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**Application Number** *21-036/S-001*

**MEDICAL REVIEW(S)**

**Medical Officer's Review  
Supplemental NDA**

**DRAFT**

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**Applicant:** Glaxo-Wellcome, Inc.  
Five Moore Drive  
Research Triangle Park, North Carolina 27709

**Drug Name:** Zanamivir (GG167)  
Relenza®

**Dosage and Administration:** 10 mg by inhalation twice daily for five days

**Dosage form:** Dry powder

**Indication:** Treatment of influenza A and B in children

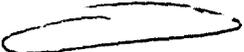
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## **I. Resume**

In support of safety and efficacy of inhaled dry powder zanamivir for treatment of influenza in pediatric patients, Glaxo Wellcome, Incorporated has submitted the results from three clinical trials, which included pediatric subjects from 5 to 12 years of age. Clinical study NAI30009 provides safety information and supports the efficacy claim for zanamivir in pediatric patients. Additional safety data are provided from pediatric patients participating in a second placebo-controlled trial, NAI30010, which was designed to evaluate safety and efficacy of zanamivir in the prevention of influenza in the family setting. Results of a third open label, single dose study, NAI1009, which examined the pharmacokinetics and safety of zanamivir in pediatric patients, were submitted as further support of this application.

Study NAI30009 was a randomized, double blind, placebo-controlled clinical trial in pediatric patients from 5 to 12 years of age. This trial provided a comparison of zanamivir 10 mg twice daily for five days by inhalation using the Diskhaler to a placebo (the lactose powder vehicle which is also present in the drug preparation). Study subjects included children with an influenza-like illness (temperature of 37.8°C or greater and an influenza-like illness as judged by the individual investigator). Influenza was confirmed as the cause of the illness by culture, serology, and investigational direct tests. All study subjects had to demonstrate the ability to use the Diskhaler to be eligible for this study. Parents of study subjects were to complete diary cards describing subject symptomatology twice daily for 14 days after enrollment on the study. The primary efficacy endpoint of this study was time to alleviation of clinically significant symptoms of influenza as noted on the diary cards; alleviation was defined as lack of fever (temperature <37.8°C); cough noted as none or mild; and muscle and joint aches and pains, sore throat, chills/feverishness, and headache noted to be absent/minimal for 3 consecutive diary card entries. Treatment with zanamivir decreased the time to alleviation of influenza symptoms by 1.25 days in the influenza positive population ( $p < 0.001$ ) and by 0.5 days in the intent to treat population ( $p = 0.011$ ).

Frequencies of most clinical and laboratory adverse events were similar in zanamivir and placebo recipients. Because placebo recipients inhaled the same lactose powder present as a vehicle in the active drug preparation, it was not possible to determine whether some gastrointestinal, respiratory, and ENT adverse events might be attributable to the drug/vehicle combination, but most events were mild and not treatment-limiting. However, there was no difference in the rate of development of complications from influenza, including the incidence of antibiotic usage and of otitis media, between the zanamivir and placebo groups.

## **II. Regulatory Background**

The initial IND for zanamivir was submitted October 27, 1993. At that time initial Phase I studies in adults had already been conducted in Western Europe. Further studies including challenge, treatment, and prophylaxis studies were conducted in both the Northern and Southern Hemisphere with 1,167 subjects enrolled in the 3 pivotal Phase III trials. Zanamivir received FDA approval on July 26, 1999 for use in the United States for treatment of uncomplicated acute illness due to influenza virus in adults and adolescents 12 years and older who have been

symptomatic for no more than 2 days. The approved dosing regimen is 10 mg inhaled twice daily for 5 days. Zanamivir for treatment of influenza among pediatric subjects has not been submitted to any foreign regulatory groups at the time of this supplemental NDA application. The final protocol for NAI30009 was submitted September 30, 1998 and the study was initiated on January 11, 1999. Study enrollment closed April 4, 1999. A proposal for the content and format of this supplemental NDA was submitted August 4, 1999 and a teleconference discussing this proposal was held September 21, 1999. Following this, the supplemental NDA along with a request for a priority review were submitted to the FDA October 25, 1999. Additional submissions regarding the sNDA were submitted to the FDA on January 14, 2000, February 2, 7, and 9, 2000, and March 9 and 21, 2000.

### III. Pediatric Clinical Studies

The original submission contained 17 volumes of which 15 had clinical data. All clinical data were reviewed, including integrated summaries of safety and efficacy, a random 3% sample of individual diary cards, and a random 5% sample of case report forms. Additional safety and efficacy data as well as additional diary cards were received as amendments to the NDA and reviewed. Data from the applicant's analyses are discussed in this review. However, there were no major differences between the applicant's and the Agency's analyses of primary and secondary endpoints.

**Table 1: Pediatric Studies of Zanamivir**

Study	No. of Patients 5-12 yrs of Age	Type of Study	Dose	Duration
NAIA1009	16	Pharmacokinetic	10 mg	Single dose
NAI30009	471	Treatment	10 mg	B.I.D. for 5 days
NAI30010	415	Treatment	10 mg	B.I.D. for 5 days
		Prophylaxis	10 mg	Daily for 10 days

As shown in the Table 1, the applicant has conducted three trials which include pediatric subjects: a phase 1 study of single dose pharmacokinetics in pediatric patients (NAIA1009), a Phase 3 trial in 471 pediatric patients (NAI30009), and a study of the prevention of influenza in family settings which included 415 subjects aged 5 to 12 years (NAI30010). Study subjects enrolled in the Phase 3 treatment study and index cases in the prevention study received a five-day treatment course of inhaled dry powder zanamivir 10 mg twice daily which was compared to a placebo consisting of the lactose powder vehicle which is also present in the zanamivir preparation. For entry, subjects were required to have a temperature of 37.8° C or greater and an influenza-like illness as judged by individual investigators. The symptom course over time was recorded twice daily by parents using diary cards with additional assessments by study staff at baseline and after treatment. Study staff also evaluated some patients at an optional day three visit.

In all three studies, ability to use the drug/device preparation satisfactorily was a requirement for enrollment, standard instructions on how to teach subjects to use the device were supplied to the

centers, and the first dose was administered under supervision at the study site at the time of enrollment, with the subject instructed to take the second dose that evening provided at least two hours had elapsed between the first and second dose.

The primary efficacy endpoint for subjects in the Phase III treatment study and for index cases in the prevention study was the time to alleviation of clinically significant symptoms of influenza as noted on three consecutive entries of the diary cards. Alleviation was defined as lack of fever (temperature  $<37.8^{\circ}\text{C}$ ); cough noted as none or mild; and muscle and joint aches and pains, sore throat, chills/feverishness, and headache noted to be absent/minimal. As noted in the review of the original NDA, the Division has considered it important to examine the primary endpoint for both subjects who have confirmed influenza and for the intent-to-treat study population. Certain important secondary endpoints were also examined and include time to alleviation of symptoms with use of relief medications taken into account, objective assessments of subjects by study personnel, and the incidence of complications of influenza.

In addition to the 138 index cases who received either zanamivir or placebo for treatment of an influenza-like illness in a study of influenza prevention in the family setting, 277 pediatric subjects received either zanamivir or placebo for prophylaxis against influenza and are included in this submission to provide further safety information. These contact cases received a ten day course of either 10 mg of zanamivir or the lactose powder vehicle as placebo given once daily.

#### **A. NAIA1009**

##### **NAIA1009: Description and Results**

Please refer to Dr. Suarez's review of this study.

NAIA1009 was a single dose pharmacokinetic study of zanamivir in 24 pediatric patients with signs and symptoms of a viral respiratory disease. Of the 24 patients enrolled in this study, 16 were from 6 to 12 years of age and were able to use the Diskhaler for zanamivir delivery. Eight additional patients from the age of 3 months to 2 years received zanamivir as a nebulized solution. Of the 16 pediatric study subjects who received zanamivir by inhalation using the Diskhaler, 5 were excluded from the final analysis because of serum zanamivir levels, which were either undetectable or very low. Only two 6 year olds participated in this study; one of these two subjects was excluded due to extremely low levels of zanamivir detected in his serum and the other had the lowest peak levels and AUC recorded for all patients using the dry powder by inhalation. Similarly, there were only two 7 years olds enrolled; one had undetectable levels of zanamivir in his serum and the other had an AUC which was less than the mean and median AUC calculated in this study. Overall, large interpatient variation in serum zanamivir levels was noted among the 11 subjects with  $C_{\text{max}}$  values ranging from 15 to 74 ng/ml and AUC ranging from 58 to 279 ng.hour/ml.

In NAIA1009 each of the 16 subjects 6 years of age and older used a Diskhaler with the mouthpiece modified to include a pressure transducer in order to measure peak inspiratory flow rate during inhalation of zanamivir. Although, several children could not inhale when requested

or there was difficulty obtaining a tracing for these children, attempts were made to measure inspiratory flow-rates for all study subjects. Of the 16 children participating in this study, 3 did not produce a measurable peak inspiratory flow rate (PIFR) because of inability to inhale on request, 3 achieved a measurable PIFR with one of their two attempted inhalations, 9 had measurable flow rates on both attempts, and no data were provided for one patient. Inspiratory flow rates for children with measurable PIFRs ranged \_\_\_\_\_ in. For the youngest 4 children, who were 6 and 7 years of age, PIFR was not measurable in two due to inadequate inhalation, data were missing for one subject, and the fourth produced PIFR \_\_\_\_\_ in for the two inhalations.

Zanamivir was well tolerated in this study. Four of the 16 subjects reported an adverse event, all of which were reported as mild. The recorded adverse events largely reflected the presence of the underlying respiratory illness and included fever, chills, and diarrhea. Only one adverse event, an episode of headache, was considered possibly to be drug related.

**NAIA1009 Results: Additional FDA Analysis**

The mean PIFR was calculated for each study subject with two measurements of their inspiratory flow rate, then the overall mean and the median were derived from the mean PIFR for subjects with more than one measurement and from a single PIFR from subjects with only one result recorded. The mean peak inspiratory flow rate for the 12 subjects with measurable PIFRs was 75.4 L/min while the median PIFR was 80.4 L/min. Four of these 12 subjects had a PIFR below 60 L/min, which is considered the optimal flow rate needed for proper use of a dry powder inhaler under standardized in vitro testing. Overall, only 8 of the 16 subjects enrolled in this study could generate the flow rate necessary for proper use of the Diskhaler. No children younger than 8 years of age were able to use the delivery device properly, i.e., could generate a PIFR over 60 L/min.

Serum concentrations of zanamivir and individual peak inspiratory flow rates are compared in Table 2 which combines data from the table on page 8 of the February 18, 2000 submission and the table on page 1 of Attachment 1 of the March 21, 2000 submission. For the 6 study subjects with either undetectable or barely detectable zanamivir serum levels, 3 also had unmeasurable peak inspiratory flow rates and the remaining 3 had PIFRs of 30.5, 40.3, and 121.2 L/min. When subjects were divided into two groups, those with unmeasurable peak flow rates or PIFRs less than 60 L/min and those with PIFRs of 60 L/min or greater, 5 of the 6 subjects with undetectable or very low zanamivir serum levels had PIFRs less than 60 L/min. The only two subjects with a PIFR of less than 60 L/min with detectable levels of zanamivir had a mean Cmax of 43.5 ng/ml and an AUC ng•hour/ml of 137. In contrast only one of the 8 subjects with a PIFR of 60 L/min or greater had an undetectable serum zanamivir level and the mean Cmax and AUC for the remaining subjects were 49.6 ng/ml and 219.7 ng•hour/ml respectively.

**Table 2: Summary of NAIA1009 Study Results**

Subject	Age (yrs)	Individual PIFR	Mean PIFR	Cmax (ng/ml)	AUC 0-inf (ng•hour/ml)

10129	6	No data	---	15	158
10117	7	Two tracings without data	---	undetectable	undetectable
10122	7	38.5, 56.5	47.5	53	151
10120	8	122.4, 119.9	121.2	undetectable	undetectable
10123	8	77.5, 65.6	71.6	74	272
10128	8	87.1	87.1	43	233
10108	9	40.3	40.3	undetectable	undetectable
10121	9	48.4, 46.5	47.5	34	123
10127	9	70.2, 77.4	73.8	40	167
10119	10	91.8, 116.5	104.2	54	229
10124	11	109.9, 100.4	105.2	48	211
10115	12	30.5	30.5	undetectable	undetectable
10118	12	91.2, 87.1	89.2	38	147
10125	12	Two tracings without data	---	undetectable	undetectable
10126	12	89.7, 84.3	87	50	279

C<sub>max</sub> and AUC are rounded up to the nearest whole number. Those C<sub>max</sub> and AUC values listed as undetectable were either undetectable at all time points or undetectable after 1.5 hours.

In summary, data from NAI1009 reveal that young children, especially those less than 8 years of age, have difficulty using the Diskhaler as evidenced by the poor inspiratory flow rates and low serum levels of zanamivir.

## B. NAI30009

Protocol NAI30009, "A double-blind, randomized, placebo-controlled, parallel-group multicenter study to investigate the efficacy and safety of zanamivir (GG167) 10 mg administered twice daily for 5 days in the treatment of symptomatic influenza A and B viral infections in children ages 5-12." was originally proposed as the central study for demonstration of treatment efficacy in the pediatric population. The study report is located in volumes 4 through 11 of the pediatric efficacy supplement of NDA 21-036.

### Study Design

This was a randomized, double-blind study designed to compare the efficacy and safety of zanamivir 10 mg twice daily for five days administered by inhalation with placebo consisting of the lactose powder vehicle for the treatment of symptomatic influenza virus infection in patients aged 5 to 12 years. The primary efficacy endpoint, termed time to alleviation of symptoms, was defined as lack of fever (temperature <37.8°C); cough noted as none or mild; and muscle and joint aches and pains, sore throat, chills/feverishness, and headache noted to be absent/minimal for 3 consecutive diary card entries. Enrollment required a temperature of 37.8°C or higher and an influenza-like illness as judged by the individual investigator when influenza was documented to be circulating in the community. Study subjects were required to be symptomatic for no more than 36 hours before the first dose of study drug. The influenza-positive subpopulation was defined as those having a positive result on culture, serology (fourfold rise in antibody titer), or

an investigational direct test using polymerase chain reaction (PCR). Ability to use the Diskhaler system was an inclusion criterion and the first dose of study drug was administered under supervision/instruction at the study site, with the subject instructed to take a second dose at bedtime if the interval between the first two doses was at least two hours; subsequently, subjects were to take two doses per day for a total of five days of therapy. Temperature, use of relief medications (acetaminophen / paracetamol and cough suppressant), and symptoms were recorded by the subject's parent on a diary card twice daily for 14 days, and subjects still symptomatic at 14 days were to record symptoms for an additional 14 days. Although cough was recorded on a scale of 0 to 3 for none to severe, the other symptoms (headache, sore throat, chills/feverishness, muscle/joint aches and pains, nasal symptoms, weakness, and loss of appetite) were recorded as present or absent/minimal.

### C. NAI30009 Efficacy Results

#### Study Population

A total of 471 patients were enrolled, including 224 in centers in the United States; 247 were randomized to placebo and 224 to zanamivir. In the placebo group 4% discontinued the study prematurely (4 "consent withdrawn", 4 lost to follow-up, 2 protocol violations, 1 "other"); in the zanamivir group, 2% discontinued prematurely (4 "consent withdrawn", 1 "other"). In the placebo group 3% discontinued study medication early, while 2% of subjects in the zanamivir group discontinued study medication early. Only one patient in the study, a 10-year-old male who developed a rash while receiving zanamivir, discontinued study medication prematurely due to an adverse event. Protocol violations were identified in 4% of each group, the most common being study drug noncompliance (8 placebo and 6 zanamivir subjects) and subjects not meeting inclusion criteria (5 placebo and 4 zanamivir subjects).

Demographic data were reasonably balanced between treatment groups; 50% of the placebo group and 41% of the zanamivir group were female while 89% of the placebo group and 90% of the zanamivir group were classified as White. The mean age of the placebo group was 9.0 years, and the mean age of the zanamivir group was 8.6 years. There were a similar numbers of "high-risk" respiratory subjects, defined as subjects with a chronic respiratory condition requiring continued use of medication with 12 in the placebo group and 10 in the zanamivir group. Two percent of placebo subjects and 3% of zanamivir subjects had received current season influenza vaccine. Study subjects were diagnosed with influenza by culture, PCR, and / or serology. Overall, 134 subjects were found to have influenza by all 3 methods; in addition, 14 subjects were diagnosed by culture alone, 12 by serology alone, and 21 by PCR alone. Another 165 subjects were diagnosed with influenza by two of the three diagnostic methods. Sources of influenza diagnosis are summarized in Table 3.

**Table 3: Influenza diagnosis in NAI30009**

<b>Influenza diagnosis</b>	<b>Placebo</b>	<b>Zanamivir</b>	<b>Total</b>
<b>Total subjects</b>	247	224	471
<b>Positive for influenza A</b>	120	106	226

<b>Positive for influenza B</b>	62	58	120
<b>Influenza positive, type unknown</b>	0	1	1
<b>Positive by culture</b>	116	110	226
<b>Positive by PCR</b>	162	144	306
<b>Positive by serology</b>	129	118	247

Source: Volume 5, Table 14

Overall symptom scores at entry were slightly worse in the zanamivir group; 32% of patients in that group had a severe pretreatment influenza score as compared to 23% of placebo subjects. Median time elapsed from onset of symptoms to the first dose of study drug was similar for both groups; 20.0 hours for the placebo group and 22.0 for the zanamivir group.

Three study populations were prospectively defined for use in efficacy analysis. The Influenza Positive population was predefined as the primary population for the assessment of efficacy analysis. All randomized subjects were included as the Intent-to-Treat population; this population was the primary population for assessment of safety and a secondary population for analysis of efficacy. Finally, the study results were also analyzed for the Per-Protocol population, which was defined as subjects in the Influenza Positive population who had no protocol deviations.

**Table 4: Study Populations for NAI30009**

<b>Population</b>	<b>Placebo</b>	<b>Zanamivir</b>	<b>Total</b>
<b>Intent-to-Treat (ITT)</b>	247	224	471
<b>Influenza Positive (IP)</b>	182	164	346
<b>Per-Protocol</b>	172	159	331

Source: Volume 5, Table 6

**Analysis of the primary efficacy endpoint (median time to alleviation of symptoms in days):**

An analysis of the primary efficacy endpoint was performed for all three study populations. There was a statistically significant reduction in the median time to alleviation of symptoms of influenza for subjects receiving zanamivir. The difference in the median time to alleviation of symptoms between the placebo and zanamivir groups ranged from as little as 0.5 days for the Intent-to-Treat population to 1.25 days for the Influenza Positive population. The results for all subjects enrolled in NAI30009 are presented in Table 5.

**Table 5: Results of Study NAI30009**

	Median Time to Alleviation in Days			
	Placebo	Zanamivir	Difference	P value
<b>Intent to Treat</b>	5.0	4.5	0.5	0.011
<b>Influenza Positive</b>	5.25	4.0	1.25	<0.001
<b>Per Protocol and Influenza Positive</b>	5.0	4.0	1.0	<0.001

Source: Volume 5, p 66

Sensitivity analysis was performed in which subjects with missing data and no evidence of having reached the endpoint were assigned as censored at their last recorded Diary Card entry at which the symptoms were not yet alleviated.

**Table 6: Censored Results of Study NAI30009**

	Median Time to Alleviation in Days			
	Placebo	Zanamivir	Difference	P value
<b>Intent to Treat</b>	5.0	4.0	1.0	0.01
<b>Influenza Positive</b>	5.0	4.0	1.0	<0.001
<b>Per Protocol and Influenza Positive</b>	5.0	4.0	1.0	<0.001

Source: Volume 5, Supporting Tables 1-3

However, the number of patients needing to be censored was *not* equally distributed between the two study arms:

**Table 7: Number of Patients Censored in NAI30009**

Population	Placebo	Zanamivir
<b>ITT</b>	30	11
<b>Influenza Positive</b>	21	6

Source: SAS datasets

The primary efficacy endpoint was also analyzed for certain subgroups including subjects enrolled in the United States, subjects 7 years of age or younger and those 8 to 12 years of age, subjects with chronic respiratory disease requiring medication, subjects with influenza A as compared to those with influenza B, and subjects starting study drug within 24 hours of developing symptoms compared to those starting after 24-36 hours of symptoms. The results for each of these subgroups are shown in the Tables 8 – 12.

**Table 8: Median Time to Alleviation of Symptoms of Influenza for Subjects in the United States**

	Number of Subjects	Placebo	Zanamivir	Difference in Days
<b>Intent to Treat</b>	262	5	4.5	0.5
<b>Influenza Positive</b>	186	5	4	1.0

Source: Volume 5, Supporting Tables 7, 8

When efficacy results were examined to delineate the influence of age, there was decreased efficacy for the cohort of children from the age of 5 to 7 years as compared to those from 8 to 12 years of age.

**Table 9: Median Time to Alleviation of Symptoms of Influenza by Age (Influenza Positive Population Only)**

	Number of subjects	Placebo (No. of patients)	Zanamivir (No. of patients)	Difference in Days
All subjects	346	5.25 (182)	4.0 (164)	1.25
5 to 7 years	103	5.0 (51)	4.0 (52)	1.0
8 to 12 years	243	5.5 (131)	4.0 (112)	1.5

Source: January 14, 2000 submission, Table 11

**Table 10: Median Time to Alleviation of Symptoms for High Risk Respiratory Subjects**

Study Population	Placebo	Zanamivir	Difference in Days	p-value
Intent-to-Treat (n=36)	5.75	3.75	2.0	P=0.204
Influenza Positive (n=22)	5.75	2.0	3.75	P=0.012

Source: February 7, 2000 submission, Table 8

**Table 11: Median Time to Alleviation of Symptoms of Influenza by Influenza Type**

	Number of Subjects	Median Time to Alleviation in Days		Difference in Days
		Placebo	Zanamivir	
Influenza A	226	5.0	4.0	1.0
Influenza B	120	6.0	4.0	2.0

Source: Volume 5, Supporting Table 6

**Table 12: Median Time to Alleviation of Symptoms of Influenza by Time Study Drug Started after Onset of Symptoms**

Time from onset of symptoms	Placebo	Zanamivir	Difference in Days
<i>Intent-to-treat Population</i>			
0 – 24 hours	5.0	4.5	0.5
>24 – 36 hours	5.0	4.0	1.0
<i>Influenza Positive Population</i>			
0 – 24 hours	5.5	4.0	1.5
>24 – 36 hours	5.0	4.0	1.0

Source: Volume 5, Supporting Tables 17, 18

### Analyses of secondary efficacy endpoints

In this study, thirteen separate secondary endpoints were examined. Antibiotic use for complications of influenza was added as a secondary endpoint subsequent to the protocol but prior to the unblinding of the data.

In order to standardize and quantify the use of supportive therapy, study subjects were provided with two relief medications by the study sponsor. In the United States and Canada subjects were supplied with dextromethorphan cough suppressant and acetaminophen; while in most other countries paracetamol and pholcodine were supplied as relief medications. Parents were to record how often these relief medications were administered to the study subject on the diary card. Other relief medications, obtained independently by the study subjects or their parents, could also be used but their use was not included in the evaluation of this secondary efficacy endpoint.

**Table 13: Time to Alleviation and No Use of Relief Medications**

	Median Time in Days		Difference in Days	P value
	Placebo	Zanamivir		
<b>Intent to Treat</b>	6.0	5.0	1.0	0.002
<b>Influenza Positive</b>	6.5	5.0	1.5	<0.001

Source: Volume 5, p. 70

Sensitivity analysis was again performed for this endpoint. In this analysis subjects with missing data and no evidence of having reached the endpoint were assigned as censored at their last recorded Diary Card entry at which the symptoms were not yet alleviated.

**Table 14: Censored Results for Time to Alleviation and No Use of Relief Medications**

	Median Time in Days		Difference in Days	P value
	Placebo	Zanamivir		
<b>Intent to Treat</b>	6.0	5.0	1.0	0.002
<b>Influenza Positive</b>	6.5	5.0	1.5	<0.001

Source: Volume 5, Supporting Tables 19, 20

Additional analyses of secondary efficacy endpoints were also performed by the sponsor. One secondary endpoint measured the number of days before a parent felt the subject could return to his or her normal activities; the information for this analysis was obtained from daily diary card entries. Separate daily questions on the diary card also inquired if the subject was able to return to school or daycare; this response was reported separately in the Assessment of Healthcare Use and Productivity. In addition, parents were to describe their child's overall symptoms daily on the diary card as none, mild, moderate, or severe; this score was analyzed as the mean overall symptom score for days 2 to 5 for each child. Parents were also supplied with tympanic thermometers and instructed to take their child's temperature and record it twice daily on the diary card. Each subject's temperature was also taken and recorded at study entry, at the optional study visit on day 3, and at the day 6 study visit. A summary of these selected secondary efficacy

endpoints is found in Table 15.

**Table 15: Summary of Selected Secondary Efficacy Endpoints for Study NAI30009**

Secondary Endpoint	Population	Placebo	Zanamivir	Difference	P value
Days to return to normal activity	ITT	6.5	5.5	1.0	0.019
	IP	6.5	5.5	1.0	0.022
Mean overall symptom score	ITT	45	41.5	3.5	0.038
	IP	47.3	42.1	5.1	0.008
Maximum daily temperature	ITT	37.8	37.7	0.1	0.012
	IP	37.9	37.7	0.2	0.002
Day 3 temperature	ITT	37.1	36.9	0.2	0.037
	IP	37.2	36.9	0.3	0.008

Source: Volume 5, Tables 25, 26, 29, 30, 47, 48, 59, 60

The rate of all complications and specific complications were also noted in the study report for NAI30009. There did appear to be slightly fewer overall complications in the subjects receiving zanamivir; however, p values were not provided by the sponsor. Importantly, there was no difference in the use of antibiotics, in the incidence of lower respiratory tract disease such as pneumonia and bronchitis, or in the incidence of otitis media between the two treatment groups.

**Table 16: Incidence of Complications of Influenza**

Type of Complication	Placebo (n=182)	Zanamivir (n=164)
Any Complication	41 (23%)	26 (16%)
Antibiotic Use	27 (15%)	17 (12%)
Pneumonia	2	1
Asthma Exacerbation	3	2
Bronchitis	2	3
Sinusitis	3	4
Otitis	17	15
Pharyngitis	8	0
Misc. Pulmonary	3	2
Misc. ENT	4	5

Source: Volume 5, Tables 27, 28

Throat swabs for influenza were obtained on day 1, day 3 (at an optional visit), and at day 6. Quantitative viral titers were compared between the placebo and zanamivir groups.

**Table 17: Virologic Data**

<b>log TCID50</b>	<b>Placebo</b>	<b>Zanamivir</b>
<b>Pre-treatment</b>	<b>N=168</b>	<b>N=152</b>
<1.05 (negative)	88 (52%)	78 (51%)
1.05 - < 2.0	32 (19%)	33 (22%)
2.0 - < 3.0	25 (15%)	21 (14%)
3.0 - < 4.0	14 (8%)	16 (11%)
4.0 and greater	9 (5%)	4 (3%)
<b>Day 3</b>	<b>N=85</b>	<b>N=83</b>
<1.05 (negative)	68 (80%)	68 (82%)
1.05 - < 2.0	8 (9%)	9 (11%)
2.0 - < 3.0	7 (8%)	5 (6%)
3.0 - < 4.0	2 (2%)	1 (1%)
<b>Day 6</b>	<b>N=162</b>	<b>N=145</b>
<1.05 (negative)	150 (93%)	140 (97%)
1.05 - < 2.0	12 (7%)	3 (2%)
2.0 - < 3.0	0	2 (1%)

Source: Volume 5, Table 57

As evidenced by data presented in Table 17, there was little or no difference in the proportion of subjects with viral shedding or the degree of shedding between the zanamivir and placebo groups. Since viral titer at day 3 was a secondary efficacy endpoint in NAI30009 and viral titer at day 6 was not, only the p value for day 3 was provided (p=0.459).

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endpoints is found in Table 15.

**Table 15: Summary of Selected Secondary Efficacy Endpoints for Study NAI30009**

Secondary Endpoint	Population	Placebo	Zanamivir	Difference	P value
Days to return to normal activity	ITT	6.5	5.5	1.0	0.019
	IP	6.5	5.5	1.0	0.022
Mean overall symptom score	ITT	45	41.5	3.5	0.038
	IP	47.3	42.1	5.1	0.008
Maximum daily temperature	ITT	37.8	37.7	0.1	0.012
	IP	37.9	37.7	0.2	0.002
Day 3 temperature	ITT	37.1	36.9	0.2	0.037
	IP	37.2	36.9	0.3	0.008

Source: Volume 5, Tables 25, 26, 29, 30, 47, 48, 59, 60

The rate of all complications and specific complications were also noted in the study report for NAI30009. There did appear to be slightly fewer overall complications in the subjects receiving zanamivir; however, p values were not provided by the sponsor. Importantly, there was no difference in the use of antibiotics, in the incidence of lower respiratory tract disease such as pneumonia and bronchitis, or in the incidence of otitis media between the two treatment groups.

**Table 16: Incidence of Complications of Influenza**

Type of Complication	Placebo (n=182)	Zanamivir (n=164)
Any Complication	41 (23%)	26 (16%)
Antibiotic Use	27 (15%)	17 (12%)
Pneumonia	2	1
Asthma Exacerbation	3	2
Bronchitis	2	3
Sinusitis	3	4
Otitis	17	15
Pharyngitis	8	0
Misc. Pulmonary	3	2
Misc. ENT	4	5

Source: Volume 5, Tables 27, 28

Throat swabs for influenza were obtained on day 1, day 3 (at an optional visit), and at day 6. Quantitative viral titers were compared between the placebo and zanamivir groups.

**Table 17: Virologic Data**

<b>log TCID50</b>	<b>Placebo</b>	<b>Zanamivir</b>
<b>Pre-treatment</b>	<b>N=168</b>	<b>N=152</b>
<1.05 (negative)	88 (52%)	78 (51%)
1.05 - < 2.0	32 (19%)	33 (22%)
2.0 - < 3.0	25 (15%)	21 (14%)
3.0 - < 4.0	14 (8%)	16 (11%)
4.0 and greater	9 (5%)	4 (3%)
<b>Day 3</b>	<b>N=85</b>	<b>N=83</b>
<1.05 (negative)	68 (80%)	68 (82%)
1.05 - < 2.0	8 (9%)	9 (11%)
2.0 - < 3.0	7 (8%)	5 (6%)
3.0 - < 4.0	2 (2%)	1 (1%)
<b>Day 6</b>	<b>N=162</b>	<b>N=145</b>
<1.05 (negative)	150 (93%)	140 (97%)
1.05 - < 2.0	12 (7%)	3 (2%)
2.0 - < 3.0	0	2 (1%)

Source: Volume 5, Table 57

As evidenced by data presented in Table 17, there was little or no difference in the proportion of subjects with viral shedding or the degree of shedding between the zanamivir and placebo groups. Since viral titer at day 3 was a secondary efficacy endpoint in NAI30009 and viral titer at day 6 was not, only the p value for day 3 was provided (p=0.459).

Influenza positive subjects receiving zanamivir also showed a statistically significant decrease in the number of days with a mild to moderate cough during days 2 to 5 of the study (p=0.001), a reduction in the number of days in which relief medications were used (p=0.005), and a decrease in the number of 12 hour period in which acetaminophen/paracetamol (p=0.041) or cough suppressant were used (p<0.001).

At each study visit the individual investigator rated the study subject's symptoms in general as none, mild, moderate, or severe; this was then recorded in the case report form as the investigator global assessment of symptoms. Parents also noted their child's overall symptom score on the diary card twice daily using the same scoring system. Although there was a statistically significant decrease in the overall symptom score noted by the parents for subjects receiving zanamivir, there was no difference in the individual investigators' assessment of subject symptoms at the study visits on day 3 or day 6.

A separate assessment of study subject incapacitation, productivity, and healthcare utilization was performed. In this analysis, parents of subjects in the zanamivir group reported less interference with their household work and with their leisure activities than parents of subjects in the placebo group. However, there was no statistical difference noted between the two treatment groups in number of days confined to bed, number of days missed from daycare or school, number of days parents missed work, or number of prescribed and over the counter medications

used.

#### D. NAI30010

Study NAI30010 entitled, "A double-blind, randomized, placebo-controlled, parallel group, multicenter study to investigate the efficacy and safety of inhaled zanamivir (GG167) 10 mg once daily for 10 days in the prevention of symptomatic influenza A and B viral infections within families," was not included in the original proposal for demonstration of efficacy but was later submitted as supporting information. A study summary is located in volume one of the pediatric efficacy supplement of NDA 21-036 and datasets were submitted electronically.

This was a randomized, double-blind, placebo controlled study of zanamivir as prophylaxis for children and adults in the family setting. Children from 5 to 12 years of age were enrolled in NAI30010 as either index cases, defined as the first member of a family to develop an influenza-like illness, or as contact cases, defined as other family members within the family of an index case who did not have an influenza-like illness at study entry. In this study, index cases in the family received five days of either zanamivir (10 mg twice daily by inhalation) or placebo and contact cases received 10 days of zanamivir (10 mg once daily) or placebo. One hundred thirty-eight children ages 5 to 12 years were included as index cases and 277 as contact cases. Although this study was submitted to support the safety of zanamivir, results of treatment of index cases in the pediatric age group were also provided to support the efficacy of zanamivir. Only index cases in this study are included in the efficacy analysis.

**Table 18: Study Populations in NAI30010**

Population	Placebo	Zanamivir	Total
Intent-to-Treat (ITT)	71	67	138
Influenza Positive (IP)	37	31	68

Source: SAS datasets

The same primary efficacy endpoint was used for index cases in this study. The median time to alleviation of symptoms of influenza is shown in the table below.

**Table 19: Median Time to Alleviation of Influenza Symptoms for Index Cases Enrolled in NAI30010**

	Median Time to Alleviation in Days			
	Placebo	Zanamivir	Difference	P value
Intent to Treat	5.5	4.0	1.5	0.033
Influenza Positive	6.0	4.0	2.0	0.018

Source: January 14, 2000 submission, p. 10

The number of patients needing to be censored in this study was equally distributed between the two study arms.

**Table 20: Number of Patients Censored in NAI30010**

Population	Placebo	Zanamivir
ITT	5	6
Influenza Positive	1	2

Source: SAS datasets

Subgroup analysis by age was also provided and is shown in the following table. As in NAI30009, there was less difference between the median time to alleviation of symptoms for younger children receiving zanamivir as compared to placebo than there was for children from 8 to 12 years of age.

**Table 21: Median Time to Alleviation of Influenza Symptoms by Age for Index Cases (Influenza Positive Population)**

	Placebo (No. of patients)	Zanamivir (No. of patients)	Difference in Days
All subjects	6.0 (37)	4.0 (31)	2.0
5 to 7 years	4.5 (11)	3.75 (8)	0.75
8 to 12 years	6.0 (26)	4.0 (23)	2.0

Source: January 14, 2000 submission, Tables 23, 24

**Selected secondary endpoints**

In the sponsor's analysis of NAI30010, only one secondary efficacy endpoint was analyzed for the index cases participating in the study. These results are provided in Table 22.

**Table 22: Median Time to Alleviation of Influenza Symptoms and No Use of Relief Medications**

	Median Time to Alleviation and No Use of Relief Medication in Days		
	Placebo	Zanamivir	P value
Intent to Treat (n=138)	6.0	4.75	0.051
Influenza Positive (n=68)	7.5	4.5	0.008

Source: January 14, 2000 submission, Tables 25, 26

**E. NAI30009 and NAI30010 Efficacy Results: Additional FDA Analysis****Study NAI30009**

Because of the smaller treatment effect of zanamivir noted in the subset of children 5 to 7 years of age compared to those 8 to 12 years of age in both NAI30009 and NAI30010 and because of the poor inspiratory flow rates and low serum zanamivir levels in children younger than 8 years

of age in NAI1009, the results of NAI30009 were analyzed further for the effect of age. Since the influenza positive population was the predetermined primary population for measurement of efficacy, the results for this population by year of age is presented in Table 23.

**Table 23: Median Time to Alleviation of Symptoms by Year of Age for the Influenza Positive Population**

Age Group	Placebo		Zanamivir		Difference in Days	Wilcoxon test P value
	n	Median	N	Median		
5	16	3.5	22	3.0	0.5	0.19
6	19	5.0	14	4.5	0.5	0.51
7	16	5.5	15	4.0	1.5	0.34
8	24	5.0	26	4.0	1.0	0.15
9	21	5.5	20	3.5	2.0	0.07
10	26	5.5	27	3.5	2.0	0.03
11	25	5.5	25	5.0	0.5	0.49
12	35	5.0	14	4.75	0.25	0.80

Source: January 14, 2000 submission, Table 13. Wilcoxon tests done by J. Ma

Although it is not statistically significant, the difference between the median time to alleviation of symptoms for the zanamivir group and the placebo group was 0.5 days for both five and six year olds. When the 5 and 6 year olds were analyzed together as one group, there was no difference between the zanamivir and placebo groups. The largest treatment effect was noted in study subjects from 7 to 10 years of age while the difference between medians was again smaller for those children aged 11 and 12 years.

Because of some patterns noted in the efficacy results in the principal phase 3 studies supporting the original NDA, results in this pediatric efficacy supplement were analyzed by the country in which the study was conducted. In this analysis, efficacy results were determined for U.S. and non-U.S. subjects since the number of subjects in each country outside of the United States was small. For subjects enrolled in the United States, there was a 0.5 day difference in days to alleviation of symptoms in the intent-to-treat population and a 1.0 day difference in the influenza-positive population. The median time to alleviation of influenza symptoms for non-U.S. study subjects in NAI30009 is shown in Table 24.

**Table 24: Median Time to Alleviation of Symptoms for Non-U.S. Subjects**

Population	Placebo	# of subjects	Zanamivir	# of subjects	Difference in Days
Intent-to-Treat	5.5	106	4.5	103	1.0
Influenza Positive	5.5	82	4.0	78	1.5

Source: SAS datasets

**Table 25: Median Time to Alleviation of Symptoms by Ethnicity for the Intent-to-Treat Population**

Ethnicity	Median time to Alleviation	Difference in Days

	<b>Placebo (No. of patients)</b>	<b>Zanamivir (No. of patients)</b>	
White	5.0 (223)	4.5 (201)	0.5
Non-white	4.25 (24)	4.5 (23)	-0.25

Source: SAS datasets

Because of the concern that their influenza-like illness may have a different course than subjects without underlying respiratory disease and because of the concern of an adverse outcome in this population, the results were also analyzed for subjects with chronic respiratory disease. Data was obtained for any patient with a history of any condition associated with wheezing noted in the line listings of medical conditions. For these subjects the median time to alleviation of symptoms of influenza is given in Table 26.

**Table 26: Median Time to Alleviation of Symptoms for Subjects with Chronic Respiratory Disease**

<b>Study Population</b>	<b>Placebo (n=29)</b>	<b>Zanamivir (n=30)</b>	<b>Difference in Days</b>
<b>Intent-to-Treat</b>	6.0	3.5	2.5

Source: Volume 5, Listing 11

This cohort of subjects with a medical condition associated with wheezing was further analyzed by cross matching them with subjects requiring concurrent medications. The median time to alleviation of symptoms for subjects with any history of wheezing and currently on bronchodilators or steroids is provided in Table 27.

**Table 27: Median Time to Alleviation of Symptoms for Subjects with Chronic Respiratory Disease Requiring Bronchodilators or Steroids**

<b>Study Population</b>	<b>Placebo (n=10)</b>	<b>Zanamivir (n=13)</b>	<b>Difference in Days</b>
<b>Intent-to-Treat</b>	5.75	4	1.75

Source: Volume 5, Listings 11, 12

### Study NAI30010

Study results in certain subgroups among the index cases of study NAI30010 were also analyzed further and are shown in Tables 28 - 31. In most cases, the numbers of study subjects were too small to reach any definite conclusions; however, trends may be noted from these results. The data were obtained from the SAS data sets provided by Glaxo-Wellcome.

When results were analyzed for study subjects by year of age, the numbers of index cases in each group were too small to reach any meaningful conclusion. For example, only 3 index cases who were 5 or 6 years of age were diagnosed with influenza and received zanamivir.

**Table 28: Median Time to Alleviation of Influenza Symptoms in Days for U.S. and non-U.S. Study Subjects (Index Cases Only)**

Population	Placebo (No. of patients)	Zanamivir (No. of patients)	Difference in Days
U.S. Study Subjects:			
ITT	5.5 (57)	4.0 (51)	1.5
IP	6.0 (31)	3.75 (24)	2.25
Non U.S. Study Subjects:			
ITT	5.75 (14)	5.0 (16)	0.75

**Table 29: Median Time to Alleviation of Influenza Symptoms in Days by Ethnicity in the Intent-to-Treat Population (Index Cases Only)**

Ethnicity	Placebo (No. of patients)	Zanamivir (No. of patients)	Difference in Days
White	5.5 (60)	4.0 (58)	1.5
Non-White	4.0 (11)	5.0 (9)	-1.0

**Table 30: Median Time to Alleviation of Influenza Symptoms in Days for High Risk Respiratory Subjects in the Intent-to-Treat Population (Index Cases Only)**

Population	Placebo (No. of patients)	Zanamivir (No. of patients)	Difference in Days
ITT	3.5 (5)	5.0 (4)	-1.5

The only drug previously approved for the treatment of influenza in children, amantadine, was approved for the treatment of influenza A only. Therefore, it was important to examine the outcome based on the type of influenza.

**Table 31: Median time to Alleviation of Influenza Symptoms in Days by Type of Influenza (Index Cases Only)**

Population	Placebo (No. of patients)	Zanamivir (No. of patients)	Difference in Days
Influenza A	5.5 (26)	4.0 (23)	1.5
Influenza B	8.5 (11)	3.75 (8)	4.75

The development of complications was a secondary efficacy endpoint in NAI30009 and so was also evaluated for subjects in NAI30010.

**Table 32: Incidence of Complications of Influenza**

Type of Complication	Placebo (n=70)	Zanamivir (n=68)
Any Complication	9 (13%)	9 (13%)
Antibiotic Use	8 (16%)	8 (12%)
Asthma Exacerbation	1	0
Bronchitis	2	1
Sinusitis	1	0
Otitis	4	4
Pharyngitis	1	3

**Pooled analysis of NAI30009 and NAI30010:**

Because of the above subgroups analyses, certain subgroups were examined by an analysis of pooled data from both studies. As above, only the index cases from NAI30010 are included. Data were again obtained from the SAS datasets.

**Table 33: Median Time to Alleviation in Days for Children from 5 to 6 Years of Age in NAI30009 and NAI30010 (Influenza Positive Population)**

Placebo	# of Patients	Zanamivir	# of Patients	Difference in Days
4.5	40	4.0	39	0.5

The pooled analysis supports the results from each study taken separately; minimal efficacy is again seen with the use of zanamivir in the youngest children.

**Table 34: Median time to Alleviation in Days from NAI30009 and NAI30010 by Country of Origin**

Population	Placebo	# of patients	Zanamivir	# of patients	Difference in Days
U.S. study subjects					
ITT	5.0	198	4.0	172	1.0
Non-U.S. study subjects					
ITT	5.5	120	4.5	119	1.0

**Table 35: Median Time to Alleviation of Influenza Symptoms in Days by Ethnicity in the Intent-to-Treat Populations of NAI30009 and NAI30010**

<b>Ethnicity</b>	<b>Placebo</b>	<b># of patients</b>	<b>Zanamivir</b>	<b># of patients</b>	<b>Difference in Days</b>
White	5.5	283	4.0	259	1.5
Non-White	4.0	35	4.5	32	-0.5

**Table 36: Median Time to Alleviation of Influenza Symptoms in Days for High Risk Respiratory Subjects in the Intent-to-Treat Population**

<b>Population</b>	<b>Placebo</b>	<b># of patients</b>	<b>Zanamivir</b>	<b># of patients</b>	<b>Difference in Days</b>
High Risk Respiratory Subjects	5.75	34	3.75	34	2.0

Note: High-risk respiratory subjects in study NAI30009 were identified as patients with a history of wheezing in Listing 11:

#### **F. NAI30009 and NAI30010 Efficacy Results: FDA Comments**

The primary efficacy endpoint in NAI30009 was the median time to alleviation of the symptoms of influenza in children from 5 to 12 years of age. In the Glaxo-Wellcome analysis of the primary efficacy endpoint, median time to alleviation of symptoms was 1.25 days shorter for the influenza-positive subjects receiving zanamivir compared with placebo. However, diary card entries were made twice daily so that time to alleviation of symptoms was reported in a unit of 0.5 days. The overall difference in median times between the two groups was calculated to be 1.25. Because no individual study subject could have an alleviation time measured in units of 0.25, a value ending in .25 actually represents an interpolated value between two measurements. Therefore, 1.25 is a highly unstable derived value. This creates the highly unusual situation that moving or omitting one subject in a study of over 400 subjects could make a large proportional difference to the estimate of treatment effect. Therefore, the overall efficacy results are most accurately represented by a difference of one day.

Because of the instability of this median value, the secondary analyses of the overall efficacy endpoint was closely evaluated. The initial analysis was also noted to be highly sensitive to the treatment of missing values, especially because there were far more missing values for time to alleviation in the placebo group than the zanamivir group (21 subjects with missing data in the placebo group as compared to 6 in the zanamivir group), and subjects with missing values were assigned the longest possible time to alleviation in the primary analysis (99 days). Because more subjects in the placebo group had missing values and because these subjects were assigned a value of 99 days, the results were skewed in the favor of the zanamivir group. When a censored analysis was done taking into account these subjects with missing data, the difference in medians between the placebo and zanamivir groups was one day. In addition, a one day difference was also noted for the Per Protocol group and in certain subgroups including: study subjects enrolled in centers located in the United States, subjects from 5 to 7 years of age, subjects infected with influenza A, and subjects starting study drug after more than 24 hours of symptoms.

Results of subgroup analysis raised questions about the efficacy of zanamivir in certain age groups. Importantly, when children were grouped into two cohorts, those 5 to 7 years of age and those 8 to 12 years of age, it was noted that the median time to alleviation was less for the younger children in both NAI30009 and NAI30010. After further analysis by year of age the treatment effect was greatest for those children from 7 to 10 years of age; the youngest children, 5 and 6 year olds, and the oldest children, 11 and 12 year olds, had a smaller treatment effect.

In the analysis of study subjects in NAI30009, in NAI30010, and in a pooled analysis by ethnicity, there was a *worse* outcome for the non-White subjects in the zanamivir group as compared to the placebo group. However, the non-White subgroup was a heterogeneous one and efficacy results for each specific ethnic minority group may not be in agreement with the results when all non-White subjects were grouped together. In addition, it is difficult to accurately analyze the results for non-White subjects because of the small number of ethnic minority subjects included in these studies. Although zanamivir did appear to be efficacious in the subgroup of subjects with chronic respiratory disease requiring regular medication in NAI30009, it did not appear to be efficacious in the small number of high-risk respiratory subjects in NAI30010.

In the analysis of secondary efficacy endpoints there was a significant difference in the use of relief medication, the time to return to normal activities, maximum daily temperature, and day 3 temperature all in favor of zanamivir. When individual symptoms were examined, it appears that the improvement in zanamivir subjects is related to a more rapid alleviation of fever and cough. Parents were asked to assess the overall symptoms of their own children twice daily and there was a significant difference in this overall symptom score for the zanamivir group than placebo. However, there was no difference between the zanamivir and placebo groups for the investigator's independent assessment of overall symptoms on day 3 and day 6. The reason for this discrepancy in the description of overall symptomatology is unclear. There was also no difference in the number of subjects shedding virus or in the amount of virus shed between the groups. Importantly, there was no statistically significant decrease in the number of complications of influenza between the two study groups; specifically there was *no* difference in the most common complication seen in children with influenza, otitis media. There was also no difference seen in the use of antibiotics between the two treatment groups; this is most likely due in part to the lack of difference in complications.

Although the number of study subjects is much smaller, the efficacy results of index cases enrolled in NAI30010 were similar to those of NAI30009 with a shorter median time to alleviation of symptoms in subjects receiving zanamivir in the intent-to-treat and influenza positive populations compared to placebo. Several important results were confirmed in NAI30010. Again, younger subjects did not do as well as subjects 8 to 12 years of age. As in NAI30009, non-White subjects receiving zanamivir in NAI30010 had a longer median time to alleviation of symptoms than those receiving placebo. As in NAI30009, there also was no difference in the number of complications of influenza including antibiotic use between the two study groups.

In summary, subjects receiving zanamivir who were enrolled in the study designed to support zanamivir's efficacy in pediatrics and pediatric subjects in a prophylaxis trial showed a modest benefit in the time to alleviation of influenza symptoms. Although there was a smaller treatment effect in younger children, the treatment benefit of zanamivir was consistent for most other subgroups and was also seen in the majority of secondary efficacy endpoints.

#### **G. NAI30009 and NAI30010 Safety Results (Summary of Applicant's Analysis)**

Although the incidence of adverse events in both the zanamivir and placebo groups was low, the capture of this information posed several dilemmas. Even though other approved drugs such as the Flovent Rotadisk® have used lactose vehicles, it is unclear if there are adverse events that might be associated with the use of such vehicles. The optimal method of accounting for adverse events which could be associated with the lactose vehicle is unclear; however, events such as cough, sore throat, and diarrhea were reported as adverse events only in small proportions of subjects (2% or less) in any group. Another difficulty in interpretation is due to the overlap between potential adverse events and influenza manifestations; signs and symptoms of influenza could be reported as adverse events if they were believed to be more severe than anticipated, any resulting imprecision in their identification could tend to obscure treatment differences. In addition, study subjects enrolled as contact cases in NAI30010 were asymptomatic on enrollment and any symptoms of influenza or any other viral infection would be documented as an adverse event.

Adverse events in the placebo and zanamivir groups were similar and infrequent. No deaths were reported in either study. Medication was discontinued prematurely due to an adverse event in only one subject receiving zanamivir among those enrolled in NAI30009 and the index cases in NAI30010. This study subject was a 10 year old white male who developed a severe rash on both arms lasting for 3 days. Among subjects receiving study medication for influenza prophylaxis in NAI30010, one patient in the zanamivir group (gastrointestinal pain) and one in the placebo group (nausea, vomiting and rash) had their medication discontinued prematurely due to an adverse event. Only one study subject required hospitalization for a complication related to influenza. This study subject was a 7 year old male with influenza A and streptococcal pharyngitis receiving zanamivir who developed pneumonitis, gastroenteritis, and dehydration. Adverse events were also similar between zanamivir and placebo in the "high-risk" respiratory subgroup in NAI30009 and the index cases of NAI30010 with no single type of adverse event predominating. However, 7 of 7 subjects with chronic respiratory disease in the zanamivir prophylaxis group had an adverse event as compared to 7 of 12 in the placebo prophylaxis group. The majority of these were viral lower respiratory tract infections that were related to their influenza-like illness which developed while receiving zanamivir as prophylaxis.

**H. NAI30009 and NAI30010 Safety Results (FDA Comments)****NAI30009 and Index Cases of NAI30010**

The overall adverse event profile appeared very similar in the zanamivir and placebo treatment groups. Adverse event reports for all treatment subjects during the actual treatment or in the after-treatment follow-up period are summarized in Table 37. Events were selected for inclusion if they were reported in at least 2% of one treatment group or if they were considered to be of special interest.

**Table 37: Adverse Events in NAI30009 and NAI30010**

<b>Adverse Event</b>	<b>Placebo (n=365)</b>	<b>Zanamivir (n=291)</b>
<b>During Treatment:</b>		
Ear, nose and throat infections	17 (5%)	15 (5%)
Ear, nose, and throat hemorrhage	5 (2%)	1 (1%)
Nausea	5 (2%)	1 (<1%)
Vomiting	10 (3%)	6 (2%)
Diarrhea	6 (2%)	5 (2%)
Cough	6 (2%)	2 (<1%)
Asthma	5 (2%)	2 (<1%)
<b>Post-Treatment:</b>		
Ear, nose and throat infections	14 (4%)	9 (3%)
Nasal signs and symptoms	4 (1%)	5 (2%)
Throat and tonsil discomfort and pain	6 (2%)	1 (<1%)
Headaches	7 (2%)	10 (3%)

Source: Integrated Summary of Safety, Table 35

The adverse events in Table 38 were felt by the individual investigator to be drug-related. No drug-related adverse events were reported in 1.5% or greater of either treatment group.

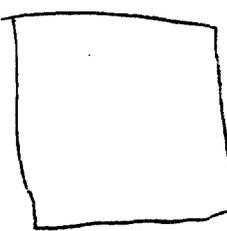
**Table 38: Drug-Related Adverse Events in NAI30009 and NAI30010**

Adverse Event --	Placebo (n=365)	Zanamivir (n=291)
<b>During Treatment:</b>		
Vocal cord disorder	0	1
Throat and tonsil signs and symptoms	1	0
Nausea	0	1
Vomiting	0	1
Diarrhea	1	1
GI signs and symptoms	0	1
Breathing disorder	0	1
Dizziness	1	1
Malaise and fatigue	1	0
Skin rash	2	1
<b>Post-treatment:</b>		
Headache	0	1

Source: Integrated Summary of Safety, Table 37

Laboratory data were obtained on day 1 and day 14 for subjects enrolled in study NAI30009; no laboratory data were obtained for subjects enrolled in NAI30010. Approximately, 75% of subjects in both treatment groups had complete blood counts; a greater proportion (approximately 90%) of patients had chemistries obtained. Laboratory values which shifted from baseline to a value outside of a predetermined threshold are listed in Table 39.

**Table 39: Changes in Laboratory Values Noted for Subjects Enrolled in NAI30009**

Laboratory Parameter	Degree of Change	Placebo	Zanamivir
Albumin		2%	1%
Bicarbonate		3%	<1%
Bicarbonate		1%	2%
Eosinophils		2%	1%
Hematocrit		5%	3%
Neutrophils		1%	4%

Source: Integrated Summary of Safety, Table 49

The degree of neutropenia noted in zanamivir recipients was mild with only one study subject having an absolute neutrophil count of less than 1,000 on day 14 of the study. This study subject had an absolute neutrophil count of 430 cells on study day 1 and again on study day 14. Overall, the mean and median neutrophil counts for both treatment groups were very similar on day 14. Laboratory abnormalities were not followed to resolution.

When study subjects with chronic respiratory disease requiring medication were analyzed further, 4 of 19 subjects in the placebo group experienced an episode of asthma during treatment as compared to only one patient of 26 in the zanamivir group. One of these high-risk respiratory

subjects in the zanamivir group did develop pneumonia during treatment while no placebo subjects were diagnosed with pneumonia during treatment. There was no increase in cough, abnormal breath sounds, or viral respiratory infections in the study subjects receiving a treatment regimen of zanamivir.

Listings of subject discontinuations and investigator comments for NAI30009 were reviewed and potentially important descriptions matched to other listings, serious adverse event narratives in the CSR, or case report forms (CRFs) by subject numbers where possible. In listings of subjects who discontinued study medication before the end of the study (Listing 2), placebo subjects included 3 consent withdrawn, 2 protocol violation, one lost to follow-up, one parent stopping drug, and one whose blister packs did not puncture. The zanamivir group included 3 with consent withdrawn, one who wasn't able to use the diskhaler, and one adverse event. Investigator comments on the trial medication (Listing 13) noted one subject as unable to operate the diskhaler properly, 7 subjects who had blisters that did not puncture, 2 who had blisters puncture prematurely, one who exhaled a dose, and 10 who lost blisters. Overall, 19 of the 471 (4%) subjects had difficulties with the delivery system.

The original submission contained a 5% random sample of case report forms (CRFs) and a 3% random sample of diary cards. These were reviewed along with an additional 44 diary cards for subjects with lower respiratory tract adverse events. The diary card for the single patient who withdrew due to a drug-related adverse event (rash) was reviewed. Adverse events noted in the CFRs and diary cards were generally compatible with those noted in the integrated summary of safety.

#### **NAI30010 Prophylaxis (Contact) Cases:**

The incidence of adverse events in the contact cases of study NAI30010 was higher compared to the incidence in index cases in NAI30010 and in subjects treated with study medication in NAI30009 in part because contact cases were asymptomatic at the time of enrollment during a winter respiratory season in which time any symptoms that occurred were noted by the parent and recorded on the diary card. Overall, 52% of subjects in both the zanamivir and placebo groups reported an adverse event. Adverse event reports for these contact cases during prophylactic treatment or during the follow-up period are summarized in the Table 40. Events were selected for inclusion if they were reported in at least 2% of either treatment group. Selected adverse events felt to be related to the study drug are also included in the last two columns of Table 40; no drug-related adverse event that occurred in more than one subject was omitted from this table. There were no drug-related adverse events in the post-treatment period.

**Table 40: Adverse Events in Contact Cases of Study NAI30010**

	<b>All Adverse Events</b>		<b>Drug-Related Adverse Events</b>	
	<b>Placebo (n=145)</b>	<b>Zanamivir (n=132)</b>	<b>Placebo (n=145)</b>	<b>Zanamivir (n=132)</b>
<b>During Treatment:</b>				
Nasal signs and symptoms	13 (9%)	26 (20%)		
Ear, nose and throat infections	3 (2%)	0		
Throat and tonsil discomfort and pain	8 (6%)	15 (11%)	0	1
Feeding problems	5 (3%)	4 (3%)		
Vomiting	1 (<1%)	3 (2%)	1	1
Cough	11 (8%)	21 (16%)	0	1
Viral respiratory infections	39 (27%)	21 (16%)	1	0
Muscle pain	4 (3%)	3 (2%)		
Musculoskeletal pain	1 (<1%)	2 (2%)		
Headaches	21 (14%)	17 (13%)	2 (1%)	7 (5%)
Malaise and Fatigue	5 (3%)	8 (6%)		
Temperature regulation	5 (3%)	7 (5%)		
<b>Post-Treatment:</b>				
Ear, nose and throat infections	2 (1%)	3 (2%)		
Nasal signs and symptoms	6 (4%)	5 (4%)		
Throat and tonsil discomfort and pain	4 (3%)	4 (3%)		
GI discomfort and pain	2 (1%)	2 (2%)		
Diarrhea	1 (<1%)	2 (2%)		
Viral respiratory infections	3 (2%)	6 (5%)		
Cough	3 (2%)	3 (2%)		
Asthma	4 (3%)	0		
Muscle pain	1 (<1%)	2 (2%)		
Headaches	8 (6%)	7 (5%)		
Temperature regulation	2 (1%)	4 (3%)		
Malaise and fatigue	3 (2%)	3 (2%)		

Source: Integrated Summary of Safety, Tables 35 and 37

The incidence of adverse events in subjects with a chronic respiratory condition requiring medication was also examined for the contact cases in NAI30010. Of 12 placebo “high-risk” respiratory subjects, 7 experienced an adverse event; of 7 “high-risk” respiratory subjects in the zanamivir group, all 7 experienced an adverse event. In addition, all 7 of these zanamivir subjects experienced an adverse event related to the lower respiratory tract. However, for all 7 the lower respiratory event was described as an influenza-like illness; these lower respiratory were further described by the sponsor as lower respiratory viral infection (5), cough (2), and asthma (1). There was one episode of asthma in a subject during the prophylactic regimen of zanamivir and one in a subject receiving placebo for prophylaxis. Adverse events occurring in more than one study subject are listed in the Table 41.

**Table 41: Adverse Events in High Risk Respiratory Contact Cases of Study NAI30010**

Adverse Event	Placebo (n=12)	Zanamivir (n=7)
<b>During Treatment:</b>		
Nasal signs and symptoms	3	1
Throat and tonsil signs and symptoms	2	0
Viral respiratory infections	4	5
Cough	1	2
Headache	2	0
Temperature regulation	2	0
<b>Post-treatment:</b>		
Asthma	4	0

Source: Integrated Summary of Safety, Table 58

No laboratory data were obtained for this study population.

In summary, adverse events were infrequent in both the placebo and zanamivir groups of NAI30009 and NAI30010. The adverse event most frequently observed in these study subjects was ear, nose, and throat infections which occurred in 5% of subjects in both the zanamivir and placebo groups. The only adverse events that were noted more frequently in the zanamivir group than in subjects receiving placebo were post-treatment nasal signs and symptoms and headaches.

Adverse events were noted more frequently in contact cases enrolled in the prophylaxis study; however, this was largely related to study design, and the increased incidence of adverse events was noted for both the zanamivir and the placebo treatment groups. Although no definite conclusions can be drawn because of the small number of "high-risk" respiratory subjects, the high proportion of "high-risk" respiratory subjects in NAI30010 with lower respiratory events is notable.

### I. Summary of Clinical Studies

Results from study NAI30009 showed a modest difference between treatment groups in time to the alleviation of influenza symptoms that would generally be considered clinically meaningful. The finding of treatment differences was supported by several of the secondary efficacy endpoints. Because of the limitations of the analysis described in the discussion of the results for NAI30009 and NAI30010, this difference is most accurately represented by a value of one day. After analysis of the results by age, a markedly smaller treatment difference was noted for the youngest and oldest children. In addition, the youngest children in study NAIA1009 had difficulty using the Diskhaler device as evidenced by both low or unmeasurable inspiratory flow rates and serum zanamivir levels; difficulty in using the Diskhaler was not seen in the majority of older children participating in NAIA1009. Because of the difficulty in the ability of young children to use the delivery device noted in NAIA1009 *and* the smaller treatment effect for the youngest children noted in NAI30009 and NAI30010, zanamivir should only be indicated for children 7 years of age and older.



sponsor. These nonserious adverse events included two cases of skin reaction / hypersensitivity which both resolved without stopping zanamivir. This report also documented one pediatric patient with each of the following: hallucinations and dizziness, nightmares, hyperactivity, migraine, and stomach cramps.

Eighty-three spontaneous adverse events reported to the sponsor in which the age of the patient is not known were also included in the safety update. Twenty of these patients experienced a respiratory adverse event including bronchospasm (9), dyspnea (3), cough (3), respiratory distress (1), breathing disorder (1), hemoptysis (1), respiratory insufficiency (1), and wheezing (1). Eleven reports described local reactions in the face and oropharynx associated with zanamivir use. Another 9 patients were reported with neuro-psychiatric events including headaches, migraines, hallucinations, and nightmares.

Finally, the update summarized adverse events in adolescents from 12 to 16 years of age who are enrolled in NAI30008, an ongoing trial designed to demonstrate the safety and efficacy of zanamivir in subjects with asthma and chronic obstructive pulmonary disease. The data from this study have not been unblinded. In this trial 22 of 36 subjects have reported adverse events; none of these adverse events have been serious. There have been 13 adverse events involving the respiratory system including 4 episodes of exacerbation of asthma. However, none of the adverse events have resulted in the subjects being withdrawn from the study, and none have been determined by the investigator to be related to the study drug.

## **VI. Labeling Issues**

A series of labeling discussions were conducted throughout the review process. It is considered important that while the package insert should represent the modest benefit that was shown in the primary efficacy study in pediatrics and should represent the study results for all children enrolled in NAI30009, the label should also restrict the use of zanamivir to children 7 years of age and older. Suggestions regarding presentation of safety data were also conveyed to the sponsor on several occasions. Discussions of salient points of potential labeling were continued throughout the review process.

## **VII. Phase IV Commitments**

The following topics were proposed phase 4 commitments requested by the Division. These requests are proposed as additions to the phase 4 commitments already agreed upon with the approval of the original NDA.

1. Provide more information on safety and efficacy in younger pediatric patients, especially those from 5 to 7 years of age. This should include, but not be limited to, information regarding the relationship of inspiratory flow rates to efficacy in children.
2. Develop, conduct, and report (complete data, as well as summary and analysis) a study to assess the ability of children and adolescents of various ages to use the zanamivir dry powder

inhalation system based on patient or parental use of proposed package instructions, identify potential obstacles to effective use by categories of potential patients arising from characteristics of the device and the instructions, and develop and test any improvements in usage instructions that may lead to more reliably effective use by the intended patients in the settings characteristic of the intended indication (primary care medical care settings, acutely ill children, need for instructions that will reliably lead to appropriate use beginning with the first dose, etc.).

3. Provide more information regarding safety and efficacy in racial and ethnic minority patients. This should incorporate evaluation for any events that might be related to lactose intolerance in populations in which this condition is common.

4. In addressing your existing Phase 4 commitments for detection and analysis of viral resistance, please indicate your proposals for improving culture yield and increasing the number of isolates examined from both clinical trials and postmarketing surveillance. In addition, provide a plan to examine cross resistance of influenza virus isolated during the clinical use of zanamivir to the range of other available anti-influenza drugs.

5. Within one month of approval of this supplement, provide your proposal for a letter to health professionals describing safety issues noted with the use of zanamivir and your proposal for dissemination of this letter. This letter should address the safety-related modifications to the package insert, including but not limited to reports of serious respiratory adverse events in patients with and without underlying respiratory disease, should remind health care professionals to also consider bacterial etiologies when patients present with influenza-like illnesses, and should address the change in pregnancy category. Following Division review of your proposal and agreement on content and mode of dissemination, such a letter should be distributed within one month (and before the drug is marketed for pediatric use). A second letter should be sent out just prior to the next influenza season (fall 2000); please provide this for review in advance so that any needed updates can be made.

6. Provide a plan to continue to study and submit reports on serious adverse events such as those involving the respiratory and cardiovascular systems, allergic and allergic-like reactions, and all fatalities. This should include but not be limited to: continued submission of 15-day reports for all serious adverse events, including events mentioned in the label; additional follow-up efforts to obtain more information about the circumstances surrounding events in the categories listed above; and a cumulative summary report and analysis at the end of the influenza season. These safety reporting provisions may be re-assessed as appropriate, if agreed between the applicant and the Division of Antiviral Drug Products, after the conclusion of the 2000-2001 influenza season.

**VIII. Recommendation for Regulatory Action**

On the basis of the results from one large trial in pediatric subjects which showed a modest treatment effect and safety data from pediatric patients in two large trials, the conclusion is that this application provides adequate evidence for the approval of zanamivir for the treatment of influenza in patients from 7 to 11 years of age.

**APPEARS THIS WAY  
ON ORIGINAL**