years and older at a dose of 10 mg (5mg per inhalation) twice daily for 10 days. Zanamivir is a potent and highly selective inhibitor of influenza virus neuraminidase that is effective against all known influenza A and B. Zanamivir is known to reduce the spread of influenza A and B by inhibiting the release of infectious virions from the epithelial cells of the respiratory tract. The outbreaks of influenza occur almost every year and the severity is determined by the antigenic composition of the virus, and the extent of pre-existing immunity in the population. Currently, there are no drugs available for the prophylaxis of influenza which is effective against both influenza A and B with an acceptable safety profile which is not associated with rapid emergence of viral resistant strains. Two drugs, amantadine and rimantadine are approved in some

countries for prophylaxis and treatment of influenza; however, their use is limited due to their safety profile and lack of activity against Influenza B.

Four sites were selected for data audit in support of this application, two sites per protocol to cover both protocols NAI30031 and NAI30034.

II. RESULTS (by protocol/site):

Name of CI and site #, if known	City, State*	Protocol	Insp. Date	EIR Received Date	Final Classification
Thomas Klein, M.D.	Wichita, KS	NAI30031	1/17/06	2/10/06	NAI
Arnolds Monto, M.D.	Ann Arbor, MI	NAI30031	12/21/05	2/10/06	VAI
Robert Bettis, M.D.	Edmonds, WA	NAI30034	1/24/06	pending	NAI*
Gerald Shockey, M.D.	Mesa, AZ	NAI30034	1/12/06	2/10/06	VAI

* based on e-mail summary statement from field investigator.

Key to Classifications
NAI = No deviation from regulations. Data acceptable.
VAI-No Response Requested= Deviations(s) from regulations. Data acceptable.
VAI-Response Requested = Deviation(s) form regulations. See specific comments below for data acceptability
OAI = Significant deviations for regulations. Data unreliable.

A. Protocol NAI30031

1. Thomas Klein, M.D. (Site 7370, enrolled 92 subjects and 5 subjects were discontinued)

   This site enrolled 92 subjects and 5 subjects were discontinued. Records for 30% of the study subjects were reviewed and no discrepancies were noted. Informed consent for all subjects including the discontinued subjects were reviewed and no deviations were noted. No Form FDA 483 was issued. There were no limitations to the inspection. Data generated appear acceptable in support of the pending application.

2. Arnold Monto, M. D. (site7440, enrolled 117 subjects)

   At this site, 347 individuals from 93 families were screened, with five individuals reported as screen failures and one family withdrew. 43 families were randomized with a total of 117 subjects randomized and enrolled in the study.

   The medical records/source documents for over 50% of the randomized subject files (70) were reviewed in depth and the source data and case report forms were compared to data listings and primary efficacy measures. Informed consent for all subjects was verified. The medical records disclosed that all subjects met inclusion criteria, received the study drug and adhered to the protocol. The adverse events experienced by subjects during the study were accurately reported in the case report forms (except for subject 89452 who experienced “cough” that was not reported). At the conclusion of the inspection, a 2-item Form FDA 483 was issued for failure to use the approved informed consent with the revised safety information; failure to obtain IRB approval for changes in research activities such as recruitment letter that was sent to subjects prior to IRB approval; and failure to report an adverse event in the case report form. None of the inspectional observations would adversely impact acceptability of the data. There were no limitations to this inspection. Data appear acceptable in support of the pending application.

B. Protocol NAI30034

1. Robert Bettis, M.D. (site 42789, enrolled 92 subjects and 7 were discontinued)

   This site screened 112 subjects, enrolled 92 and 4 subjects were discontinued. The first subject was enrolled on 10/31/01 and the last subject was enrolled on 12/6/05.
   The field investigator reviewed 84 subjects' files. Informed consent for all subjects were reviewed and no significant deviations were noted. No FDA 483 was issued. Data appear acceptable in support of the pending application.

2. Gerald Shockey, M.D. (site 46140, enrolled 87 subjects)

   At this site 87 subjects were enrolled; 112 subjects screened; 15 withdrew consent; six subjects did not show for treatment; and four subjects were reported as screen failures.

   The medical records/source documents for 30 randomized subjects were reviewed in depth and the source data were compared to data listings and primary efficacy measures. Informed consent for all subjects was verified. The medical records disclosed that all subjects met inclusion criteria, received the study drug and adhered to the protocol (except for two subjects 71394 and 75199 who were noncompliant in taking their medication). The adverse events experienced by subjects during the study were accurately reported in the case report forms. A 2-item Form FDA 483 was issued. The findings included the non-reporting of concomitant medication for six subjects (75223, 75198, 71401, 75194, 75209 and 75215). In addition, the medical records for four subjects (75236, 75231, 75233 and 75217) were off site and were not available for review in order to verify the use of concomitant medication. The medications used by study subjects were not prohibited by the protocol. In general the records reviewed were accurate and no significant problems were noted that would impact the acceptability of the data. The clinical investigator acknowledged the inspectional observations (not recording of all concurrent medication in the case report forms) and promised to exercise more care in future studies. Data from this site appear acceptable in support of the pending application.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

The inspections of Drs. Klein, Monto, Bettis and Schokey did not identify any significant observations that would compromise the integrity of the data. Therefore, the data reviewed are acceptable. Should the EIR from the inspection of Dr. Bettis contain additional information that would affect the application, it will be forwarded to the review division as soon as it becomes available.

{See appended electronic signature page}

Antoine El-Hage, Ph.D.
Regulatory Pharmacologist
Good clinical practice Branch I, HFD-46
Division of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Constance Lewin, M.D., M.P.H.
Acting Branch Chief
Good Clinical Practice Branch I

Division of Scientific Investigations

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/s/

Antoine El-Hage
2/24/2006 10:43:12 AM
CSO

Constance Lewin
2/24/2006 10:49:34 AM
MEDICAL OFFICER

MEMORANDUM **DEPARTMENT OF HEALTH AND HUMAN SERVICES**
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: January 27, 2006

TO: Debra Birnkrant, MD, Director
Division of Anti-Viral Products

FROM: Claudia Karwoski, PharmD, Scientific Coordinator
Office of Drug Safety

DRUG: Relenza (zanamivir for inhalation)

NDA#: 21-036 s-008

SPONSOR: Glaxo-Smith-Kline

SUBJECT: ODS Review of Proposed Risk Management Plan (RMP) submitted November 4, 2005

PID #: D050657

The Office of Drug Safety (ODS) has reviewed the proposed Risk Management Plan (RMP) for zanamivir, as submitted on November 4, 2005, and concludes that it does not appear to differ substantially from routine risk management measures, such as FDA-approved professional labeling and routine post-marketing surveillance. The RMP was submitted on November 4, 2005 as part of an efficacy supplement for new indication of prophylaxis of influenza A and B.

The risk management plan for zanamivir currently consists of:

1. Continuation of the routine activities of signal detection/management
2. Fulfillment of the legal and regulatory reporting requirements.
3. Providing support for the neuraminidase inhibitors susceptibility network as an important part of disease management activity.

The sponsor's stated goal of the risk management plan is:

- Continuing routine proactive pharmacovigilance
- Defining further work to quantify the risk

The sponsor states that the safety profile of zanamivir is under regular review (routine signal detection, evaluation and management by the sponsor) and the Core Safety Information (CSI) is updated as new adverse reactions are identified. Furthermore, the sponsor does not identify any outstanding, unresolved safety issues associated with zanamivir use at this time which would necessitate an update of the CSIor additional risk management activities.

The sponsor proposes to increase surveillance activities in a pandemic situation with the following plan of action. In an influenza pandemic situation where there is the possibility of widespread use of zanamivir, in addition to the routine signal detection activities, the sponsor states that they could increase the frequency of signal detection activities as necessary, based on the volume of reports received, to identify any new or unexpected adverse events or safety concerns. The sponsor also states that any newly emerging safety signals would be identified and evaluated promptly and appropriate action initiated in consultation with the Regulatory bodies. We agree with this proposal.

The Office of Drug Safety has reviewed the submitted RMP and has determined that it does not identify a specific safety concern for which a Risk Minimization Action Plan (RiskMAP) to minimize risk would be normally associated. . If the sponsor or the review division identifies a safety concern and determines that a RiskMAP is warranted or should the review division wish ODS to review any proposed Phase IV protocols or epidemiological post-marketing studies, please provide a consult request.

ODS RMP Team
Melissa M. Truffa, R.Ph., Safety Evaluator Team Leader
Cherye Milburn, Regulatory Health Project Manager, ODS-IO

_____
Claudia B. Karwoski, Pharm.D., Scientific Coordinator
Office of Drug Safety

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/s/

Cherye Milburn
1/27/2006 10:31:20 AM
CSO

Claudia Karwoski
1/30/2006 08:17:13 AM
DRUG SAFETY OFFICE REVIEWER

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 21036 Supplement # 008 Efficacy Supplement Type SE- 1

Trade Name: Relenza
Established Name: zanamivir
Strengths: inhalation

Applicant: GlaxoSmithKline
Agent for Applicant: Sherman Alfors

Date of Application: November 4, 2005
Date of Receipt: November 4, 2005
Date clock started after UN:
Date of Filing Meeting: December 9, 2005
Filing Date: December 9, 2005
Action Goal Date (optional): User Fee Goal Date: November 4, 2005

Indication(s) requested: Prophylaxis of Influenza A and B

Type of Original NDA: (b)(1) ☐ (b)(2) ☐
OR
Type of Supplement: (b)(1) ☒ (b)(2) ☐

NOTE:
(1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application is a (b)(2), complete Appendix B.

(2) If the application is a supplement to an NDA, please indicate whether the NDA is a (b)(1) or a (b)(2) application:

☒ NDA is a (b)(1) application OR ☐ NDA is a (b)(2) application

Therapeutic Classification: S ☐ P ☒
Resubmission after withdrawal? ☐ Resubmission after refuse to file? ☐
Chemical Classification: (1,2,3 etc.) 1
Other (orphan, OTC, etc.)

Form 3397 (User Fee Cover Sheet) submitted: YES ☒ NO ☐

User Fee Status: Paid ☒ Exempt (orphan, government) ☐
Waived (e.g., small business, public health) ☐

NOTE: *If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling.*

If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the user fee staff.

- Is there any 5-year or 3-year exclusivity on this active moiety in an approved (b)(1) or (b)(2) application? YES ☐ NO ☒
  If yes, explain:

- Does another drug have orphan drug exclusivity for the same indication? YES ☐ NO ☒

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?
  YES ☐ NO ☐

  If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES ☐ NO ☒
  If yes, explain:

- If yes, has OC/DMPQ been notified of the submission? YES ☐ NO ☐

- Does the submission contain an accurate comprehensive index? YES ☒ NO ☐

- Was form 356h included with an authorized signature? YES ☒ NO ☐
  If foreign applicant, both the applicant and the U.S. agent must sign.

- Submission complete as required under 21 CFR 314.50? YES ☒ NO ☐
  If no, explain:

- If an electronic NDA, does it follow the Guidance? N/A ☐ YES ☒ NO ☐
  If an electronic NDA, all forms and certifications must be in paper and require a signature.
  Which parts of the application were submitted in electronic format? All

  Additional comments:

- If an electronic NDA in Common Technical Document format, does it follow the CTD guidance?
  N/A ☐ YES ☒ NO ☐

- Is it an electronic CTD (eCTD)? N/A ☐ YES ☒ NO ☐
  If an electronic CTD, all forms and certifications must either be in paper and signed or be electronically signed.

  Additional comments:

- Patent information submitted on form FDA 3542a? YES ☒ NO ☐

- Exclusivity requested? YES, 3 Years NO ☐
  NOTE: *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*

- Correctly worded Debarment Certification included with authorized signature? YES ☒ NO ☐
  If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

NOTE: *Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge . . . ."*

- Financial Disclosure forms included with authorized signature? YES ☒ NO ☐
  (Forms 3454 and 3455 must be included and must be signed by the APPLICANT, not an agent.)
  NOTE: *Financial disclosure is required for bioequivalence studies that are the basis for approval.*

- Field Copy Certification (that it is a true copy of the CMC technical section)? Y ☐ NO ☒

- PDUFA and Action Goal dates correct in COMIS? YES ☐ NO ☒
  If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.

- List referenced IND numbers:

- End-of-Phase 2 Meeting(s)? Date(s) _____ NO ☒
  If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) June 29, 2005 NO ☐
  If yes, distribute minutes before filing meeting.

Project Management

- Was electronic "Content of Labeling" submitted? YES ☒ NO ☐
  If no, request in 74-day letter.

- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC?
  YES ☐ NO ☒

- Risk Management Plan consulted to ODS/IO? N/A ☐ YES ☒ NO ☐

- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? Y ☐ NO ☒

- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? N/A ☐ YES ☐ NO ☒

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted?
  N/A ☒ YES ☐ NO ☐

If Rx-to-OTC Switch application:

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS? N/A ☒ YES ☐ NO ☐

- Has DOTCDP been notified of the OTC switch application? YES ☐ NO ☐

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff?
  YES ☐ NO ☐

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES ☒ NO ☐
  If no, did applicant submit a complete environmental assessment? YES ☐ NO ☐
  If EA submitted, consulted to Florian Zielinski (HFD-357)? YES ☐ NO ☐

- Establishment Evaluation Request (EER) submitted to DMPQ? YES ☐ NO ☐

- If a parenteral product, consulted to Microbiology Team (HFD-805)? YES ☐ NO ☐

ATTACHMENT

MEMO OF FILING MEETING

DATE: December 9, 2005

BACKGROUND: Relenza is an approved product and this efficacy supplement is for a prophylaxis of influenza A and B in defined setting indication.
(Provide a brief background of the drug, e.g., it is already approved and this NDA is for an extended-release formulation; whether another Division is involved; foreign marketing history; etc.)

ATTENDEES: Debra Birnkrant, Jeff Murray, Kim Struble, Andreas Pikis, Greg Soon, Fraser Smith, Narayana Battula, Kuei-Meng Wu, Barbara Styrt, Thomas Hammerstrom, David Roeder, Edward Cox, and Mark Goldberger

ASSIGNED REVIEWERS (including those not present at filing meeting) :

Discipline	**Reviewer**
Medical:	Andreas Pikis, M.D.
Secondary Medical:	
Statistical:	Fraser Smith, Ph.D.
Pharmacology:	Kuei-Meng Wu, Ph.D.
Statistical Pharmacology:	
Chemistry:	George Lunn, Ph.D.
Environmental Assessment (if needed):	
Biopharmaceutical:	Kellie Reynolds, Pharm.D.
Microbiology, sterility:	
Microbiology, clinical (for antimicrobial products only):	Narayana Battula, Ph.D.
DSI:	Tony El Hage
Regulatory Project Management:	David Araojo, Pharm.D.
Other Consults:	DDMAC, ODS

Per reviewers, are all parts in English or English translation? YES ☒ NO ☐
If no, explain:

CLINICAL FILE ☒ REFUSE TO FILE ☐

- Clinical site inspection needed? YES ☒ NO ☐
- Advisory Committee Meeting needed? YES, date if known _____ NO ☒
- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?
  N/A ☒ YES ☐ NO ☐

CLINICAL MICROBIOLOGY N/A ☐ FILE ☒ REFUSE TO FILE ☐

STATISTICS N/A ☐ FILE ☒ REFUSE TO FILE ☐

BIOPHARMACEUTICS FILE ☒ REFUSE TO FILE ☐

- Biopharm. inspection needed? YES ☐ NO ☒

PHARMACOLOGY N/A ☐ FILE ☒ REFUSE TO FILE ☐

- GLP inspection needed? YES ☐ NO ☒

CHEMISTRY FILE ☒ REFUSE TO FILE ☐

- Establishment(s) ready for inspection? YES ☐ NO ☐
- Microbiology YES ☐ NO ☐

ELECTRONIC SUBMISSION:
Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:
(Refer to 21 CFR 314.101(d) for filing requirements.)

☐ The application is unsuitable for filing. Explain why:

☒ The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.

- ☐ No filing issues have been identified.
- ☒ Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1. ☐ If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.
2. ☐ If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
3. ☒ Convey document filing issues/no filing issues to applicant by Day 74.

David Araojo, Pharm.D.
Regulatory Project Manager, HFD-530

Appendix A to NDA Regulatory Filing Review

An application is likely to be a 505(b)(2) application if:

(1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
(2) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)
(4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

Appendix B to NDA Regulatory Filing Review
Questions for 505(b)(2) Applications

1. Does the application reference a listed drug (approved drug)? YES ☐ NO ☐

   *If "**No**," skip to question 3.*

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s):

3. The purpose of this and the questions below (questions 3 to 5) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval and that should be referenced as a listed drug in the pending application.

   (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved?

   YES ☐ NO ☐

   (***Pharmaceutical equivalents*** are drug products in identical dosage forms that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and (3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))

   *If "**No**," skip to question 4. Otherwise, answer part (b).*

   (b) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? YES ☐ NO ☐
   (The approved pharmaceutical equivalent(s) should be cited as the listed drug(s).)

   *If "**Yes**," skip to question 6. Otherwise, answer part (c).*

   (c) Have you conferred with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007)? YES ☐ NO ☐

   *If "**No**," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.*

4. (a) Is there a pharmaceutical alternative(s) already approved? YES ☐ NO ☐

   (***Pharmaceutical alternatives*** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

   *If "**No**," skip to question 5. Otherwise, answer part (b).*

   (b) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES ☐ NO ☐
   (The approved pharmaceutical alternative(s) should be cited as the listed drug(s).)

   ***NOTE:** If there is more than one pharmaceutical alternative approved, consult the Director, Division of*

Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007) to determine if the appropriate pharmaceutical alternatives are referenced.

*If "**Yes**," skip to question 6. Otherwise, answer part (c).*

(c) Have you conferred with the Director, Division of Regulatory Policy II, ORP? YES ☐ NO ☐

*If "**No**," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.*

5. (a) Is there an approved drug product that does not meet the definition of "pharmaceutical equivalent" or "pharmaceutical alternative," as provided in questions 3(a) and 4(a), above, but that is otherwise very similar to the proposed product?

YES ☐ NO ☐

*If "**No**," skip to question 6.*

*If "**Yes**," please describe how the approved drug product is similar to the proposed one and answer part (b) of this question. Please also contact the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007), to further discuss.*

(b) Is the approved drug product cited as the listed drug? YES ☐ NO ☐

6. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").

7. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)). YES ☐ NO ☐

8. Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application should be refused for filing under 21 CFR 314.101(d)(9)). YES ☐ NO ☐

9. Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application should be refused for filing under 21 CFR 314.101(d)(9). YES ☐ NO ☐

10. Are there certifications for each of the patents listed for the listed drug(s)? YES ☐ NO ☐

11. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)
Patent number(s):

NOTE: *IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must* ***subsequently*** *submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)].*

☐ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)
Patent number(s):

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).
Patent number(s):

☐ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.
Patent number(s):

12. Did the applicant:

- Identify which parts of the application rely on information (e.g. literature, prior approval of another sponsor's application) that the applicant does not own or to which the applicant does not have a right of reference?

  YES ☐ NO ☐

- Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?

  YES ☐ NO ☐

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?

  N/A ☐ YES ☐ NO ☐

- Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv).?

  N/A ☐ YES ☐ NO ☐

13. If the (b)(2) applicant is requesting 3-year exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4):

    - Certification that at least one of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a).

      YES ☐ NO ☐

    - A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval.

      YES ☐ NO ☐

    - EITHER

      The number of the applicant's IND under which the studies essential to approval were conducted.

      IND# _____ NO ☐

      OR

      A certification that the NDA sponsor provided substantial support for the clinical investigation(s) essential to approval if it was not the sponsor of the IND under which those clinical studies were conducted?

      YES ☐ NO ☐

14. Has the Associate Director for Regulatory Affairs, OND, been notified of the existence of the (b)(2) application?

    YES ☐ NO ☐

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/s/

David Araojo
1/5/2006 02:20:10 PM
CSO

Kimberly Struble
1/5/2006 03:12:13 PM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021036/S-008

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 21-036 SUPPL # S-008 HFD # 530

Trade Name RELENZA

Generic Name zanamivir for inhalation

Applicant Name GlaxoSmithKline

Approval Date, If Known

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1), SE1

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

n/a

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

n/a

d) Did the applicant request exclusivity?

YES ☒ NO ☐

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

n/a

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 21-036 zanamivir for inhalation

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered “NO” for original approvals of new molecular entities.)
IF “YES,” GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of

summary for that investigation.

YES ☒ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☒ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☒

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☒

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Study NAI30010, NAI30031, NAI30034, and NAIA3005

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES ☐	NO ☒
Investigation #2	YES ☐	NO ☒

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES ☐	NO ☒
Investigation #2	YES ☐	NO ☒

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Study NAI30010, NAI30031

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1		!
		!
IND # 43776	YES ☒	! NO ☐
		! Explain:

Investigation #2		!
		!
IND # 46050	YES ☒	! NO ☐
		! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☒

If yes, explain:

==========

Name of person completing form: David Araojo, Pharm.D.
Title: Regulatory Project Manager
Date: March 16, 2006

Name of Office/Division Director signing form: Debra Birnkrant, M.D.
Title: Division Director, DAVP

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Debra Birnkrant

3/28/2006 02:58:24 PM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA # : 21-036 **Supplement Type (e.g. SE5):** SE1 **Supplement Number:** 008

Stamp Date: November 4, 2005 **Action Date:**

HFD 530 **Trade and generic names/dosage form:** RELENZA (zanamivir for inhalation)

Applicant: GlaxoSmithKline **Therapeutic Class:** 7030120

Indication(s) previously approved: Treatment of influenza

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: Prophylaxis of influenza A and B in defined settings

Is there a full waiver for this indication (check one)?

☒ **Yes: Please proceed to Section A.**

☐ **No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed**
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

☐ **Products in this class for this indication have been studied/labeled for pediatric population**
☐ **Disease/condition does not exist in children**
☐ **Too few children with disease to study**
☐ **There are safety concerns**
☒ **Other: Children under the age of 5 years of age are not likely to be able to use this product.**

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min_____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for partial waiver:

☐ **Products in this class for this indication have been studied/labeled for pediatric population**
☐ **Disease/condition does not exist in children**
☐ **Too few children with disease to study**
☐ **There are safety concerns**
☐ **Adult studies ready for approval**
☐ **Formulation needed**

❑ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____

Reason(s) for deferral:

❑ **Products in this class for this indication have been studied/labeled for pediatric population**
❑ **Disease/condition does not exist in children**
❑ **Too few children with disease to study**
❑ **There are safety concerns**
❑ **Adult studies ready for approval**
❑ **Formulation needed**
Other:_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

_____
Regulatory Project Manager

cc: NDA ##-###
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 12-22-03)

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

Is there a full waiver for this indication (check one)?

- ❑ **Yes: Please proceed to Section A.**

- ❑ **No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed**
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- ❑ **Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**
- ❑ **There are safety concerns**
- ❑ **Other:_____**

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg____ mo._____ yr._____ Tanner Stage_____

Reason(s) for partial waiver:

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- ❑ **Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**
- ❑ **There are safety concerns**
- ❑ **Adult studies ready for approval**
- ❑ **Formulation needed**
- ❑ **Other:_____**

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- ❑ **Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**
- ❑ **There are safety concerns**
- ❑ **Adult studies ready for approval**
- ❑ **Formulation needed**
- ❑ **Other:_____**

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

_____
Regulatory Project Manager

cc: NDA ##-###
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 10-14-03)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

David Araojo

3/28/2006 01:51:16 PM

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information			
NDA 21-036	Efficacy Supplement Type SE-1	Supplement Number 008	
Drug: RELENZA® (zanamivir for inhalation)		Applicant: GlaxoSmithKline	
RPM: David Araojo, PharmD		HFD-530	Phone # 301-796-0669

Application Type: **(x)** 505(b)(1) **( )** 505(b)(2) (This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.) **If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information (including patent certification information) that is no longer correct.** **( )** Confirmed and/or corrected	Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):

❖ Application Classifications:	
• Review priority	**( )** Standard **(x)** Priority
• Chem class (NDAs only)	1
• Other (e.g., orphan, OTC)	
❖ User Fee Goal Dates	May 4, 2006
❖ Special programs (indicate all that apply)	**(x)** None Subpart H **( )** 21 CFR 314.510 (accelerated approval) **( )** 21 CFR 314.520 (restricted distribution) **( )** Fast Track **( )** Rolling Review **( )** CMA Pilot 1 **( )** CMA Pilot 2
❖ User Fee Information	
• User Fee	**(x)** Paid UF ID number PD3006210
• User Fee waiver	**( )** Small business **( )** Public health **( )** Barrier-to-Innovation **( )** Other (specify) _____
• User Fee exception	**( )** Orphan designation **( )** No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) **( )** Other (specify) _____
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	**( )** Yes **(x)** No

• This application is on the AIP	( ) Yes (x) No
• Exception for review (Center Director's memo)	
• OC clearance for approval	
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification & certifications from foreign applicants are cosigned by US agent.	(x) Verified
❖ Patent	
• Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	(x) Verified
• Patent certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ( ) Verified 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
• [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	**N/A**
• [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next box below (Exclusivity)).*	(x) N/A (no paragraph IV certification) ( ) Verified
• [505(b)(2) applications] For each paragraph IV certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation. Answer the following questions for each paragraph IV certification: (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))). *If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).* (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? *If "**Yes,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "**No**," continue with question (3).* (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?	( ) Yes ( ) No ( ) Yes ( ) No ( ) Yes ( ) No

(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))). *If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.* (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? *If "**Yes,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "**No**," continue with question (5).* (5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.*	**( )** Yes **( )** No **( )** Yes **( )** No
❖ Exclusivity (approvals only)	
• Exclusivity summary • Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)	Enclosed
• Is there existing orphan drug exclusivity protection for the "same drug" for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	**( )** Yes, Application #_____ **(x)** No
❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	N/A

General Information	
❖ Actions	
• Proposed action	**(x)** AP **( )** TA **( )** AE **( )** NA
• Previous actions (specify type and date for each action taken)	N/A
• Status of advertising (approvals only) N/A	**( )** Materials requested in AP letter **( )** Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	**(x)** Yes **( )** Not applicable
• Indicate what types (if any) of information dissemination are anticipated	**( )** None **(x)** Press Release **( )** Talk Paper **( )** Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	Attached to Approval Letter
• Most recent applicant-proposed labeling	
• Original applicant-proposed labeling	
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	
• Applicant proposed	
• Reviews	
❖ Post-marketing commitments	See Approval letter
• Agency request for post-marketing commitments	
• Documentation of discussions and/or agreements relating to post-marketing commitments	
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	Enclosed
❖ Memoranda and Telecons	Enclosed
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	
• Pre-NDA meeting (indicate date)	March 8, 2005 and June 29, 2005
• Pre-Approval Safety Conference (indicate date; approvals only)	
• Other	
❖ Advisory Committee Meeting	N/A
• Date of Meeting	
• 48-hour alert	
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	N/A

Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	Enclosed
Clinical Information	
❖ Clinical review(s) *(indicate date for each review)*	Enclosed
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	Enclosed
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	Enclosed
❖ Risk Management Plan review(s) *(indicate date/location if incorporated in another rev)*	Enclosed
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	Enclosed
❖ Demographic Worksheet *(NME approvals only)*	N/A
❖ Statistical review(s) *(indicate date for each review)*	Enlcosed
❖ Biopharmaceutical review(s) *(indicate date for each review)*	Enclosed
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	Enclosed
• Bioequivalence studies	N/A
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	Enclosed
❖ Environmental Assessment	N/A
• Categorical Exclusion *(indicate review date)*	
• Review & FONSI *(indicate date of review)*	
• Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Microbiology (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	N/A
❖ Facilities inspection (provide EER report)	Date completed: ( ) Acceptable ( ) Withhold recommendation
❖ Methods validation	( ) Completed ( ) Requested ( ) Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	Enclosed
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	N/A
❖ CAC/ECAC report	N/A

Appendix A to NDA/Efficacy Supplement Action Package Checklist

An application is likely to be a 505(b)(2) application if:

(1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
(2) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)
(4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

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/s/

David Araojo
3/28/2006 01:44:36 PM

RECORD OF FDA TELECONFERENCE

Date of Meeting: **March 23, 2006**

NDA: **21-036/SE1/S-008**

Drug: **RELENZA® (zanamivir for inhalation)**

Sponsor: **GlaxoSmithKline**

Subject: **Labeling and Post Marketing Commitments**

Division of Antiviral Products (DAVP) Participants:

Kim Struble, PharmD, Medical Team Leader
Andreas Pikis, MD, Medical Reviewer
David Araojo, PharmD, Regulatory Project Manager

GlaxoSmithKline (GSK) Participants:

Mike Ossi, M.D., Clinical Research
Dorothea Griffiths, M.D., Ph.D., Clinical Research
(b) (6)
David Cocchetto, Ph.D., Regulatory Affairs
Sherman Alfors, M.S., Regulatory Affairs

Background

This teleconference was held at the request of DAVP to discuss labeling and post marketing commitments (PMC) for GSK's efficacy supplement to include an indication of prophylaxis of influenza A and B, in adults and pediatric patients 5 years of age and older, in defined settings. GSK provided an updated proposed label via email on March 21, 2006 (Attachment A) and draft PMCs via email on March 22, 2006 (Attachment B).

Discussion Points

DAVP opened the meeting by accepting GSK's changes in the label (b) (4)

(b) (4)

Moving on to PMCs, GSK will revise wording to PMC#2, in Attachment B, as follows:

Submit a postmarketing adverse drug experience report to DAVP as a "15-Day Alert Report" for each of the following serious adverse events:

- anaphylaxis
- bronchospasm or other pulmonary adverse event
- cardiovascular adverse event
- any adverse event with a fatal outcome.

Consistent with 21 CFR 314.80, GSK will make diligent efforts to obtain as complete a set of information as possible, including information about antecedent and concomitant medical circumstances of the adverse experience or fatality, results of laboratory tests, a copy of any available medical records, and a copy of the autopsy report (if performed). A "15-Day Alert Report - Follow Up" will be submitted to DAVP if additional information is obtained after the deadline for submission of the initial report. The 15-Day Alert Reports due to DAVP each week will be collected and submitted as a batch, once a week, to DAVP. Each such submission will be sent to NDA 21-036 as "General Correspondence: Safety Reports per Postmarketing Commitment". Timeline: Such Alert Reports will be prepared and submitted by GSK for the specified events occurring through May 31, 2009.

GSK will revise PMC #3 to include wording on the planned distribution of the wall charts.

(b) (4)

Action Items Summary

- GSK will submit revised draft labeling.
- GSK will revise PMC #3 to include wording on the planned distribution of the wall charts.

Attachment A

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/s/

David Araojo
3/28/2006 11:22:46 AM
CSO

Kimberly Struble
3/28/2006 11:31:45 AM
MEDICAL OFFICER

RECORD OF FDA TELECONFERENCE

Date of Meeting: **March 20, 2006**

NDA: **21-036/SE1/S-008**

Drug: **RELENZA® (zanamivir for inhalation)**

Sponsor: **GlaxoSmithKline**

Subject: **Labeling and Post Marketing Commitments**

Division of Antiviral Products (DAVP) Participants:

Kim Struble, PharmD, Medical Team Leader
Andreas Pikis, MD, Medical Reviewer
Jules O'Rear, PhD, Microbiology Team Leader
Narayana Battula, PhD, Microbiology Reviewer
David Araojo, PharmD, Regulatory Project Manager

GlaxoSmithKline (GSK) Participants:

Mike Ossi, M.D., Clinical Research
Dorothea Griffiths, M.D., Ph.D., Clinical Research
(b) (6)
David Cocchetto, Ph.D., Regulatory Affairs

Background

This teleconference was held at the request of DAVP to discuss labeling and post marketing commitments (PMC) for GSK's efficacy supplement to include an indication of prophylaxis of influenza A and B, in adults and pediatric patients 5 years of age and older, in defined settings. DAVP provided labeling comments to GSK in a March 17, 2006, email correspondence (Attachment A).

Discussion Points

GSK opened the meeting by agreeing to consolidate the package insert WARNING section as proposed in the March 17, 2006 email from DAVP. Additionally, GSK

proposes to update the section with study results submitted to IND 46,050 (SN 160), dated September 22, 2000.
DAVP needs to review the final study report before accepting any revisions.

DAVP agreed to a change in the order of Important Information on Use of Relenza in the INDICATIONS AND USAGE section as follows:

- RELENZA is not recommended for treatment or prophylaxis of influenza in individuals with underlying airways disease (such as asthma or chronic obstructive pulmonary disease) (see WARNINGS) due to risk of serious bronchospasm.
- RELENZA has not been proven effective for treatment of influenza in individuals with underlying airways disease.
- RELENZA has not been proven effective for prophylaxis of influenza in the nursing home setting.
- RELENZA is not a substitute for early vaccination on an annual basis as recommended by the Centers for Disease Control's Immunization Practices Advisory Committee.

For the Patient Package Insert, DAVP agreed to GSK's proposal to replace (b) (4) with (b) (4)

DAVP encouraged GSK to voluntarily submit the Relenza label in the Physician Labeling Rule format prior to the next flu season.

GSK will submit revised draft labeling, based on today's teleconference comments.

Moving on to PMCs, DAVP requested the following:

- Please provide annual updates on the emergence of resistance to zanamivir and cross-resistance of zanamivir to other anti-influenza drugs by integrating reports of the Neuraminidase Inhibitor Surveillance Network, GlaxoSmithKline and the published literature. Please also include a report on the current methodologies used in these studies.
  Annual reports starting August 2007 to July 2011 (5 reports)
- Please submit post-marketing adverse drug experience with a fatal outcome as expedited report (i.e., 15 day report). Please ensure that diligent efforts were made to obtain additional information about antecedent and concomitant medical circumstances of the fatality. These efforts will include a copy of the medical records, results of laboratory tests, and an autopsy report (if an autopsy was performed).

  Please also submit reports of serious adverse events of anaphylaxis, cardiovascular, bronchospasm and other pulmonary adverse events as

expedited reports (i.e., 15 day reports). Please make diligent efforts to obtain additional information about antecedent and concomitant medical circumstances of the adverse event, a copy of the medical records, and results of laboratory tests. For both deaths and serious adverse events please submit a safety follow-up report if needed. We recommend deaths and the above serious adverse events reports be submitted for a minimum of three years after approval of this sNDA.

In addition, DAVP asked GSK to propose a PMC for supplementary educational material, such as a wall chart or storyboard, which could be used in a doctor's office or pharmacy for those patients without access to the internet or DVD to view the Relenza instructional video.

(b) (4)

DAVP stated that the PMC proposal from GSK for (b) (4) of Relenza is not necessary as a PMC. DAVP will consider the old PMC's as released, waived, or renegotiated.

DAVP will convey PMC language regarding the microbiology and post marketing adverse drug events to GSK. GSK will then submit a draft letter of the PMC's.

Lastly, GSK is not planning a Press Release because they currently have (b) (4) treatment packs (5 day treatment/10 day prophylaxis).

Action Items Summary

1. GSK will submit revised draft labeling, based on today's teleconference comments.

2. DAVP will convey PMC language regarding the microbiology and post marketing adverse drug events to GSK.

3. GSK will submit a draft letter of PMC's.

6 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

David Araojo
3/22/2006 10:33:17 AM
CSO

Kimberly Struble
3/28/2006 11:29:11 AM
MEDICAL OFFICER

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE IV

FACSIMILE TRANSMITTAL SHEET

DATE: March 21, 2006

To: David Cocchetto US Regulatory Affairs	**From:** David Araojo, Regulatory Project Manager
Company: GSK	Division of Antiviral Products
Fax number: (919)483-5756	**Fax number:** (301)796-9883
Phone number: (919)483-6030	**Phone number:** (301)796-0669

Subject: Post marketing commitments

Total no. of pages including cover: 3

Comments:

Document to be mailed: ☐ YES ☒ NO

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF FACSIMILE CORRESPONDENCE

NDA: 21-036/S-008

Drug: Relenza® (zanamivir)

Date: March 21, 2006

Sponsor: GlaxoSmithKline (GSK)

From: David Araojo, Pharm.D., Regulatory Project Manager

Through: Kim Struble, Pharm.D., Medical Team Leader
Andreas Pikis, M.D., Medical Reviewer
Jules O'Rear, Ph.D., Microbiology Team Leader
Narayana Battula, Ph.D., Microbiology Reviewer

Subject: Post Marketing Commitments

Reference is made to your submission to NDA 21-036, dated November 4, 2005. Reference is also made to the teleconference held between the division and GSK on March 20, 2006. The following post marketing commitments are conveyed on behalf of the clinical and microbiology review teams.

Clinical

Please submit post-marketing adverse drug experience with a fatal outcome as expedited report (i.e., 15 day report). Please ensure that diligent efforts were made to obtain additional information about antecedent and concomitant medical circumstances of the fatality. These efforts will include a copy of the medical records, results of laboratory tests, and an autopsy report (if an autopsy was performed).

Please also submit reports of serious adverse events of anaphylaxis, cardiovascular, bronchospasm and other pulmonary adverse events as expedited reports (i.e., 15 day reports). Please make diligent efforts to obtain additional information about antecedent and concomitant medical circumstances of the adverse event, a copy of the medical records, and results of laboratory tests. For both deaths and serious adverse events please submit a safety follow-up report if needed. We recommend deaths and the above serious adverse events reports be submitted for a minimum of three years after approval of this sNDA.

Microbiology

Please provide annual updates on the emergence of resistance to zanamivir and cross-resistance of zanamivir to other anti-influenza drugs by integrating reports of the Neuraminidase Inhibitor Surveillance Network, GlaxoSmithKline and the published literature. Please also include a report on the current methodologies used in these studies.
Annual reports starting August 2007 to July 2011 (5 reports).

We are providing the above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me if you have any questions regarding the contents of this transmission.

_____

David Araojo, Pharm.D.
Regulatory Health Project Manager
Division of Antiviral Drug Products

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/s/

David Araojo
3/21/2006 12:37:24 PM
CSO

Kimberly Struble
3/28/2006 11:26:18 AM
MEDICAL OFFICER

RECORD OF FDA TELECONFERENCE

Date of Meeting: **March 9, 2006**

NDA: **21-036/SE1/S-008**

Drug: **RELENZA® (zanamivir for inhalation)**

Sponsor: **GlaxoSmithKline**

Subject: **Serology source document request**

Division of Antiviral Products (DAVP) Participants:

Debra Birnkrant, MD, Division Director
Kim Struble, PharmD, Medical Team Leader
Andreas Pikis, MD, Medical Reviewer
Greg Soon, PhD, Statistics Team Leader
Fraser Smith, PhD, Statistics Reviewer
Tony El Hage, PhD, DSI
David Araojo, PharmD, Regulatory Project Manager

GlaxoSmithKline (GSK) Participants:

Mike Ossi, M.D., Clinical Research
Dorothea Griffiths, M.D., Ph.D., Clinical Research
(b) (6)
David Cocchetto, Ph.D., Regulatory Affairs
Sherman Alfors, Regulatory Affairs

Background

This teleconference was held at the request of DAVP to discuss the Agency's February 17, 2006, and February 28, 2006, facsimile request for copies of individual serology source documents. To date, GSK has submitted laboratory datasets, used to produce the line listings, provided from the contracted lab. GSK provided a summary of the step by step handling of specimens and data for serology (Attachment A).

Discussion Points

GSK opened the meeting by describing the step by step handling of specimens and data for serology (Attachment A). GSK stated that when the serum is collected, the same number (Subject ID) stays with the sample. In addition, serology, PCR, and culture results are not reported back to the investigator sites.

GSK confirmed that they are working on providing the handwritten serology results described in Step 4 of Attachment A. However, GSK claimed there is no order to the results and they have to search through over 4000 records. GSK may be able to search the records using the date the sample arrived.

GSK will provide updates on the timeline of the expected submission of the handwritten serology results.

Attachment A

Sequence of Events from Collection of Specimens for Serology to GSK's Analysis of Results for Studies NAI30031 and NAI30034 to Preparation of Datasets included in NDA 21-036/S-008

(the items in red with underlining are items that have been submitted to FDA)

Step 1

- Clinical Investigator or Investigator's study personnel collects blood sample for serology
- Serum was prepared and stored with refrigeration until transport

Step 2

Serum specimens (barcoded and labeled with subject id) were transported by courier on the day of or day after collection to a regional contract laboratory (b) (4) for storage and accrual prior to shipping of batches of specimens to the (b) (4) For transport from the investigator to a regional contract laboratory, specimens were sent using standard packing supplies provided by (b) (4)

- Investigators in the US and Canada sent samples to (b) (4) facility in (b) (4) (b) (4)
- Investigators in Europe and South Africa sent samples to (b) (4) facility in (b) (4) (b) (4)
- Investigators in Australia and New Zealand sent samples to (b) (4) facility in (b) (4). (b) (4) then shipped samples to (b) (4) facility in (b) (4) for subsequent handling.

Step 3

- Upon receipt of specimens at a (b) (4), specimens were stored frozen (-20°C) until approximately 50 paired samples were available. At that point, (b) (4) sent the batch of paired samples to (b) (4) for assay. Samples were packed in dry ice and transported by express shipment to (b) (4).
- Neither (b) (4) nor (b) (4) had the treatment codes for any subjects.

Step 4

- A laboratory scientist at (b) (4) handwrote results of serology assays on their "Clinical Trial Serology" data forms (per (b) (4) SOP, page 12, item 1). A copy of (b) (4) procedure was sent to FDA as Attachment 3 in our response of February 22 to FDA. A copy of (b) (4) Clinical Trial Serology forms were requested again by GSK, on March 8, for each patient in studies NAI30031 and NAI30034 listed in FDA's fax of February 17, 2006.

Step 5

- [redacted] entered results of serology assays in a computerized record (see [redacted] procedure, page 12, items 2-8 for details). A copy of [redacted] procedure was sent to FDA as Attachment 3 in our response of February 22 to FDA.

Step 6

- [redacted] transferred the serology results as a "SAS dataset" in transport format, generated using the SAS PROC COPY command (containing subject number and serology results) to [redacted]. (Please see [redacted] SOP page 12, item 8 for details. Note that GGR=Glaxo Group Research.)

Step 7

- [redacted] had responsibility for ensuring the serology data was formatted as specified with GSK identifiers and included with the final transfer of datasets to GSK.

Step 8

- [redacted] provided "raw SAS datasets" to GSK Data Management

Step 9

- GSK Data Management made the raw SAS datasets available to GSK's Statisticians

Step 10

- GSK's Statisticians prepared a "derived serology SAS dataset" by removing unnecessary variables: FLUASRLU (=R for all records), INVID (for NAI30031), MDP (=NAI for all records) for NAI30031, PTREID (=1 for all records), REPEAT (=1 for all records), SERMTD (=HI for all records), and PAGE (for NAI30034).

Step 11

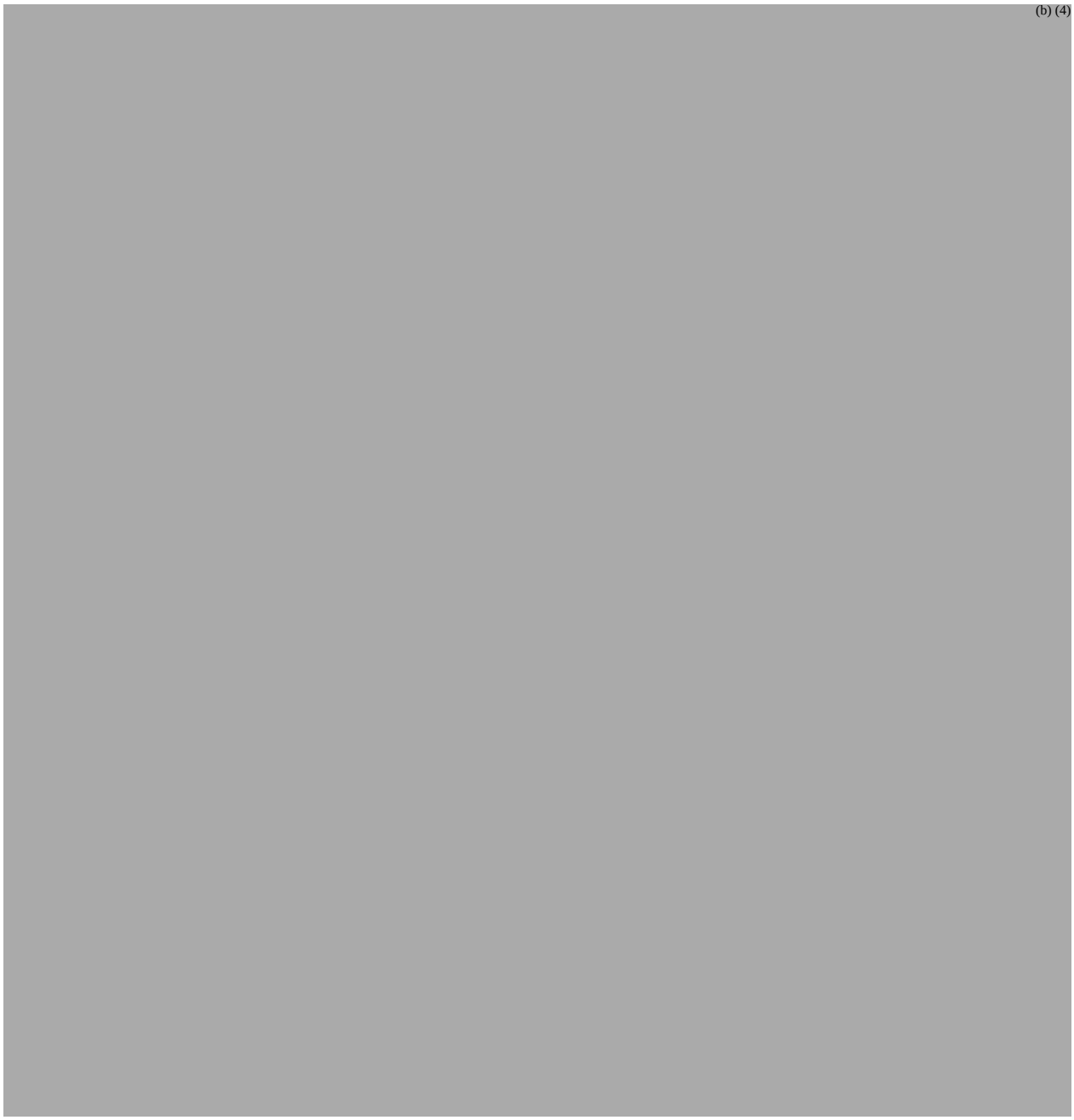
- GSK's Statisticians used the derived serology SAS dataset to prepare tables and listings of serology results for each Clinical Study Report and submission documents.

Step 12

- GSK's Statisticians used the derived serology SAS dataset to prepare the serology dataset in the format required by FDA for submission with the Supplemental NDA by deleting VSDT (for NAI30031) and adding investigator ID, treatment group, sex, race, age, and decode variables.

Non-GSK Collaborators for Serology Work for Studies NAI30031 and NAI30034

(b) (4)



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/s/

David Araojo
3/17/2006 07:19:25 AM
CSO

Kimberly Struble
3/17/2006 07:39:12 AM
MEDICAL OFFICER

RECORD OF FDA TELECONFERENCE

Date of Meeting: **March 7, 2006**

NDA: **21-036/SE1/S-008**

Drug: **RELENZA® (zanamivir for inhalation)**

Sponsor: **GlaxoSmithKline**

Subject: **Serology source document request**

Division of Antiviral Products (DAVP) Participants:

Debra Birnkrant, MD, Division Director
Kim Struble, PharmD, Medical Team Leader

GlaxoSmithKline (GSK) Participants:

David Cocchetto, PhD, Regulatory Affairs
Sherman Alfors, MS, Regulatory Affairs

Background

This teleconference was held at the request of the sponsor to discuss DAVP's February 17, 2006, and February 28, 2006, facsimile request for copies of individual serology source documents. To date, GSK has submitted laboratory datasets, used to produce the line listings, provided from the contracted lab. GSK stated that no further serology source documents are available.

Discussion Points

Deb Birnkrant and Kim Struble spoke with David Cocchetto regarding the upcoming March 9, 2006, teleconference to discuss the status of the serology source documents. This call was in response to a voice message left by Dr. Cocchetto. Dr. Birnkrant reiterated the importance of the source documents in order for the statistical review team to independently confirm the primary endpoint for the prophylaxis studies in sNDA 21-036. This information is critical for the completion of the reviews and action for this sNDA. Dr. Struble requested GSK prepare and discuss the process from sample collection to submission to FDA, including the laboratory shipment, processing, transcription, and transmission procedures for the serology samples.

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/s/

David Araojo
3/9/2006 11:36:08 AM
CSO

Kimberly Struble
3/10/2006 08:40:32 AM
MEDICAL OFFICER

RECORD OF FDA TELECONFERENCE

Date of Meeting: **March 8, 2006**

NDA: **21-036/SE1/S-008**

Drug: **RELENZA® (zanamivir for inhalation)**

Sponsor: **GlaxoSmithKline**

Subject: **Serology source document request**

Division of Antiviral Products (DAVP) Participants:

Kim Struble, PharmD, Medical Team Leader
David Araojo, PharmD, Regulatory Project Manager

GlaxoSmithKline (GSK) Participants:

David Cocchetto, PhD, Regulatory Affairs
Sherman Alfors, MS, Regulatory Affairs

Background

This teleconference was held at the request of the sponsor to discuss DAVP's February 17, 2006, and February 28, 2006, facsimile request for copies of individual serology source documents. To date, GSK has submitted laboratory datasets, used to produce the line listings, provided from the contracted lab. GSK stated that no further serology source documents are available.

Discussion Points

Dr. Cocchetto opened by stating that the (b) (4) does have hand written records recorded by the laboratory technician who did the assays. They are trying to retrieve the records stored in the facility and hope the records will be available today. However, GSK stated it would take a long time for (b) (4) to copy the records and suggested sending GSK clinical monitors to the lab to make the copies. GSK could not estimate a time frame on the availability of the records.
GSK also stated that the lab is blinded and treatment codes are held by GSK statisticians. GSK will provide DAVP with a flow chart of the step by step handling of sampling and data for serology for the scheduled March 9, 2006 teleconference.

Action Items

GSK will provide a flow chart of the step by step handling of sampling and data for serology.

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/s/

David Araojo
3/9/2006 11:37:36 AM
CSO

Kimberly Struble
3/9/2006 11:47:08 AM
MEDICAL OFFICER

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE IV

FACSIMILE TRANSMITTAL SHEET

DATE: February 28, 2006

To: Sherman Alfors US Regulatory Affairs	**From:** David Araojo, Regulatory Project Manager
Company: GSK	Division of Antiviral Products
Fax number: (919)483-5756	**Fax number:** (301)796-9883
Phone number: (919)483-6030	**Phone number:** (301)796-0669

Subject: Information request for Relenza.

Total no. of pages including cover: 2

Comments:

Document to be mailed: ☐ YES ☒ NO

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF FACSIMILE CORRESPONDENCE

NDA: 21-036

Drug: Relenza® (zanamivir)

Date: February 28, 2006

Sponsor: GlaxoSmithKline (GSK)

From: David Araojo, Pharm.D., Regulatory Project Manager

Through: Kim Struble, Pharm.D., Medical Team Leader
Andreas Pikis, M.D., Medical Reviewer
Greg Soon, Ph.D., Statistics Team Leader
Fraser Smith, Ph.D., Statistics Reviewer

Subject: Information request

Reference is made to your submission to NDA 21-036, dated November 4, 2005. Reference is also made to the Agency's February 17, 2006 facsimile correspondence and February 27, 2006 teleconference between the Division of Antiviral Products (DAVP) and GSK's contact, Dr. David Cocchetto.

DAVP requests copies of original individual serology source documents from the contracted laboratory for the subjects listed in the February 17, 2006 facsimile. Please also consider providing PCR and culture source documents for the same subjects.

We are providing the above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me if you have any questions regarding the contents of this transmission.

David Araojo, Pharm.D.
Regulatory Health Project Manager
Division of Antiviral Drug Products

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/s/

David Araojo
2/28/2006 01:12:50 PM
CSO

Kimberly Struble
3/8/2006 04:28:41 PM
MEDICAL OFFICER

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE IV

FACSIMILE TRANSMITTAL SHEET

DATE: February 17, 2006

To: Sherman Alfors US Regulatory Affairs	**From:** David Araojo, Regulatory Project Manager
Company: GSK	Division of Antiviral Products
Fax number: (919)483-5756	**Fax number:** (301)796-9883
Phone number: (919)483-6030	**Phone number:** (301)796-0669

Subject: Chemistry request for Relenza.

Total no. of pages including cover: 6

Comments:

Document to be mailed: ☐ YES ☒ NO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF FACSIMILE CORRESPONDENCE

NDA: 21-036

Drug: Relenza® (zanamivir)

Date: February 17, 2006

Sponsor: GlaxoSmithKline

From: David Araojo, Pharm.D., Regulatory Project Manager

Through: Kim Struble, Pharm.D., Acting Medical Team Leader
Andreas Pikis, M.D., Medical Reviewer
Greg Soon, Ph.D., Statistics Team Leader
Fraser Smith, Ph.D., Statistics Reviewer

Subject: Information request

Reference is made to your submission to NDA 21-036, dated November 4, 2005. The following request is being conveyed to you on behalf of the review team. Please note that we are requesting a response from GlaxoSmithKline by Wednesday, February 22, 2006.

Requests

1. Please submit an integrated summary of all subjects with renal insufficiency enrolled in the Relenza prophylaxis studies. Please ensure the following information for each subject is provided: Subject ID number, study protocol, treatment assignment, degree of renal insufficiency (mild, moderate, and severe), laboratory findings on which you based your decision to characterize the degree of renal insufficiency, and all adverse events.

2. Please submit copies of original individual serology source documents from the contracted laboratory (b) (4) for the following subjects:

Obs	PTID	INVEST	INVID	SUBJECT	COUNTRY
1	NAI30031	Dr. Michael E. Pichichero	2421	90803	USA
2	NAI30031	Dr. Michael E. Pichichero	2421	90804	USA
3	NAI30031	Dr. Michael E. Pichichero	2421	90810	USA
4	NAI30031	Dr. Michael E. Pichichero	2421	90816	USA

5	NAI30031	Dr. Michael E. Pichichero	2421	90817	USA
6	NAI30031	Dr. Michael E. Pichichero	2421	90823	USA
7	NAI30031	Dr. Michael E. Pichichero	2421	90824	USA
8	NAI30031	Dr. Michael E. Pichichero	2421	90837	USA
9	NAI30031	Dr. Ronald B. Turner	2422	93813	USA
10	NAI30031	Dr. Ronald B. Turner	2422	93814	USA
11	NAI30031	Dr Corinne Rebelle	41037	85690	France
12	NAI30031	Dr Corinne Rebelle	41037	85691	France
13	NAI30031	Dr Corinne Rebelle	41037	85692	France
14	NAI30031	Dr Corinne Rebelle	41037	85694	France
15	NAI30031	Dr Corinne Rebelle	41037	85695	France
16	NAI30031	Dr Corinne Rebelle	41037	85696	France
17	NAI30031	Dr Corinne Rebelle	41037	85697	France
18	NAI30031	Dr Corinne Rebelle	41037	96080	France
19	NAI30031	Dr Corinne Rebelle	41037	96081	France
20	NAI30031	Dr Corinne Rebelle	41037	96082	France
21	NAI30031	Dr Corinne Rebelle	41037	96083	France
22	NAI30031	Dr. James A. Hedrick	4251	87309	USA
23	NAI30031	Dr. James A. Hedrick	4251	87322	USA
24	NAI30031	Dr. James A. Hedrick	4251	87356	USA
25	NAI30031	Dr. John S. Perry	42721	90302	USA
26	NAI30031	Dr. John S. Perry	42721	90309	USA
27	NAI30031	Dr. John S. Perry	42721	90311	USA
28	NAI30031	Dr. John S. Perry	42721	90312	USA
29	NAI30031	Dr. John S. Perry	42721	90332	USA
30	NAI30031	Dr. John S. Perry	42721	90333	USA
31	NAI30031	Dr. John S. Perry	42721	90334	USA
32	NAI30031	Dr. John S. Perry	42721	90336	USA
33	NAI30031	Dr. John S. Perry	42721	90352	USA
34	NAI30031	Dr Pierre Triot	43494	85717	France
35	NAI30031	Dr Phillipe Buffler	45220	85758	France
36	NAI30031	Dr Phillipe Buffler	45220	85759	France
37	NAI30031	Dr Phillipe Buffler	45220	85760	France
38	NAI30031	Dr Phillipe Buffler	45220	85762	France
39	NAI30031	Dr Phillipe Buffler	45220	85763	France
40	NAI30031	Dr Phillipe Buffler	45220	85764	France
41	NAI30031	Dr Phillipe Buffler	45220	85765	France
42	NAI30031	Dr Phillipe Buffler	45220	96102	France
43	NAI30031	Dr Phillipe Buffler	45220	96103	France
44	NAI30031	Dr Phillipe Buffler	45220	96104	France
45	NAI30031	Dr Phillipe Buffler	45220	96105	France
46	NAI30031	Dr Phillipe Buffler	45220	96106	France
47	NAI30031	Dr Phillipe Buffler	45220	96107	France
48	NAI30031	Dr Phillipe Buffler	45220	96108	France
49	NAI30031	Dr. Robert E. Broker	49164	94806	USA
50	NAI30031	Dr. Robert E. Broker	49164	94820	USA
51	NAI30031	Dr. Dan C. Henry	6249	87829	USA
52	NAI30031	Dr. Dan C. Henry	6249	87839	USA
53	NAI30031	Dr. Bryan Pogue	7070	91301	USA

54	NAI30031	Dr. Bryan Pogue	7070	91305	USA
55	NAI30031	Dr. Mark T. Thompson	77526	92802	USA
56	NAI30031	Dr. Mark T. Thompson	77526	92803	USA
57	NAI30031	Thierry Caspar	78519	99211	France
58	NAI30031	Dr Gérard Lalanne	87972	96028	France
59	NAI30031	Dr Gérard Lalanne	87972	96068	France
60	NAI30031	Hans Wolfgang Spiess	89768	85709	France
61	NAI30031	Olivier Demarcq	89774	99289	France
62	NAI30031	Dr. Richard M. Tucker	9042	93300	USA
63	NAI30031	Dr. Richard M. Tucker	9042	93302	USA
64	NAI30031	Dr. Richard M. Tucker	9042	93336	USA
65	NAI30031	Dr. Richard M. Tucker	9042	93343	USA
66	NAI30031	Dr. Richard M. Tucker	9042	93344	USA
67	NAI30031	Dr. Richard M. Tucker	9042	93345	USA
68	NAI30031	Dr Jean-Louis Felipe	91119	95994	France

Obs	PTID	INVEST	INVID	SUBJECT	COUNTRY
1	NAI30034	Alain Morand	89402	98144	France
2	NAI30034	Cecile Redon-Renaudin	89566	98540	France
3	NAI30034	Charles Bon	89294	96647	France
4	NAI30034	Christian Jautrou	79566	98054	France
5	NAI30034	Christian Nicolas	89403	98472	France
6	NAI30034	Daniel Zamboni	89590	97857	France
7	NAI30034	Dominique Tetaud	89576	98601	France
8	NAI30034	Dr Dominique Buisson	41064	96674	France
9	NAI30034	Dr Gérard Heintz	89675	98030	France
10	NAI30034	Dr Gérard Heintz	89675	98031	France
11	NAI30034	Dr Gérard Heintz	89675	98032	France
12	NAI30034	Dr Gérard Heintz	89675	98033	France
13	NAI30034	Dr Jacques Quadrelli	89656	98526	France
14	NAI30034	Dr Michael S. Kennedy	49913	70832	USA
15	NAI30034	Dr Michael S. Kennedy	49913	70835	USA
16	NAI30034	Dr Michael S. Kennedy	49913	70836	USA
17	NAI30034	Dr Michael S. Kennedy	49913	70839	USA
18	NAI30034	Dr Michael S. Kennedy	49913	70841	USA
19	NAI30034	Dr Michael S. Kennedy	49913	70842	USA
20	NAI30034	Dr Michael S. Kennedy	49913	70847	USA
21	NAI30034	Dr Michael S. Kennedy	49913	70852	USA
22	NAI30034	Dr Michael S. Kennedy	49913	74020	USA
23	NAI30034	Dr Michael S. Kennedy	49913	74022	USA
24	NAI30034	Dr Michael S. Kennedy	49913	74042	USA
25	NAI30034	Dr Michael S. Kennedy	49913	74043	USA
26	NAI30034	Dr Michael S. Kennedy	49913	74045	USA
27	NAI30034	Dr Michael S. Kennedy	49913	74049	USA
28	NAI30034	Dr Michel Aucouturier	89658	96580	France
29	NAI30034	Dr Milos Pesek	53011	96375	Czech Republic
30	NAI30034	Dr Milos Pesek	53011	96376	Czech Republic

31	NAI30034	Dr Milos Pesek	53011	96377	Czech Republic
32	NAI30034	Dr Milos Pesek	53011	96378	Czech Republic
33	NAI30034	Dr Milos Pesek	53011	96379	Czech Republic
34	NAI30034	Dr Milos Pesek	53011	96380	Czech Republic
35	NAI30034	Dr Milos Pesek	53011	96381	Czech Republic
36	NAI30034	Dr Milos Pesek	53011	96382	Czech Republic
37	NAI30034	Dr Milos Pesek	53011	96383	Czech Republic
38	NAI30034	Dr Milos Pesek	53011	96384	Czech Republic
39	NAI30034	Dr Milos Pesek	53011	96385	Czech Republic
40	NAI30034	Dr Milos Pesek	53011	96386	Czech Republic
41	NAI30034	Dr Milos Pesek	53011	96387	Czech Republic
42	NAI30034	Dr Milos Pesek	53011	96388	Czech Republic
43	NAI30034	Dr Milos Pesek	53011	96389	Czech Republic
44	NAI30034	Dr Milos Pesek	53011	96390	Czech Republic
45	NAI30034	Dr Vit Waldhauser	90113	96422	Czech Republic
46	NAI30034	Dr Vitezslav Kolek	10368	96394	Czech Republic
47	NAI30034	Dr Vitezslav Kolek	10368	96403	Czech Republic
48	NAI30034	Dr. Lance A. Rudolph	5844	71240	USA
49	NAI30034	Dr. Lance A. Rudolph	5844	71259	USA
50	NAI30034	Dr. Lance A. Rudolph	5844	74310	USA
51	NAI30034	Dr. Lance A. Rudolph	5844	74320	USA
52	NAI30034	Dr. Lance A. Rudolph	5844	74328	USA
53	NAI30034	Dr. Lance A. Rudolph	5844	74329	USA
54	NAI30034	Dr. Lance A. Rudolph	5844	74330	USA
55	NAI30034	Dr. Lance A. Rudolph	5844	74341	USA
56	NAI30034	Dr. Robert M. Cohen	4530	70519	USA
57	NAI30034	Dr. Robert M. Cohen	4530	70525	USA
58	NAI30034	Dr. Robert M. Cohen	4530	70529	USA
59	NAI30034	Dr. Robert M. Cohen	4530	70534	USA
60	NAI30034	Dr. Robert M. Cohen	4530	73369	USA
61	NAI30034	Dr. Robert M. Cohen	4530	73383	USA
62	NAI30034	Dr. Robert M. Cohen	4530	73406	USA
63	NAI30034	Dr. Robert M. Cohen	4530	73411	USA
64	NAI30034	Dr. Robert M. Cohen	4530	73414	USA
65	NAI30034	Dr. Robert M. Cohen	4530	73415	USA
66	NAI30034	Dr. Robert M. Cohen	4530	73419	USA
67	NAI30034	Francois Delomier	89324	96729	France
68	NAI30034	Jacques Roisan	89569	97864	France
69	NAI30034	Jean Francois Masse	78692	97813	France
70	NAI30034	Jean-Marc Lejoly	89388	98103	France
71	NAI30034	Jean-Marc Lejoly	89388	98105	France
72	NAI30034	Laurent Magot	89397	97964	France
73	NAI30034	Laurent Magot	89397	97965	France
74	NAI30034	Laurent Magot	89397	97966	France
75	NAI30034	Laurent Magot	89397	97967	France
76	NAI30034	Michel Terrail	89575	97839	France
77	NAI30034	Philippe Bayle	78111	97948	France
78	NAI30034	Philippe Eyraud	89335	97758	France
79	NAI30034	Philippe Mainetti	85106	98122	France

80	NAI30034	Philippe Peytour	89410	97853	France
81	NAI30034	Pierre Razongles	89565	97878	France

We are providing the above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me if you have any questions regarding the contents of this transmission.

_____

David Araojo, Pharm.D.
Regulatory Health Project Manager
Division of Antiviral Drug Products

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/s/

David Araojo
2/22/2006 01:41:25 PM
CSO

Kimberly Struble
2/28/2006 09:17:43 AM
MEDICAL OFFICER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 21-036/S-008

GlaxoSmithKline
Attn: Sherman N. Alfors, US Regulatory Affairs
PO Box 13398
Five Moore Drive
Research Triangle Park, NC 27709

Dear Mr. Alfors:

Please refer to your November 4, 2005 supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for RELENZA® (zanamavir for inhalation) for influenza prophylaxis.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on December 9, 2005, in accordance with 21 CFR 314.101(a).

In our filing review, we have identified the following issues:

Clinical

1. We would like to bring to your attention the absence of routine laboratory tests (hematology and chemistry) in the two household studies and in one of the community studies. In the other community study (NAIA3005), routine laboratory tests were performed at baseline and at one week after the last dose of study medication. Please provide us with the rationale for not performing routine laboratory tests in these studies. Please also submit any additional laboratory data, if available, supporting the safety of the drug, particularly when used for a prolonged time.

2. Please refer to your outstanding phase 4 commitments to provide information on use of the Diskhaler device and improvement of instructions. Please submit your proposals to assess the ability of children, adolescents, and elderly subjects to use the Diskhaler device and to study patient instruction use, improvement of patient instructions and assessment of outcomes using improved patient instructions. Please submit these proposals and timelines for initiating these studies within 30 days.

Microbiology

3. Please provide an integrated summary of resistance data including any updates (from sequencing studies in progress and other sources) on the phenotypic and genotypic changes in all of the Relenza treatment and prophylaxis studies. In the report, provide sub-summaries for the family, community-dwelling, and nursing home studies.

4. Please provide a summary report on the number (%) of matches and discordance for source of infection of index and contact cases by immunoassays and by genotyping.

5. Please provide a report (if data is available from studies in progress) on the sequencing of HA from the pre- and post-treatment (day 1 and day 5).

6. Please provide a virology report for the community prophylaxis study NAIA 3005.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

If you have any questions, call David Araojo, Pharm.D., Regulatory Project Manager, at (301) 796-0669.

Sincerely,

{See appended electronic signature page}

Debra Birnkrant, M.D.
Director
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

Debra Birnkrant
1/17/2006 11:59:18 AM
NDA 21-036

From: Araojo, David
Sent: Friday, December 23, 2005 10:08 AM
To: 'sherman.n.alfors@gsk.com'
Cc: david.m.cocchetto@gsk.com
Subject: NDA 21-036: GSK - Relenza

Sherman,

DAVP would like the Division of Drug Marketing, Advertising, and Communications (DDMAC) to review the [redacted] (b) (4)

However, DDMAC requires direct submission from sponsors in order to review the video.

Please submit the video to DDMAC for review.

Thanks,
David

****

David E. Araojo, Pharm.D., LT USPHS
Regulatory Health Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research, FDA
Ph: (301) 796-0669
Fax: (301) 796-9883
Email: david.araojo@fda.hhs.gov

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/s/

David Araojo
12/23/2005 11:22:09 AM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 21-036/S-008

PRIOR APPROVAL SUPPLEMENT

GlaxoSmithKline
Attn: Sherman N. Alfors, US Regulatory Affairs
PO Box 13398
Five Moore Drive
Research Triangle Park, NC 27709

Dear Mr. Alfors:

We have received your supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: RELENZA® (zanamavir for inhalation)

NDA Number: 21-036

Supplement number: 008

Review Priority Classification: Priority (P)

Date of supplement: November 4, 2005

Date of receipt: November 4, 2005

This supplemental application seeks approval for Relenza for the prophylaxis of influenza A and B, in adults and pediatric patients 5 years of age and older, (b) (4)

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have submitted pediatric studies with this application. Once the review of this application is complete we will notify you whether you have fulfilled the pediatric study requirement for this application.

Please cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Antiviral Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, call David Araojo, Pharm.D., Regulatory Project Manager, at (301) 796-0669.

Sincerely,

{See appended electronic signature page}

Anthony DeCicco, R.Ph.
Chief, Project Management Staff
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

Tony DeCicco

12/8/2005 12:25:59 PM

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: November 22, 2005

TO: HFD-530: Division File

FROM: HFD-530: David Araojo, Regulatory Project Manager

SUBJECT: Dataset issues and virology study request for NDA 21-036 (SE1/008) Relenza

DAVP participants: Kim Struble, PharmD, Acting Medical Team Leader
Greg Soon, PhD, Statistics Team Leader
Fraser Smith, PhD, Statistics Reviewer
David Araojo, PharmD, Regulatory Project Manager

GSK participants: Sherman Alfors, Regulatory Affairs
(b) (6)

On November 22, 2005, a teleconference was held with GlaxoSmithKline.

Background:
This phone conversation was requested by the division to discuss the datasets and programs in the submission.

Discussion:
GSK confirmed submission of a full response to FDA statistics comments dated November 10, 2005. The response stated GSK has corrected the problem so that the xpt files should create unique dataset names when opened. Also, data for each additional study is provided on a CD-ROM in the submission.

The division reminded GSK the data provided should be capable of uploading in the FDA's electronic document room.

Lastly, the division requested GSK submit the virology study reports for study NAIA3005.

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/s/

David Araojo
11/23/2005 10:19:04 AM
CSO

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*: Office of Drug Safety

FROM (*Name, Office/Division, and Phone Number of Requestor)*: Kimberly Struble, PharmD 301 796 0819

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
11/22/05		21036	NDA submission	11/4/05

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Relenza	Yes	antiviral - prophylaxis of influenza A and B	60 days

NAME OF FIRM: GSK

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: GSK submitted a risk management plan with the NDA. The risk management plan can be found at the following site under the folder Other: file name risk-management. Please review and provide comments regarding this plan as submitted \\Cdsesub1\n21036\S_008\2005-11-04\N021036

SIGNATURE OF REQUESTOR

Kimberly Struble, PharmD

METHOD OF DELIVERY (Check one)
☒ DFS ☒ EMAIL ☐ MAIL ☐ HAND

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PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

David Araojo

11/22/2005 02:57:53 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*: Office of Drug Safety

FROM (*Name, Office/Division, and Phone Number of Requestor)*: Kimberly Struble, PharmD 301 796 0819

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
11/22/05		21036	NDA submission	11/4/05

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Relenza	Yes	antiviral - prophylaxis of influenza A and B	60 days

NAME OF FIRM: GSK

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☒ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☒ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☒ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: Please provide an update to the postmarketing safety review on pulmonary adverse events and deaths reported for Relenza. The safety review was completed on June 16, 2005 by Evelyne Edwards. In addition, please review the postmarketing safety summary as submitted by GSK in the NDA and can be found at the following site. In addition, please identify any discrepancies between your evaluation of the postmarketing data and the summary provided by GSK. \\Cdsesub1\n21036\S_008\2005-11-04\N021036

SIGNATURE OF REQUESTOR

Kimberly Struble, PharmD

METHOD OF DELIVERY (Check one)
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/s/

David Araojo

11/22/2005 02:54:51 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*: Division of Scientific Investigations

FROM (*Name, Office/Division, and Phone Number of Requestor)*:
David Araojo, PharmD, RPM
Division of Antiviral Products
301-796-0669

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
11/21/05		21-036	SE1	11/4/05

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Relenza	Yes	7030120	2/24/2006

NAME OF FIRM: GlaxoSmithKline

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
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- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

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- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

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- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☒ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: DAVP requests inspection of the following investigator sites for NDA 21-036 SE1/008 submitted 11/4/05: Study NAI30031 (Drs. Thomas Klein and Arnold Monto) and Study NAI30034 (Drs. Robert Bettis and Gerald Shockey). The submission with site addresses are available in the electronic document room.

SIGNATURE OF REQUESTOR
David Araojo, Pharm.D., RPM

METHOD OF DELIVERY (Check one)
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David Araojo

11/21/2005 09:42:00 AM

From: Araojo, David
Sent: Thursday, November 10, 2005 7:48 AM
To: 'sherman.n.alfors@gsk.com'
Subject: NDA 21-036: sNDA datasets and programs comments

Sherman,

The following comments are conveyed on behalf of the statistics review team. Please refer to your NDA 21-036 submissions dated September 14, 2005 and November 4, 2005.

We have reviewed some of the Relenza datasets submitted on September 14, 2005 and November 4, 2005. They appear to have unique physical names (e.g., derived.xpt) but they are all called test when opened. The NDA should have unique names so the data can be saved and merged.

Only the program that created the derived datasets for each study was available in the September 14, 2005 and November 4, 2005 submissions. We also need to have some of the programs used for key analyses in each Relenza study.

In order to be run in SAS, the SAS programs need to be in ASCII text format (as opposed to pdf format).

Please feel free to contact me if you have any questions.

Regards,
David

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David E. Araojo, Pharm.D., LT USPHS
Regulatory Health Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center For Drug Evaluation and Research, FDA
Ph: (301) 796-0669
Fax: (301) 796-9883
Email: david.araojo@fda.gov

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David Araojo
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