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Viral shedding

No significant treatment-group effects were seen in proportion of subjects with positive throat swab virus cultures at days 3 and 6 in the Phase 3 treatment studies. However, only a subgroup of subjects were examined and the proportion positive, even in the placebo group, was very small. There were fewer day 3 positive results on zanamivir than on placebo but results did not reach statistical significance.

On-treatment or post-treatment culture information was available only for two of the three principal phase 3 treatment studies. The submission also contained information from previous studies in which both nasal washings and throat swabs were used for viral cultures, suggesting that throat swabs were markedly less sensitive for recovery of virus. Therefore, it cannot be assumed that subjects with negative throat swab cultures were no longer shedding influenza virus.

Table III-D18. Throat swab results from phase 3 studies

# with positive viral titer/ # tested*	NAIB3002 placebo	NAIB3002 zanamivir	NAIA3002 placebo	NAIA3002 zanamivir
Day 1	5/62	8/59	46/155	83/177
Day 3	2/62	1/59	17/156	11/174 (p=.135)
Day 6	0/62	0/59	1/145	3/161

* These values are from Table 38 of the two CSRs and reflect the intent-to-treat population. The individual study summaries above contain throat swab results from the influenza positive populations of these two studies.

Use of Standard Symptom Relief Medications

All of the principal phase 3 treatment studies reportedly provided standard supplies of acetaminophen and a cough suppressant (dextromethorphan or pholcodine) for symptomatic relief. Use of these relief medications varied across studies (generally higher in NAIA3002 than NAIB3002 and intermediate in NAIB3001, as illustrated by the following data provided by the FDA statistical reviewer for the Advisory Committee briefing document. Mean use of acetaminophen was very similar in placebo and zanamivir groups for NAIB3001 and NAIA3002. Mean use of acetaminophen in NAIB3002, and mean use of cough suppressant in all three studies, was somewhat lower in the zanamivir group than in the placebo group: this suggested that patients on active drug might have had a reduction in perceived need for symptomatic relief medications, but any such effect did not appear to be large or consistent in magnitude.

Table III-D19. Use of acetaminophen and cough syrup in phase 3 studies

Use of standard relief medications (flu+)	NAIB3001 (Southern Hemisphere)	NAIB3002 (Europe)	NAIA3002 (North America)
Mean tablets of acetaminophen, total for days 1-5			
Placebo	13	8	15
Zanamivir	13	6	14
Mean doses of cough suppressant, total for days 1-5			
Placebo	13	9	13
Zanamivir	10	6	10
Mean tablets of acetaminophen, total for days 1-14			
Placebo	17	11	22
Zanamivir	17	9	21
Mean doses of cough suppressant, total for days 1-14			
Placebo	17	15	20
Zanamivir	14	11	17

IV. Phase 2 Clinical Treatment Trials

Several phase 2 treatment trials were conducted prior to institution of the phase 3 program. These trials differed from the phase 3 trials and among themselves in numerous ways including differences in size of study, entry criteria, endpoint definitions, and duration of symptom recording. There were also differences in treatment regimens, as the phase 2 trials used a combination of inhaled and intranasal zanamivir for one of the study arms; three of the four phase 2 trials summarized here also included an inhaled zanamivir arm in a three-arm study design (placebo, inhaled zanamivir, inhaled plus intranasal zanamivir). These studies were reviewed as supporting documentation only. The NDA submission also contained mentions of small trials in Japan from which reports were not yet available; as described in the submission, enrollment numbers in those trials were expected to be sufficiently small to limit the possibility of conclusive additional results.

IV-A. Clinical Study NAIA2005

Protocol NAIA2005, "A double-blind, randomized, placebo-controlled multicenter study to investigate the efficacy and safety of inhaled and intranasal GG167 in the treatment of

influenza A and B viral infections," was submitted to IND [redacted] in the original IND submission. Points of note from protocol and review documents include protocol definition of alleviation as loss of FEVER and other symptoms absent or mild [protocol section 5.3.6 "Alleviation of major influenza symptoms is defined as loss of fever and two of four (headache, myalgia, cough and sore throat) symptoms which satisfied the inclusion criteria recorded as "none" or "mild", all of which must be maintained over the next 24 hours"], and the sponsor's proposal to submit individual reports of results from NAIA2005 and non-IND non-U.S. study NAIB2005 plus combined reports from the two studies and to conduct treatment-by-protocol interactions "to assess the appropriateness of this strategy," a proposal with which DAVDP statistics reviewers did not agree according to documents in file. The understanding according to FDA documents was that NAIA2005 (which was submitted for protocol review prior to conducting the study) and NAIB2005 would be considered as separate studies, and any combined analysis would be considered exploratory. The study report is located in volumes 78 through 80 in NDA 21-036.

IV-A1. NAIA2005 Study Design

Study NAIA2005 [information from study synopsis, vol. 78] was carried out in the United States and Canada. Eligible subjects had temperature at least 37.8 C and influenza-like symptoms present for less than 48 hours. [Amended protocol section 3.1 Inclusion Criteria "Duration of influenza-like illness (ILI) for ≤ 48 hours, defined as fever (≥ 37.8 C or 100.1° F) and at least two of the following: headache, myalgia, cough, sore throat."] High-risk and currently vaccinated individuals (and any potential subjects taking other intranasal or inhaled medications), and individuals judged not able to use the Rotadisk/Diskhaler device, were excluded. Randomization was to zanamivir inhaled plus intranasal, inhaled zanamivir plus intranasal placebo, or placebo by both routes, all with twice-daily dosing. Doses (section 3.3.3) were two inhalations (5 mg per inhalation) twice daily plus two intranasal sprays per nostril twice daily (0.1 ml per spray of 16 mg/ml preparation): thus, the inhalation dose was comparable to the phase 3 treatment studies, while intranasal zanamivir dose was apparently 1.6 mg per spray, 4 sprays BID or 6.4 mg BID. Culture and antibody titers were the principal means to define the influenza-positive subpopulation (see discussion under NAIB2005 below). In the influenza-positive population, 74% had influenza A and 26% had influenza B. According to the CSR (section 3.3.3), "All patients administered their first dose of study medication during the Day 1 visit, under instruction from the investigator or co-worker. They were instructed to take the inhaled medication before the intranasal medication and to take the second dose that evening." Patients without documented alleviation were counted as day 10 (5.6.1.1) for purposes of analysis.

IV-A2. NAIA2005 Efficacy Results (Summary of Applicant's Analysis)

A total of 220 subjects were enrolled (sample size calculations targeted 273 including 30% overage): 81 randomized to placebo, 68 to inhaled zanamivir (ZI), and 71 to

inhaled/intranasal zanamivir (ZI2). Numbers are summarized from CSR Tables 1-12. Two in the inhaled and two in the inhaled/intranasal zanamivir group withdrew due to adverse events. Baseline characteristics did not show major imbalances across treatment groups. Table 13 lists influenza diagnosis by "diagnostic sample result", "serology sample result", and "viral titer result"; 37% of subjects were classified as influenza A, 13% as influenza B, and 48% as influenza negative. Alleviation of symptoms was analyzed as headache, myalgia, cough, sore throat none or mild with no feverishness and then separately as headache, myalgia, cough, sore throat none or mild with temperature $<37.8^{\circ}\text{C}$ (see previous subsection regarding the protocol-predefined endpoint), and mean days to alleviation were compared (assigning a value of 10 to those with alleviation at or after day 10; note the same value of 10 was assigned for eradication of all symptoms in those without positive evidence of eradication), in contrast to the principal phase 3 studies in which medians were compared and alleviation was defined as no feverishness AND temperature $<37.8^{\circ}\text{C}$ and other symptoms none or mild. Selected outcome measures are listed in the following table.

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Table IV-A2a. Selected outcomes in NAIA2005

Outcome	Placebo	Inhaled zanamivir	Inhaled/intranasal Z
All randomized subjects (ITT population)			
Mean days to alleviation (CSR Table 16: feverishness definition) (ITT)	5.9	5.4	5.5
Percent alleviated by day 9 (CSR Table 16: feverishness definition) (ITT)	83%	85%	79%
Center-stratified p value for comparison with placebo (CSR Table 16: feverishness definition) (ITT)		.647	.800
Mean days to alleviation (CSR Table 16: temperature definition) (ITT)	5.5	5.3	5.2
Percent alleviated by day 9 (CSR Table 16: temperature definition) (ITT)	84%	85%	79%
Center-stratified p value for comparison with placebo (CSR Table 16: temperature definition) (ITT)		.946	.966
Mean days to symptom eradication (CSR Table 18) (ITT)	8.5	8.3	8.0
Percent with eradication by day 9 (CSR Table 18) (ITT)	37%	44%	55%
Center-stratified p value for comparison with placebo (CSR Table 18) (ITT)		.851 (feverishness definition) .816 (temperature definition)	.278 (feverishness definition) .257 (temperature definition)
Mean days with any moderate or severe symptom (CSR Table 38) (ITT)	5.8	5.7	5.7
Mean days to return to normal activities (CSR Table 42) (ITT)	3.7	3.7	4.0
Post-treatment investigator assessment of symptoms (CSR Table 47) (ITT)	28% no symptoms, 65% mild, 5% moderate, 3% severe	38% no symptoms, 52% mild, 9% moderate	35% no symptoms, 59% mild, 4% moderate, 1% severe

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Table IV-A2a. Selected outcomes in NAIA2005 (continued from previous page)

Outcome	Placebo	Inhaled zanamivir	Inhaled/intranasal Z
Influenza positive subjects			
Mean days to alleviation (CSR Table 56: flu +, feverishness definition)	6.1	5.5	5.0
Percent alleviated by day 9 (CSR Table 56: flu +, feverishness definition)	83%	89%	88%
Center-stratified p value for comparison with placebo (Table 56: flu +, feverishness definition)		.321	.228
Mean days to alleviation (CSR Table 56: flu+, temperature definition)	5.7	5.2	4.8
Percent alleviated by day 9 (CSR Table 56: flu +, temperature definition)	83%	89%	88%
Percent alleviated by day 6 (CSR Table 56: flu +, temperature definition)	60%	68%	82%
Center-stratified p value for comparison with placebo (Table 56: flu +, temperature definition)		.440	.579
Mean days to symptom eradication (Table 60, flu+)	8.6	8.4	8.0
Percent with eradication by day 9 (Table 60, flu +)	38%	43%	59%
Center-stratified p value for comparison with placebo (CSR Table 60) (flu +)		.872 (feverishness definition) .840 (temperature definition)	.510 (feverishness definition) .464 (temperature definition)
Mean days with any moderate or severe symptom (Table 80, flu +)	6.0	5.4	5.3
Mean days to return to normal activities (CSR Table 84, flu +)	4.0	3.9	3.6
Post-treatment investigator assessment of symptoms (CSR Table 89, flu +)	23% no symptoms, 72% mild, 5% moderate	29% no symptoms, 63% mild, 9% moderate	29% no symptoms, 65% mild, 6% moderate

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IV-A3. NAIA2005 Efficacy Results (FDA Comments)

It seems particularly important to look at NAIA2005 as a separate study not only because it was reviewed as an independent protocol and a pre-planned independent submission, but also because it provides the only additional North American treatment comparisons using the proposed marketed dose and regimen of zanamivir to support the results from NAIA3002. Comparisons were difficult from the primary study report in the NDA because the CSRs for NAIA2005 and NAIB2005 compare mean time to alleviation (while medians, not given in the CSR, were used for primary analyses of the phase 3

treatment studies), and because the definitions of the "alleviation" endpoint differed slightly between studies. Some median values were obtained from the end-of-phase-2 briefing document () see table under NAIB2005 below). Additional analyses (including some which used uniform definitions across phase 2 and phase 3 studies), summarized and discussed in later sections of this review, were requested as review progressed in the effort to find common ground between studies.

IV-A4. NAIA2005 Safety Results (Summary of Applicant's Analysis)

Adverse event profiles were considered similar in all three treatment groups. It was noted that "detrimental changes in physical examination" in the ENT system from pre to post treatment occurred in 7 (9%) of placebo group, 8 (12%) of ZI and 16 (23%) of ZI2 subjects (Table 93). One subject was discontinued from the study because of a serious adverse event that was not considered drug related, a motorcycle accident with cervical vertebral fracture on day 15 of the study (10 days after completion of inhaled/intranasal zanamivir).

IV-A5. NAIA2005 Safety Results (FDA Comments)

Adverse event reports (Table 94) included nausea/vomiting, nasal signs & symptoms, headaches, cough, throat/tonsil discomfort/pain in 10% or more during treatment in 2 or more groups. Diarrhea was reported for 6% of the placebo and ZI2 groups and 1% of the ZI group. There were no clear patterns distinguishing zanamivir from placebo recipients. No deaths were reported, 2 SAEs (one motorcycle accident at day 15, one rectal malignancy at 8 weeks). One patient was withdrawn due to urticaria and one due to swollen labia (both on ZI) and one due to vertigo, nausea, sore throat and cough (on ZI2). Lab shifts (change from baseline to beyond threshold) included no glucose below 0.75 LLN in any group, 2 to 3 per group with any liver value beyond threshold.

Case report forms were submitted for 4 subjects withdrawn due to adverse events. These contained information consistent with that in the CSR.

IV-A6. Summary of Study NAIA2005

There were no clearly significant differences between groups in any clinical efficacy measurement. Mean days to alleviation endpoints, and investigator assessment of proportion asymptomatic at the post-treatment visit, had point estimates slightly favoring inhaled zanamivir over placebo but with highly inconclusive p values. In contrast to some of the phase 3 results, time until feeling able to return to normal activities (CSR Table 42) appeared to be faster than protocol-defined alleviation. Overall, no impressive treatment effects and no impressive safety concerns were documented in this study.

IV-B. Clinical Study NAIB2005

NAIB2005 was designated as a Phase 2 study entitled "A double-blind, randomized, placebo-controlled, parallel-group, multicenter study to investigate the efficacy and safety of inhaled and intranasal zanamivir in the treatment of influenza A and B viral infections." This was a non-IND study with a protocol similar to NAIA2005, but differing in numerous aspects of diagnostic definitions. Review documents indicate that there was discussion at the time of NAIA2005 protocol review, concerning whether analyses of the two studies would be pooled, and that the conclusion was that "exploratory" pooled analyses might be performed. For both NAIA2005 and NAIB2005, it was evident prospectively that multiple comparisons were being performed (including each of two active treatment arms against placebo). The CSR for NAIB2005 is contained in volumes 81 through 83 of NDA 21-036.

IV-B1. NAIB2005 Study Design

Study design was similar to NAIA2005 above, with several points of potential difference including the following. Influenza diagnosis could be determined by "standard methodology (antigen detection and/or positive culture)" on nasal/pharyngeal samples, or seroconversion on acute and convalescent serum specimens. The protocol-predefined primary endpoint was alleviation defined as feverishness "none" and headache/myalgia "none" or "mild" (protocol section 9.1). Inclusion criteria (protocol section 5.2) included ability to use the devices "satisfactorily" and "Duration of influenza-like illness for ≤ 48 hours (ie feverishness and at least two of the following symptoms: headache, myalgia, cough, sore throat)." This is also different from NAIA2005 which had an objective temperature requirement. Sample size calculation was "based on the assumption that 50% of patients on placebo will have alleviation of major symptoms of influenza by day 6 (post treatment visit). A clinically relevant difference is defined as an increase in the number of patients with alleviation of major symptoms of influenza by Study Day 6 to 75% or greater." NAIA2005 made a similar assumption but specified that it was with respect to the influenza-positive population. Laboratory diagnostics for definition of influenza positives also appeared to differ between NAIA2005 and NAIB2005 in that antigen detection appeared to be mentioned as an adequate criterion in NAIB2005 but not in NAIA2005, but this could not be conclusively confirmed from the CSRs; therefore, the question was raised during a teleconference with the applicant, and the applicant confirmed verbally that this was a difference in criteria for influenza positivity between the two studies.

IV-B2. NAIB2005 Efficacy Results (Summary of Applicant's Analysis)

From CSR Tables 1-9: a total of 198 subjects were enrolled from 10 countries (Belgium, Finland, France, Germany, Italy, Netherlands, Norway, Spain, Sweden, U.K.; target was 273 allowing 30% overage for dropouts and patients without laboratory-confirmed influenza), randomized 63 to placebo, 64 to inhaled zanamivir, 70 to inhaled/intranasal

zanamivir. Influenza was diagnosed in 151 (76%), of which 65 (43%) were influenza A and 86 (57%) influenza B. Withdrawals for adverse events were noted in 5 placebo, 2 inhaled zanamivir, and 1 inhaled/intranasal zanamivir subjects. Major protocol deviations were recorded in 22%, 22%, and 11%, the most common being no evidence of feverishness at entry (6%, 13%, 4%) and missed or incorrect treatment doses (17%, 8%, 4%). Demographics were reasonably balanced. Table 13 has influenza diagnosis categories for "diagnostic sample" and "serology sample" and as for NAIA2005, there is no clear differentiation between culture and antigen detection or breakdown of specific assays used. Selected outcome measures are summarized in the following table.

Table IV-B2a. Selected outcomes in NAIB2005

Outcome	Placebo	Inhaled zanamivir	Inhaled/intranasal Z
All randomized subjects (ITT population)			
Mean days to alleviation (CSR Table 16: ITT, feverishness definition)	6.2	5.2	5.4
Percent alleviated by day 9 (CSR Table 16: ITT, feverishness definition)	70%	86%	81%
Center-stratified p value for comparison with placebo (Table 16: ITT, feverishness definition)		.117	.214
Mean days to alleviation (CSR Table 16: ITT, temperature definition)	6.0	5.0	5.3
Percent alleviated by day 9 (CSR Table 16: ITT, temperature definition)	70%	86%	79%
Center-stratified p value for comparison with placebo (Table 16: ITT, temperature definition)		.137	.273
Mean days to symptom eradication (Table 18, ITT)	8.7	8.3	8.5 (feverishness) 8.6 (temperature)
Percent with eradication by day 9 (Table 18, ITT)	38%	39% (feverishness) 38% (temperature)	36% (feverishness) 33% (temperature)
Center-stratified p value for comparison with placebo (Table , ITT)		.261 (feverishness) .390 (temperature)	.892 (feverishness) .879 (temperature)
Mean days with any moderate or severe symptom (Table 36, ITT)	6.2	5.5	5.4
Mean days to return to normal activities (CSR Table 39, ITT)	5.3	5.2	4.5
Post-treatment investigator assessment of symptoms (CSR Table 44, ITT)	48% no symptoms, 44% mild, 8% moderate	52% no symptoms, 42% mild, 6% moderate	60% no symptoms, 33% mild, 7% moderate

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Table IV-B2a. Selected outcomes in NAIB2005 (continued from previous page)

Outcome	Placebo	Inhaled zanamivir	Inhaled/intranasal Z
Influenza positive subjects			
Mean days to alleviation (CSR Table 52: flu +, feverishness definition)	6.4	5.4	5.5
Percent alleviated by day 9 (CSR Table 52: flu +, feverishness definition)	67%	81%	78%
Center-stratified p value for comparison with placebo (Table 52: flu +, feverishness definition)		.159	.359
Mean days to alleviation (CSR Table 52: flu +, temperature definition)	6.3	5.0	5.4
Percent alleviated by day 9 (CSR Table 52: flu +, temperature definition)	67%	83%	74%
Center-stratified p value for comparison with placebo (Table 52: flu +, temperature definition)		.028	.281
Mean days to symptom eradication (Table 56, flu+)	-8.8	8.4 (feverishness) 8.5 (temperature)	8.3 (feverishness) 8.5 (temperature)
Percent with eradication by day 9 (Table 56, flu +)	33%	33%	39% (feverishness) 35% (temperature)
Center-stratified p value for comparison with placebo (Table 56, flu +)		.656 (feverishness) .626 (temperature)	.884 (feverishness) .974 (temperature)
Mean days with any moderate or severe symptom (Table 74, flu +)	6.4	5.8	5.5
Mean days to return to normal activities (CSR Table 77, flu +)	5.7	5.2	4.6
Post-treatment investigator assessment of symptoms (CSR Table 82, flu +)	46% no symptoms, 46% mild, 8% moderate	48% no symptoms, 48% mild, 4% moderate	63% no symptoms, 30% mild, 7% moderate
Mean days to alleviation of headache and myalgia and eradication of feverishness (CSR Table 17, ITT)	4.8	4.3	4.6
Percent with alleviation of headache and myalgia and eradication of feverishness by day 6 (cf protocol defined endpoint and assumptions for sample size calculations) (CSR Table 17, ITT)	75%	86%	80%
Center-stratified p value for comparison with placebo (Table 17, ITT)		.470	.953
Mean days to alleviation of headache and myalgia and eradication of feverishness (protocol predefined)	4.9	4.3	4.7

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primary endpoint) (CSR Table 55, flu +)			
Percent with alleviation of headache and myalgia and eradication of feverishness by day 6 (cf protocol predefined primary endpoint and assumptions for sample size calculation) (CSR Table 55, flu +)	73%	85%	78%
Center-stratified p value for comparison with placebo (Table 55, flu +)		.316	.875
Influenza subtypes			
Mean days to alleviation, influenza A (CSR Table 53, feverishness definition)	6.9	4.4	5.2
Mean days to alleviation, influenza A (CSR Table 53, temperature definition)	6.6	4.3	5.3
Mean days to alleviation, influenza B (CSR Table 54, feverishness definition)	6.0	6.1	5.8
Mean days to alleviation, influenza B (CSR Table 54, temperature definition)	6.1	5.5	5.5

IV-B3. NAIB2005 Efficacy Results (FDA Comments)

Median values for time to alleviation, shown below, were found in the End-of-Phase-2 briefing document [redacted]. The marked change in treatment effect in NAIB2005 when analysis was restricted to subjects febrile at entry may be a consequence of the fact that objective fever was not an entry requirement for NAIB2005, so that subjects febrile and afebrile at entry would each be expected to account for a sizable proportion of entrants; however, it was difficult to assess possible differences in baseline temperature because of differences in the way these were presented in the two study reports. According to NAIB2005 CSR Table 14, "Summary of investigator assessment of pre-treatment symptoms of influenza: intent-to-treat population," entry temperatures ranged from 35.6 to 40.1°C with a mean of 37.7 or 37.8 in each treatment group. NAIA2005 CSR Table 14, with the same title, gives entry temperatures "recorded by investigator" ranging from 35.8 to 39.7 with a mean of 37.7 to 37.9 in each treatment group, but also includes a category of "Maximum temperature recorded at home by patient" which ranges from 37.4 to 40.0 with mean of 38.5 to 38.6 in each group. As the corresponding table from NAIB2005 does not make this distinction and simply has a single category headed "Temperature", it was not possible to assess from these tables whether and to what extent the baseline temperature characteristics differed between the two studies, but outcome differences between studies did appear to be enhanced when analyses were restricted to patients defined as febrile in the analysis.

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Table IV-B3a. Selected outcome measures in NAIA2005 compared with NAIB2005

Treatment Effect, Placebo – Inhaled Zanamivir	NAIB2005 (Europe)	NAIA2005 (North America)
Median days to alleviation, feverishness definition (ITT)	0.5	1.0
Median days to alleviation, temperature definition (ITT)	0.5	0.2
Mean days to alleviation, feverishness definition (flu+)	1.0	0.8
Mean days to alleviation, temperature definition (flu+)	1.5 (p=.028)	1.5
Mean days to alleviation, feverishness definition (febrile patients)	4.0	1.2
Mean days to alleviation, temperature definition (febrile patients)	3.2 (p=.019)	1.5

IV-B4. NAIB2005 Safety Results (Summary of Applicant's Analysis)

Adverse event profiles were similar across treatment groups. Detrimental changes in ENT exam were reported in 7 (11%) placebo, 2 (3%) ZI, and 4 (6%) ZI2 subjects (Table 86). Withdrawals due to adverse events on placebo included palpitations (2325), headache (2683), diarrhea (2887), throat dryness/vomiting/diarrhea (2891), and nausea (2896); on ZI chest tightness (2323) and fever/cough (2712), on ZI2 numb palate/epistaxis/nasal block/headache (2640).

IV-B5. NAIB2005 Safety Results (FDA Comments)

No striking differences were seen between treatment groups (Table 87). Post-treatment (but not during-treatment) ENT events were somewhat more common in the two active treatment groups. Two subjects in each of the three treatment groups had a shift to any hepatic test beyond the threshold value (Table 92).

CRFs were received for eight patients withdrawn due to adverse events. For subject 2323, chest tightness was recorded as having been present for some weeks. For subject 2712, study drug was recorded as having been interrupted due to mouth irritation, sneezing, lack of appetite, and sensation of swollen palate, and discontinued due to fever and cough. For subject 2887, in addition to diarrhea, reasons for withdrawal were recorded as "Fear for experimental drug. Feels powder of drug in throat. Fear that diarrhea is a side effect of the experimental drug."

IV-B6. Summary of Study NAIB2005

For a study with three treatment arms, NAIB2005 was of rather modest size and power. Treatment effects were also modest, and of questionable (clinical or statistical) significance, although generally in the direction of a benefit from zanamivir. There was

no clear evidence that inhaled plus intranasal zanamivir was superior or inferior to inhaled zanamivir alone, but such a difference could not be ruled out from a study of this size.

IV-C. Combined Applicant Analysis of NAIA2005 and NAIB2005

In the NDA submission, the applicant proposed a combined analysis of NAIA2005 and NAIB2005 (described in Volume 84) as an additional "adequate and well-controlled study" to be considered together with the phase 3 studies. Descriptions of the primary treatment effect for the two studies combined, from information in the original NDA submission (excluding additional analyses in amendments), include the following. The proposed draft label (volume 1) lists a "Study 1" with the same numbers of influenza-positive subjects (85 inhaled zanamivir, 89 placebo) as the combined analysis, with median time to alleviation of 4.5 days on placebo and 3.5 days on zanamivir. The Integrated Summary of Efficacy (volume 134) has a table under 5.1.2, Primary Endpoint Results (5.1.2.1, Primary Treatment Studies: Influenza Positive Population) giving 4.5 and 3.5 days for a "feverishness" endpoint definition ($p=.053$) and 4.5 and 3.0 days for a "temperature" endpoint definition ($p=.023$). The analysis in volume 84, under Efficacy Results (section 4), Primary Efficacy Parameter (4.3), Time to alleviation of major signs and symptoms of influenza (4.3.1), contains a table titled "Summary of median and mean day of alleviation of major symptoms of influenza for the influenza positive population" giving "median day of alleviation" as 5.0 for placebo and 4.0 for ZI with a p value of .053 for "feverishness definition" and 5.0 for placebo and 4.0 for ZI with a p value of .023 for "temperature definition." Table 15 of volume 84 is headed "Time to alleviation of major symptoms of influenza: influenza positive population" and contains median values "Based on day number" of 5.0 for placebo and 4.0 for ZI ($p=.053$) and median values "Based on time in half-days" of 4.5 for placebo and 3.5 for ZI (no p value listed); the definition of alleviation in this table includes "no feverishness" but no reference to temperature. Table 16 of volume 84 is also headed "Time to alleviation of major symptoms of influenza: influenza positive population" and contains median values "Based on day number" of 5.0 for placebo and 4.0 for ZI ($p=.023$) and median values "Based on time in half-days" of 4.5 for placebo and 3.0 for ZI (no p value listed); the definition of alleviation in this table includes "temperature $<37.8^{\circ}\text{C}$ " but no reference to feverishness.

The applicant's draft Advisory Committee briefing document (January 15, 1999) contains a table under 7.4.4, Summary of Primary Endpoint Results, Influenza Positive Population, titled "Comparison of median time (days) to alleviation of influenza symptoms: primary treatment studies, influenza positive population." For the study listed as NAIA/B2005, again with 89 placebo and 85 inhaled zanamivir patients, this table shows values of 4.5 and 3.5 days with a p value of .044.

In addition to the lack of prospective agreement on such a strategy, and the difficulty in

determining which of the available descriptions should be considered as definitive, the differences in design between NAIA2005 and NAIB2005 delineated above suggest that a combined analysis should be interpreted with caution because it is a combination of dissimilar components. Furthermore, it is not clear what meaning can be attached to the p value of the combined analysis when it is an additional analysis in a setting where at least eight other principal comparisons were performed (placebo vs ZI and placebo vs ZI2, each using a temperature definition and a feverishness definition of the primary endpoint, for NAIA2005 and for NAIB2005). Values below .05 cannot be assumed to be "statistically significant" in this multiple-comparison situation, and it is again noteworthy that only a minority of analyses in these two studies even achieved this cutoff, although a number of point estimates suggested modest differences in favor of zanamivir.

More information may be derivable from comparing NAIA2005 and NAIB2005 results against one another than from combining these two studies for analysis. In addition to the values given above under NAIB2005 efficacy analysis, the following comparisons from the original NDA submission (as described above in summaries of the individual studies) were considered of potential interest. All of the analyses in Table IV-B3a and IV-C1 showed differences between placebo and inhaled zanamivir that favored the zanamivir arm (i.e. mean or median days of symptoms greater on placebo) but differences were generally small with inconclusive p values, and treatment effect was smaller in NAIA2005 than NAIB2005 for most of these analyses. Some further analyses will be discussed under review of post-Advisory Committee amendments.

Table IV-C1. Additional outcome comparisons in NAIA2005 and NAIB2005

Treatment Effect, Placebo – Inhaled Zanamivir	NAIB2005 (Europe)	NAIA2005 (North America)
Mean days to alleviation, feverishness definition (ITT)	1.0	0.5
Mean days to alleviation, temperature definition (ITT)	1.0	0.2
Mean days with any moderate or severe symptom (ITT)	0.7	0.1
Mean days to alleviation, feverishness definition (flu+)	1.0	0.6
Mean days to alleviation, temperature definition (flu+)	1.3	0.5
Mean days with any moderate or severe symptom (flu+)	0.6	0.6

IV-D. Clinical Study NAIB2007

NAIB2007 is entitled "A double-blind, randomized, placebo-controlled, parallel-group, multicenter study to investigate the efficacy and safety of inhaled and inhaled plus intranasal zanamivir in the treatment of influenza A and B viral infections." The CSR is located in volumes 85 through 88 of NDA 21-036.

IV-D1. NAIB2007 Study Design

This is a non-U.S. study which collected symptom diary information only for five days. It compared placebo, inhaled zanamivir, and inhaled plus intranasal zanamivir (same doses as NAIA2005 and NAIB2005 above), and measured the proportion of subjects experiencing alleviation by day 4 or earlier (see following section for change in method of estimating treatment effect). Definition of alleviation is temperature $<37.8^{\circ}\text{C}$ and no feverishness, with headache, myalgia, cough, and sore throat none or mild. A "high-risk" population (age 65 and over, cardiovascular or respiratory disease, diabetes) was not protocol-defined (in fact, subjects with asthma were excluded during the initial part of the recruitment period), but a "decision to analyze this population was documented in the Data Analysis Plan issued prior to unblinding" (CSR Section 5.4.1.4).

IV-D2. NAIB2007 Efficacy Results (Summary of Applicant's Analysis)

From CSR Tables 1-2: A total of 571 subjects were recruited, 554 were randomized (183 placebo, 188 inhaled zanamivir, 183 inhaled plus intranasal zanamivir), and 549 were randomized and took at least one dose of study medication (250 Australia, 93 New Zealand, 206 South Africa). Of 348 classified as influenza positive (63% of those randomized), 319 (92%) were listed as influenza A, 20 (6%) as influenza B, and 9 (3%) as unknown type. Selected outcomes are listed in the following table. In the ITT population, treatment differences were less and p values were greater (despite larger numbers) in subjects with shorter duration of symptoms before entry (CSR Tables 16-19), while baseline temperature appeared to have little relationship to treatment effect (if anything, treatment effect appeared greater in patients with lower baseline temperature; CSR Tables 20-21), and findings for influenza-positive subjects were similar (CSR Tables 46-51): these findings are in contrast to similar subgroup analyses in other studies. "High-risk" enrollees included 66 subjects of whom 46 were classified as respiratory, 10 cardiovascular, 8 diabetes, 9 elderly (Table 72; outcomes given only for aggregate high-risk group, not for diagnostic subgroups). The planned primary analysis was time to alleviation defined as in the phase 3 studies. The Synopsis in the CSR notes, "For the primary endpoint, fewer than 50% of patients had influenza symptom alleviation on day 4 or earlier. Therefore estimates of treatment effects were calculated as the difference in the proportion of patients with alleviation of clinically significant symptoms of influenza on or before Day 4."

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Table IV-D2a. Selected outcomes in NAIB2007

Outcome	Placebo	Inhaled zanamivir	Inhaled/intranasal
Percent alleviated by day 4 (CSR Table 15)	23%	37% (p=.003)	34% (p=.028)
Return to normal activities by day 4 (CSR Table 31)	54%	60% (p=.204)	62% (p=.254)
Median days with at least one symptom moderate or severe (CSR Table 34)	5	5 (p=.010)	5 (p=.171)
Investigator's post-treatment assessment (CSR Table 38)	22% no symptoms, 55% mild, 10% moderate, 1% severe	20% no symptoms, 55% mild, 9% moderate, 2% severe (p=.848)	28% no symptoms, 49% mild, 10% moderate, <1% severe (p=.595)
Anti-infectives for complications (CSR Table 39)	21%	12% (p=.025)	15% (p=.221)
Percent alleviated by day 4 (Table 45, flu +)	23%	37% (p=.070)	38% (p=.020)
Return to normal activities by day 4 (CSR Table 63, flu +)	52%	58% (p=.448)	56% (p=.418)
Median days with at least one symptom moderate or severe (CSR Table 66, flu +)	5	5 (p=.011)	5 (p=.062)
Investigator's post-treatment symptom assessment (CSR Table 70, flu +)	20% no symptoms, 63% mild, 13% moderate, 2% severe	22% no symptoms, 65% mild, 6% moderate, 3% severe (p=.224)	31% no symptoms, 56% mild, 9% moderate, <1% severe (p=.347)
Anti-infectives for complications (CSR Table 71, flu +)	20%	12% (p=.098)	13% (p=.169)
Percent alleviated by day 4 (CSR Table 76, high risk)	33%	57% (p=.828)	32% (p=.739)
Percent alleviated by day 4 (CSR Table 77, high risk flu +)	29%	53% (p=.700)	38% (p=.848)

IV-D3. NAIB2007 Efficacy Results (FDA Comments)

The proposed draft label in volume 1 includes this among "five ... Phase II and Phase III studies" and states "The primary efficacy endpoint in four of the five studies was the time to alleviation of major symptoms of influenza defined as no fever (i.e., temperature <37.8°C and/or feverishness recorded as "none") and an assessment of "none" or "mild" for headache, myalgia, cough, and sore throat.... In the other study, influenza symptoms were collected only during treatment (days 1 through 5). Due to this difference in study design, it was not possible to pool data from this study with the other four studies." However, the CSR does not confirm a prospectively defined difference in endpoint, but rather a failure to reach the endpoint in enough subjects to derive median estimates.

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This study enrolled subjects in three countries. The by-country breakdown of percent alleviated by day 4 or earlier (Appendix 2 of CSR) is given in the following table.

Table IV-D3a. Treatment effect by country in NAIB2007 (number and % alleviated by day 4)

Country	Placebo	Inhaled zanamivir	Inhaled/intranasal
Australia	16 (19%)	31 (37%)	35 (42%)
New Zealand	14 (44%)	20 (63%)	13 (43%)
South Africa	13 (19%)	19 (26%)	14 (20%)

IV-D4. NAIB2007 Safety Results (Summary of Applicant's Analysis)

Dizziness was reported by 3% in each zanamivir group and no placebo subjects. Nausea and vomiting were reported by 5% of ZI, 1% of ZI2, and 1% of placebo subjects. Other adverse events were considered largely compatible with influenza-like illness.

Withdrawals due to possibly drug-related adverse events were confined to the two zanamivir groups and events included headache (4202), wheezing (4423), nausea and vomiting (5312), stomatitis (5325), and cough and dry throat (4716). Rises in potassium were frequent and were attributed to improper handling of samples in all study groups. Overall, safety of zanamivir was considered comparable to placebo.

IV-D5. NAIB2007 Safety Results (FDA Comments)

Investigator's comments on medication use (Appendix 7) include numerous comments (e.g. 4040, 4011, 3901, 3903, 3904, 4921, 4929) that patient had taken one medication blister per dose instead of two, in some instances taking two inhalations but without turning the disk to a new blister. There were also comments that individual patients stopped drug because of diarrhea (4354), headache (4202), wheezing/coughing/dry throat & need to use ventolin (4423, ZI), bloody nose before last dose (4699), cough & dry throat (4716 ZI2), nausea and vomiting (5310), stomatitis and secondary URTI (5325), bronchospasm (5330, ZI). There were also comments regarding puncture on only one side (5063), "disk haler failure" (5139), and "failure of perforating mechanism" (5140). One investigator appears to have withdrawn 18 randomized subjects because of negative or lost diagnostic specimens.

CRFs were supplied for nine subjects withdrawn due to adverse events (including those listed in the previous section and others not considered drug-related). Patient 4423, withdrawn from zanamivir due to wheezing (requiring use of bronchodilator in setting of underlying asthma) and nausea, was also noted in the CRF as having blood work diagnostic of infectious mononucleosis and day 6 LFT elevations improving at day 28, attributed as "resolving hepatitis secondary to EBV."

IV-D6. Summary of Study NAIB2007

Although several of the principal comparisons show treatment differences in favor of zanamivir over placebo, the differences are modest and variable. Statistical evaluations require cautious interpretation especially in view of the multiple comparisons and *post hoc* modification of the primary description of treatment effect. Investigators' comments suggest that some subjects had difficulty interpreting their instructions to achieve appropriate use of the inhalation component of treatment. A number of subjects appear to have been withdrawn after randomization on the basis of diagnostic test results; while these withdrawals would not be expected to affect the efficacy analysis of influenza positive subjects, it is not possible to determine whether they would affect any conclusions regarding safety or intent-to-treat efficacy analyses.

IV-E. Clinical Study NAIA/B2008

NAIA/B2008, "A double-blind, randomized, placebo-controlled, multicenter, parallel-group study to investigate the efficacy and safety of GG167 administered twice or four times a day for the treatment of influenza A and B viral infections," was a phase 2 study which used combinations of inhaled and intranasal zanamivir, so the dosage and regimen differ from (exceed) that proposed for marketing. Selected results will be summarized because this is one of the largest studies performed with this drug, it did use an inhaled preparation (in combination with intranasal), it enrolled a substantial number of North American subjects, and it provides some safety information from experience with a higher dose of zanamivir than the proposed marketed regimen. This protocol was submitted to IND [redacted] The CSR is in volumes 89 through 96 of NDA 21-036. An article containing results from this study was published shortly after the end of the NDA review period (J Infect Dis 1999;180:254-261).

IV-E1. NAIA/B2008 Study Design

The design of study NAIA/B2008 was similar to that of NAIA3002 in many respects; however, inclusion criteria for influenza-like illness were feverishness plus at least two of the standard four symptoms present for no more than 48 hours (no absolute temperature criterion), while the primary endpoint required both normalization of temperature and absence of feverishness with other major symptoms absent or mild (CSR sections 3.2.1 and 4.1.1). Subjects had to be able to use the devices to be entered. Influenza positivity was defined by culture, serology, or rapid test (any one being positive) for the secondary efficacy population. Currently vaccinated subjects had to have laboratory confirmation before entry. High-risk subjects were identified retrospectively after the study was unblinded. Symptoms were recorded for 10 days. Subjects were randomized to receive inhaled plus intranasal zanamivir twice daily (same doses as NAIA2005), the same zanamivir doses four times daily (i.e. total daily dose twice as high as the BID treatment arm), or placebo (section 3.3.3). There were two separate placebo groups, one receiving

placebo preparations BID and the other QID. Review documents from the protocol development stage suggest that analyses comparing BID drug to BID placebo and QID drug to QID placebo were to be performed; however, in the original CSR all analyses appear to reflect use of a single placebo group combining BID and QID use.

IV-E2. NAIA/B2008 Efficacy Results (Summary of Applicant's Analysis)

From CSR Tables 1-3: a total of 1256 subjects were randomized, 694 in the U.S., 99 in Canada, and the remainder in Belgium (28), Denmark (15), Finland (34), France (95), Germany (42), Italy (13), Netherlands (41), Norway (36), Spain (34), Sweden (54), and U.K. (71). Of those enrolled, 722 (57%) were designated as influenza positive (665 influenza A, 47 influenza B, 10 unknown type). Randomization allocated 422 to placebo, 419 to bid zanamivir, and 415 to qid zanamivir; of these, 12, 13, and 10 withdrew due to adverse events. Selected outcome measures are summarized below. When ITT patients were divided according to duration of symptoms before entry (with breakpoint at either 30 or 36 hours), those with earlier entry showed lower p values (and for the 30 hour breakpoint and QID zanamivir, slightly larger point estimates) for differences in median times to alleviation; however, the larger proportion of subjects fell into the earlier-entry categories (CSR Tables 16-19). Treatment groups were reasonably balanced by gender; in the ITT population, median times to alleviation on placebo were longer for female than male subjects but treatment effects were more similar, as median time to alleviation differed between active drug and placebo by 0.5 days for male and 0.5 to 1.0 days for female subjects (Appendix 3). Point estimates of treatment effects were larger, and p values lower, for subjects with temperature at least 37.8° C at entry (CSR Tables 20-21). However, these relationships were not reliably reproduced for the influenza positive population (CSR Tables 48-53). For many of the comparisons (e.g. days to eradication, time to normal activities), no summary statistics are given, only cumulative distributions and p values. Separate analysis of North American subjects was not found in the original CSR except for the median ITT time to alleviation by country, and was requested from the applicant during the review process. In retrospective analysis, 68 placebo, 48 BID, and 42 QID subjects (Table 80) were defined as "at-risk" (elderly, cardiovascular, respiratory, and/or endocrine/metabolic condition; results were given for the aggregate high-risk group but not for the component subgroups by diagnosis).

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