Table IV-E2a. Selected outcomes in NAIA/B2008

Outcome	Placebo	BID Zanamivir	QID Zanamivir
All randomized subjects (ITT population)			
Median days to alleviation (ITT; CSR Table 15)	7.0	6.0 (p=.012)	6.0 (p=.014)
Median days with all symptoms recorded as none or mild (ITT; CSR Table 35)	2	3 (p=.004)	3 (p=.004)
Post-treatment investigator assessment of symptoms (ITT; CSR Table 40)	29% no symptoms, 50% mild, 12% mild/moderate, 6% moderate, 2% moderate/severe, <1% severe	32% no symptoms, 51% mild, 12% mild/moderate, 4% moderate, 1% moderate/severe, p=.057	35% no symptoms, 52% mild, 9% mild/moderate, 3% moderate, <1% moderate/severe, 1% severe, p=.003
Anti-infective for secondary infection (ITT; CSR Table 41)	13%	10% (p=.140)	13% (p=.911)
Influenza positive subjects			
Median days to alleviation (flu +; CSR Table 47)	7.0	5.5 (p=.108)	5.5 (p=.055)
Median days with all symptoms recorded as none or mild (flu +; CSR Table 69)	2	3 (p=.025)	3 (p=.007)
Post-treatment investigator assessment of symptoms (flu +; CSR Table 74)	26% no symptoms, 54% mild, 13% mild/moderate, 5% moderate, 2% moderate/severe, 1% severe	30% no symptoms, 54% mild, 13% mild/moderate, 3% moderate, <1% moderate/severe, p=.007	35% no symptoms, 53% mild, 8% mild/moderate, 3% moderate, <1% moderate/severe, 1% severe, p=.004
Anti-infective for secondary infection (flu+; CSR Table 75)	14%	6% (p=.005)	11% (p=.395)
Influenza subtypes			
Median days to alleviation, influenza A (CSR Table 54)	7.0 (n=222)	5.5 (n=220)	5.5 (n=223)
Median days to alleviation, influenza B (CSR Table 55)	8.0 (n=15)	5.5 (n=17)	5.0 (n=15)
"At-risk" subjects			
Median days to alleviation (ITT, "at-risk"; CSR Table 81)	7.8	6.3 (p=.137)	5.0 (p=.042)
Median days to alleviation (flu +, "at-risk"; CSR Table 82)	8.0	5.3 (p=.016)	5.0 (p=.009)

IV-E3. NAIA/B2008 Efficacy Results (FDA Comments)

Appendices 1 and 2 contain separate results for time to primary endpoint for BID placebo and QID placebo, without statistical comparisons.

Table IV-E3a. Treatment effect with separate placebo groups in NAIA/B2008

Median days to alleviation	Placebo	Zanamivir
ITT, BID	7.0 (n=208)	6.0 (n=419)
ITT, QID	6.5 (n=214)	6.0 (n=415)
Flu+, BID	7.0 (n=116)	5.5 (n=241)
Flu+, QID	5.5 (n=124)	5.5 (n=241)

Treatment effect by country is given in appendix 4, for the intent-to-treat analysis only.

Table IV-E3b. Treatment effect by country in NAIA/B2008

Country	N (All randomized)	All Placebo vs BID Z	All Placebo vs QID Z
All	1256	P 7.0 days, Z 6.0 days, difference 1.0 days	P 7.0 days, Z 6.0 days, difference 1.0 days
Belgium	28	P 7.5 days, Z 6.0 days, difference 1.5 days	P 7.5 days, Z 3.8 days, difference 3.7 days
Canada	99	P 7.0 days, Z 4.0 days, difference 3.0 days	P 7.0 days, Z 3.8 days, difference 3.2 days
Denmark	15	P 5.0 days, Z 6.3 days, difference -1.3 days	P 5.0 days, Z 9.0 days, difference -4.0 days
Finland	34	P 4.0 days, Z 5.3 days, difference -1.3 days	P 4.0 days, Z 5.0 days, difference -1.0 days
France	95	P 7.5 days, Z 5.0 days, difference 2.5 days	P 7.5 days, Z 4.5 days, difference 3.0 days
Germany	42	P 8.5 days, Z 7.5 days, difference 1.0 days	P 8.5 days, Z 9.0 days, difference -0.5 days
Italy	13	P 6.0 days, Z 6.0 days, difference 0 days	P 6.0 days, Z 4.5 days, difference 1.5 days
Netherlands	41	P 7.5 days, Z 7.3 days, difference 0.2 days	P 7.5 days, Z 6.5 days, difference 1.0 days
Norway	36	P 4.5 days, Z 5.5 days, difference -1.0 days	P 4.5 days, Z 4.8 days, difference -0.3 days
Spain	34	P 9.0 days, Z 8.3 days, difference 0.7 days	P 9.0 days, Z 9.0 days, difference 0 days
Sweden	54	P 9.0 days, Z 6.5 days, difference 2.5 days	P 9.0 days, Z 8.0 days, difference 1.0 days
U.S.	694	P 6.5 days, Z 5.5 days, difference 1.0 days	P 6.5 days, Z 6.0 days, difference 0.5 days
U.K.	71	P 7.3 days, Z 5.0 days, difference 2.3 days	P 7.3 days, Z 6.8 days, difference 0.5 days

Most countries did not have enough patients enrolled for any kind of stability of effect (average less than 15 per treatment arm). All countries with more than 50 subjects, except the U.S., showed a more than 2-day point estimate of treatment effect for BID

zanamivir, while the U.S. point estimate is 1.0 day. The U.S. also had the lowest point estimate for treatment effect of QID drug among these countries (tied with U.K.; Sweden, France, Canada all higher). These estimates are all based on the ITT population as a separate analysis of influenza positive subjects by country was not found in the submission.

Table IV-E3c. Treatment effect for countries with largest enrollments in NAIA/B2008

NAIA/B2008: Point Estimate for Treatment Effect by Country for Countries Entering >50 Subjects (Median Days to Alleviation, ITT))	N	Difference in Median Days to Alleviation, Placebo vs BID Z	Difference in Median Days to Alleviation, Placebo vs QID Z
Canada	99	3.0	3.2
France	95	2.5	3.0
Sweden	54	2.5	1.0
U.S.	694	1.0	0.5
U.K.	71	2.3	0.5

Because of questions arising in the course of review regarding North American populations and regarding possible effects of the placebo preparations, additional analyses were requested to explore effects in different populations and to explore possible differences between BID and QID administration. No direct comparisons to the phase 3 studies can be made because of the differences in treatment regimen and the multiple *post hoc* analyses. A submission of January 18, 1999 (tables 42 and 44; these contain a column for zanamivir BID, a column for zanamivir QID, and a single column for placebo subjects which is headed "Placebo bid" but has N values suggesting the combined placebo group), contained an analysis of influenza positive subjects at North American sites yielding a 1.0 day difference in median times to the standard phase 3 endpoint between zanamivir BID and placebo (p=.114), while all sites combined showed a 1.5 day difference between medians for zanamivir and placebo (p=.045). The applicant's Advisory Committee briefing document (dated February 5, 1999; Appendix 1) contained an analysis of influenza positive subjects for all sites combined, comparing BID drug to BID placebo and QID drug to QID placebo, which showed a 1.5 day difference between medians for BID zanamivir vs BID placebo and no difference in median times to alleviation between zanamivir and placebo for the QID treatment groups (5.5 days for each). Additional analyses were provided in post-Advisory Committee submissions and will be discussed in later sections of this review.

IV-E4. NAIA/B2008 Safety Results (Summary of Applicant's Analysis)

Serious adverse events were reported in three placebo recipients (pyelonephritis/vaginitis/UTI, epileptic attack, slipped disc) and five zanamivir recipients (pneumonia/EBV infection, renal colic, nausea/vomiting/diarrhea, colon and ovarian tumor, hospitalization for alcoholism, all considered unrelated or unlikely related to study drug) (CSR section 12). Two pregnancies (one placebo, one BID zanamivir) were

reported: the one on zanamivir resulted in spontaneous abortion, with the following description of the 18-year-old subject (CSR section 12.1): "Concurrently she received birth control pills, fluoxetine and paroxetine. While on study drug it was discovered that she was pregnant from a sexual assault prior to starting the study....Thirteen days after stopping study drug she developed painful contractions and bleeding. The following day, she had a diagnosis of spontaneous miscarriage .... In the investigator's opinion the events were unrelated to the use of the study drug." Adverse events were reported as generally similar across treatment groups and as compatible with influenza-like illness except for reports of diarrhea, nausea, and vomiting. Adverse events reported as possibly drug-related (in all treatment groups, Table 85) included ENT events, headaches, dizziness, and gastrointestinal symptoms. For laboratory value changes (CSR section 8.5.2), glucose decreases were reported in 12% of placebo, 16% of BID zanamivir, and 11% of QID zanamivir recipients; neutrophil decreases in 24%, 21%, and 22%; glucose increases in 13%, 10%, and 12%; ALT increases in 9%, 10%, and 10%. Detrimental changes in ENT exam (Table 83) were reported in 10%, 10%, and 9%.

IV-E5. NAIA/B2008 Safety Results (FDA Comments)

Selected adverse events from CSR Table 84 are listed in the following table, based on occurrence in at least 5% of any treatment group, or were considered of special interest. According to Table 84, urticaria were reported during treatment in one BID zanamivir and one placebo recipient, and Stevens-Johnson syndrome in one placebo recipient (this does not appear to have been reported among the serious adverse event narratives). Table 88 indicates withdrawal due to adverse events for 12 (3%) placebo, 13 (3%) zanamivir BID, and 10 (2%) zanamivir QID recipients; these included one "blindness and low vision" in the zanamivir BID group (again, no serious adverse event was reported, and this adverse event code was routinely used for transient blurred vision in other reports), and "breathing disorders" in three placebo recipients. Overall, there was no evident pattern of adverse events that appeared to be commonly or strongly associated with either of the active-drug regimens.

Because of the report of spontaneous abortion a few weeks after study drug in a patient also exposed to several other drugs, other pregnancy exposures were reviewed at this point (section 16 of ISS, volume 136). There were five pregnancy reports from other studies (also described in the review summaries of those studies): in NAIA3005 (below) one placebo recipient elected to terminate pregnancy, one zanamivir recipient was variably reported as having decided to terminate or being undecided, and one (zanamivir) had an ongoing pregnancy without known defect; in NAIB3002 one subject (placebo) had bleeding during pregnancy and another (placebo) had an ongoing pregnancy without known defect. Thus, in the combined review of multiple large studies, four pregnancies were reported in placebo recipients and three in zanamivir recipients, one bleeding episode was reported in a placebo recipient and one spontaneous abortion in a zanamivir recipient. The overall number appeared likely to reflect the recruitment of relatively young healthy populations, and no clear conclusions could be drawn to suggest any specific relationships.

Table IV-E5a. Selected adverse events in NAIA/B2008

Adverse event	Placebo (n=422)	BID zanamivir (n=419)	QID zanamivir (n=415)
During treatment:			
Any adverse event	139 (33%)	118 (28%)	121 (29%)
Any ENT event	44 (10%)	31 (7%)	38 (9%)
Nasal signs & symptoms	14 (3%)	7 (2%)	12 (3%)
Throat/tonsil signs/sx	0	4 (1%)	3 (1%)
Any GI event	38 (9%)	32 (8%)	30 (7%)
Diarrhea	11 (3%)	11 (3%)	16 (4%)
Nausea & vomiting	14 (3%)	7 (2%)	13 (3%)
Abnormal LFTs	1 (<1%)	3 (1%)	1 (<1%)
Any lower respiratory event	29 (7%)	9 (2%)	20 (5%)
Bronchitis	11 (3%)	3 (1%)	6 (1%)
Pneumonia	0	0	3 (1%)
Cough	3 (1%)	0	2 (<1%)
Asthma	1 (<1%)	0	2 (<1%)
Any neurologic event	25 (6%)	23 (5%)	12 (3%)
Headaches	9 (2%)	8 (2%)	6 (1%)
Dizziness	5 (1%)	7 (2%)	1 (<1%)
Migraines	0	1 (<1%)	2 (<1%)
Vertigo	0	2 (<1%)	1 (<1%)
Post treatment:			
Nasal signs & symptoms	8 (2%)	11 (3%)	9 (2%)
Sinusitis	4 (1%)	6 (1%)	8 (2%)
Throat & tonsil signs/sx	3 (1%)	3 (1%)	5 (1%)
Nausea & vomiting	3 (1%)	3 (1%)	6 (1%)
Diarrhea	3 (1%)	6 (1%)	3 (1%)
Bronchitis	6 (1%)	4 (1%)	9 (2%)
Cough	6 (1%)	7 (2%)	5 (1%)
Pneumonia	1 (<1%)	5 (1%)	1 (<1%)
Headaches	11 (3%)	15 (4%)	15 (4%)
Vertigo	0	2 (<1%)	0

Laboratory tabulations were provided in a different format in this study compared to the phase 3 studies. Laboratory value shifts (Tables 89 and 90) for selected measures are given in the following table. Laboratory shift to any hepatic value outside threshold was reported for 33 (8%) placebo, 24 (6%) zanamivir BID, and 16 (4%) zanamivir QID subjects (Table 89). No pattern suggestive of clear drug relationships was detected. As in the other studies already summarized, the most frequent laboratory abnormalities appear to overlap with those seen during the course of acute viral illnesses.

Table IV-E5b. Laboratory values in NAIA/B2008

Shift from baseline	Placebo	BID zanamivir	QID zanamivir
ALT to >normal	37/411 (9%)	36/394 (9%)	38/397 (10%)
ALT to >2xULN	17/411 (4%)	13/394 (3%)	6/397 (2%)
Bilirubin to >normal	5/406 (1%)	4/392 (1%)	1/393 (<1%)
Bilirubin to >1.5xULN	1/406 (<1%)	3/392 (<1%)	0/393
GGT to >normal	34/412 (8%)	15/396 (4%)	17/397 (4%)
GGT to >2xULN	25/412 (6%)	12/396 (3%)	10/397 (3%)
CPK to >normal	10/411 (2%)	23/393 (6%)	18/397 (4%)
CPK to >5xULN	0/411	0/393	2/397
Creatinine to >normal	0	0	0
Creatinine to >1.3xULN	0/413	0/398	1/399
Lymphocytes to <normal	3/391	4/380	5/390
Lymphocytes to <0.8xLLN	3/391	1/380	4/390
Neutrophils to <normal	56/391 (14%)	40/380 (10%)	40/390 (10%)
Neutrophils to <0.8xLLN	26/391 (7%)	22/380 (6%)	14/390 (4%)

In Appendix 9 (investigators' comments on deviations from planned treatment schedule), there are notes of several subjects taking half as many doses as directed, usually but not always specified as one blister at a time instead of two (A3342 "read the instructions", B6937, B6938, B7563, B7249, A3742, A3743, A3335, A3201, A7144, A4843, A4845), of "incorrect method of use" (B7513), and of patients stopping because they felt an adverse event was associated with medication (dizziness B7486 ZBID, A3297 ZBID "attributed adverse event to taking study med", B7044 PBID "feeling uncomfortable", B7131 ZQID nausea and vomiting, B7159 ZBID dryness in oral & nasal mucosa, B6769 PQID "felt adverse event", B6799 ZBID "feeling of uncomfort", B6802 "burning sense in the nose when taking the studymedicine. No problem to inhale.", A3170 ZQID migraine after first dose, A3660 PQID wheezing, A3256 ZQID missed 4 evening doses because of "feeling short of breath with evening dose and being asleep at time med was due", A3838 PQID headache, A4238 P "adverse event", A3582 "adverse event", A3586 "adverse event"). Half-pierced medication blisters were noted in a few instances (B7222, B7238, B6805 "It is obvious from the returned study medication, ie rotadisks, that patient believed she complied. However she never succeed to puncture both foils in all cases.", B6812 "Several doses wasn't punctured. The patient didn't understand that she was doing wrong.", A7252 "6 blisters with top punctured but bottom intact therefore 3 doses missed", A7253 "1 blister with top punctured but bottom intact", A7254 "1 blister with top punctured but bottom intact", A7264, A7267, A3127, A3135, A3997, A7124, A4467, A3899, A3445, A3449, A3495). One patient was reported as having "much powder left in each opened blister of the rotodisk inhaler. Patient states unable to extract all of powder upon each inhalation." Another was reported as returning disks that "were powdery as if inhalation was incomplete."

CRFs were received for 35 subjects withdrawn due to adverse events. Subject 3168 (the pregnancy report described in greater detail above) was described on study entry as "Pt.

suffering from past events – depression" and later as having a negative urine and positive serum pregnancy test. Subject 3297 (BID zanamivir) had reports of "dizziness on standing, shakiness, blurry vision, hair loss with combing." Subject 3443 (placebo) was withdrawn because of "dysphoria." Overall information was generally compatible with that already summarized.

IV-E6. Summary of Study NAIA/B2008

This study again suggested modest effects in favor of zanamivir, with no clear ability to document whether BID or QID administration had a greater or lesser effect. There was no clear pattern of adverse events or evident dose-related toxicity associated with the QID dosing regimen as compared with BID (and in fact little difference from placebo). Multiple comparisons and multiple approaches to analyses, as well as the lack of any treatment arm using the proposed marketed regimen, limit the quantitative interpretations that can be placed on these data.

IV-F. Summary of Additional Analyses of North American Results in Phase 2

The following analyses are among those received in the applicant's submission of January 18, 1999, and described above under studies NAIA2005, NAIB2005, and NAIA/B2008. Additional analyses received in April will be summarized in later sections.

Table IV-F1. Analysis of time to standard phase 3 definition of alleviation applied to influenza-positive subjects in phase 2 studies having North American and European subjects

Treatment effect (difference in days to alleviation, p)	North American and European sites combined	North American sites only
NAIA2005 plus NAIB2005 (placebo versus ZI)	1.0 day, p=.044, n=174	0.75 day, p=.347, n=77
NAIA/B2008 (all placebo versus BID ZI2)	1.5 day, p=.045, n=481	1.0 day, p=.114, n=280

V. Studies in Subjects Without Influenza-Like Illness at Entry

Safety and limited efficacy information were available from several studies enrolling volunteers who were not acutely ill at entry. Some of these were pilot studies which will not be described in detail. Several of these studies used the once-daily inhaled zanamivir regimen under study for possible use in prophylaxis: because no submission for a prophylaxis indication has been received at this time and the current NDA is proposed only for a treatment indication, the focus here will be principally on safety information.

V-A. Clinical Study NAI10901

Protocol NAI10901, "A double-blind, randomized, placebo-controlled study to evaluate the effect of inhaled zanamivir 10 mg od for 28 days on anti-hemagglutinin antibody production following co-administration with Fluvirin trivalent influenza vaccine in healthy subjects," was submitted to IND [redacted] The study report is contained in volumes 76 through 77 of NDA 21-036.

V-A1. NAI10901 Study Design

Healthy volunteers were randomized to receive inhaled zanamivir or placebo in conjunction with administration of trivalent inactivated influenza vaccine. Study objectives (CSR section 2) refer to "co-administration" of drug with vaccine; the Treatment Administration section (3.3.3) indicates that all subjects received a single intramuscular dose of vaccine and were then randomized to receive active drug or placebo for 28 days.

V-A2. NAI10901 Efficacy Results (Summary of Applicant's Analysis)

A total of 138 subjects were recruited, of whom 68 were assigned to placebo and 70 to zanamivir. The "per protocol population" included 65 placebo and 69 zanamivir subjects. One subject in each group discontinued prematurely (one adverse event in placebo group, one loss to follow-up in zanamivir group) and 4 subjects were identified as non-compliant (3 placebo and 1 zanamivir). Placebo subjects were somewhat less likely to be identified as female (56%, vs 69% of zanamivir subjects) and "White" (85% vs 97%). Selected outcomes are summarized in the following table.

Table V-A2a. Selected outcomes in NAI10901 (number and percent of subjects)

Outcome	Placebo	Zanamivir
Influenza B, 4-fold titer rise, baseline to week 2 (from CSR Table 12, mITT)	40/67 (60%)	38/70 (54%)
Influenza B, 4-fold titer rise, baseline to week 4 (from CSR Table 12, mITT)	39/68 (57%)	37/70 (53%)
Influenza A/H1N1, 4-fold titer rise, baseline to week 2 (from CSR Table 12, mITT)	50/67 (75%)	58/70 (83%)
Influenza A/H1N1, 4-fold titer rise, baseline to week 4 (from CSR Table 12, mITT)	48/68 (71%)	56/70 (80%)
Influenza A/H3N2, 4-fold titer rise, baseline to week 2 (from CSR Table 12, mITT)	43/67 (64%)	55/70 (79%)

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Table V-A2a. Selected outcomes in NAI10901 (continued from previous page)

Outcome	Placebo	Zanamivir
Influenza A/H3N2, 4-fold titer rise, baseline to week 4 (from CSR Table 12, mITT)	42/68 (62%)	52/70 (74%)
Influenza B, 4-fold titer rise, baseline to week 2 (from CSR Table 17, per protocol)	40/65 (62%)	37/69 (54%)
Influenza B, 4-fold titer rise, baseline to week 4 (from CSR Table 17, per protocol)	38/65 (58%)	36/69 (52%)
Influenza A/H1N1, 4-fold titer rise, baseline to week 2 (from CSR Table 17, per protocol)	49/65 (75%)	57/69 (83%)
Influenza A/H1N1, 4-fold titer rise, baseline to week 4 (from CSR Table 17, per protocol)	47/65 (72%)	55/69 (80%)
Influenza A/H3N2, 4-fold titer rise, baseline to week 2 (from CSR Table 17, per protocol)	43/65 (66%)	54/69 (78%)
Influenza A/H3N2, 4-fold titer rise, baseline to week 4 (from CSR Table 17, per protocol)	41/65 (63%)	51/69 (74%)
Influenza B, titer ≥1:40, week 2 (from CSR Table 13, mITT)	37/67 (55%)	33/70 (47%)
Influenza B, titer ≥1:40, week 4 (from CSR Table 13, mITT)	37/68 (54%)	31/70 (44%)
Influenza A/H1N1, titer ≥1:40, week 2 (from CSR Table 13, mITT)	63/67 (94%)	69/70 (99%)
Influenza A/H1N1, titer ≥1:40, week 4 (from CSR Table 13, mITT)	64/68 (94%)	69/70 (99%)
Influenza A/H3N2, titer ≥1:40, week 2 (from CSR Table 13, mITT)	63/67 (94%)	61/70 (87%)
Influenza A/H3N2, titer ≥1:40, week 4 (from CSR Table 13, mITT)	63/68 (93%)	61/70 (87%)
Influenza B, titer ≥1:40, week 2 (from CSR Table 18, per protocol)	37/65 (57%)	32/69 (46%)
Influenza B, titer ≥1:40, week 4 (from CSR Table 18, per protocol)	36/65 (55%)	30/69 (43%)
Influenza A/H1N1, titer ≥1:40, week 2 (from CSR Table 18, per protocol)	61/65 (94%)	68/69 (99%)
Influenza A/H1N1, titer ≥1:40, week 4 (from CSR Table 18, per protocol)	61/65 (94%)	68/69 (99%)

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Table V-A2a. Selected outcomes in NAI10901 (continued from previous page)

Outcome	Placebo	Zanamivir
Influenza A/H3N2, titer ≥1:40, week 2 (from CSR Table 18, per protocol)	62/65 (95%)	60/69 (87%)
Influenza A/H3N2, titer ≥1:40, week 4 (from CSR Table 18, per protocol)	61/65 (94%)	60/69 (87%)

V-A3. NAI10901 Efficacy Results (FDA Comments)

Overall post-immunization antibody against the influenza B antigen appeared less than to either of the influenza A antigens when compared in terms of either 4-fold rise in titer or proportion with titer at least 1:40. It was also notable that many subjects had titers of at least 1:40 against the A antigens at baseline. No definitive clinically important relationship between overall antibody responses and treatment group was demonstrated. There was also no evident difference between week 2 and week 4 antibody responses in this subject population.

V-A4. NAI10901 Safety Results (Summary of Applicant's Analysis)

Adverse events were similar between placebo and zanamivir recipients. The most frequent adverse event (headache) is noted as "documented on the datasheet of the Fluvirin™ trivalent vaccine as a side-effect." Temporal relationship is not described. It is also noted that "the laboratory reported that blood glucose samples were taken in standard gel and clot activator tubes which is likely to have resulted in artefactually low glucose levels."

V-A5. NAI10901 Safety Results (FDA Comments)

Because this study involved administration of drug or vehicle to subjects who did not already have influenza-like symptoms, it provides an opportunity to look at adverse events that might be associated with zanamivir and/or inhaled lactose even where these have symptomatic overlap with clinical presentation of influenza. However, it is not possible to compare rigorously with the expected occurrence of the same symptoms in a healthy population followed for the same period of time without intervention of any kind.

Headaches, throat and tonsil discomfort and pain, nasal signs and symptoms, and cough were all designated as drug-related in at least some cases (CSR Table 20); the possible association of these symptoms with treatment is consistent with other studies. Respiratory symptoms showed little difference between drug and placebo but a relationship to the lactose vehicle (received by both groups) cannot be ruled out. Symptoms did not appear to be treatment-limiting in that only one person discontinued for an adverse event; from comparisons among data listings the reason appears to have been "viral infection."

Table V-A5a. Selected adverse events in NAI10901 (common or of particular interest)

Event (from CSR Table 19)	Placebo (n=68)	Zanamivir (n=70)
Any event	46 (68%)	51 (73%)
Headaches	30 (44%)	33 (47%)
Dizziness	2 (3%)	3 (4%)
Throat/tonsil discomfort/pain	9 (13%)	13 (19%)
Nasal signs/symptoms	8 (12%)	8 (11%)
Malaise & fatigue	8 (12%)	2 (3%)
Temperature regulation disturbances	3 (4%)	4 (6%)
Cough	11 (16%)	5 (7%)
Diarrhea	3 (4%)	5 (7%)
Nausea & vomiting	3 (4%)	5 (7%)
GI discomfort & pain	1 (1%)	4 (6%)
Musculoskeletal pain	4 (6%)	5 (7%)

Table V-A5b. From Tables 23 and 24, laboratory abnormalities in NAI10901

Event	Placebo (n=68)	Zanamivir (n=70)
Post-treatment		
ALT>ULN	1	3
AST>ULN	2	1
Bilirubin>ULN	8	3
Bilirubin>1.5xULN	3	0
CPK>5xULN	1	1
Creatinine>ULN	3	0
GGT>ULN	4	2
GGT>2xULN	0	1
Lymphocytes <LLN	0	0
PMNs<LLN	2	2
Glucose<.75LLN	1	10
Shift from baseline to postRx		
To elevated bilirubin	3	2
To elevated CPK	4	8
To elevated creatinine	2	0
To elevated GGT	1	0
To decreased glucose	7	13
To decreased PMNs	0	2

V-A6. Summary of Study NAI10901

Zanamivir did not appear to have a striking effect on antibody titers within the limits of this study. No major safety concerns were identified but the possibility that some events such as headache and ENT symptoms were related to drug or lactose vehicle cannot be excluded. The apparent excess of post-treatment low glucose measurements was ascribed by the applicant to improper sample handling and did not appear to be replicated in other studies; other laboratory abnormalities were not common and did not show clear differences between treatment groups.

V-B. Clinical Study NAIA3005

Protocol NAIA3005, "A double-blind, randomized, placebo-controlled, parallel-group, single center study to investigate the efficacy and safety of inhaled zanamivir (GG167) 10 mg administered by inhalation once a day for 28 days in the prevention of symptomatic influenza A and B viral infections in young, community-dwelling adults," was submitted to IND [redacted] The study report is contained in volumes 125 through 132 of NDA 21-036.

V-B1. NAIA3005 Study Design

In this study, adults aged 18 and over in two university communities were recruited in the autumn before influenza season, and surveillance was carried on for influenza activity in the communities. When influenza was determined to be circulating, subjects were to be recalled and randomized to receive zanamivir 10 mg once daily by inhalation, or placebo, for 28 days, and were asked to record symptoms on diary cards. The primary efficacy population was to be unvaccinated subjects and the primary efficacy endpoint was to be development of symptomatic laboratory-confirmed (by culture or serology) influenza A or B. Because this is a single prophylaxis study, and a prophylaxis indication has not been requested at this time but may be the subject of a future efficacy supplement, efficacy results will not be discussed in detail in this review. Safety results were reviewed as supporting information for the treatment studies, particularly because this study involved administration of drug or placebo to subjects who did not have influenza-like illness at study entry and may be less prone to confounding by overlap between influenza symptoms and possible drug-related adverse events.

V-B2. NAIA3005 Efficacy Results (Summary of Applicant's Analysis)

A total of 1107 subjects were enrolled in 2 U.S. centers. These were predominantly healthy young adults in university communities. To summarize a few of the principal endpoints briefly, the applicant reported approximately 60% protection against laboratory-confirmed clinical influenza illness. Duration of febrile illness was also reported as shorter in the zanamivir group than in the placebo group. The primary efficacy endpoint was defined as symptomatic laboratory confirmed influenza A or B infection where symptomatic influenza required the presence of at least two from among the following: temperature at least 37.8 C, cough, headache, sore throat, myalgia, feverishness. These should be present for at least two consecutive diary card entries.

Table V-B2a. Selected outcomes in NAIA3005 (number and % developing symptomatic laboratory-confirmed influenza; all influenza confirmations were influenza A)

From CSR 7.1.1	Placebo	Zanamivir	p-value	Relative odds (95% CI)
Non-vaccinated, n	475	473		
Non-vaccinated, influenza	28 (6%)	11 (2%)	.009	0.38 (0.17, 0.80)
Per protocol, n	439	452		
Per protocol, influenza	26 (6%)	10 (2%)	.008	0.36 (0.15, 0.78)
ITT, n	554	553		
ITT, influenza	34 (6%)	11 (2%)	<.001	0.31 (0.14, 0.64)

V-B3. NAIA3005 Efficacy Results (FDA Comments)

Although incidence of disease was low and the number of cases small, if supported by additional review and by data from other studies and other populations, these results can be viewed as contributory supporting evidence for anti-influenza-virus activity of the zanamivir preparation. The Discussion (Section 10) notes that the study showed "60% protection from symptomatic, laboratory confirmed influenza A which was circulating in the community at the time of the outbreak. Based on the profile of the drug, an equivalent protective effect against influenza B is expected." However, no evidence is presented that any subjects were in fact exposed to, or protected from, influenza B.

V-B4. NAIA3005 Safety Results (Summary of Applicant's Analysis)

Adverse event reports were similar in the two treatment groups. Seven placebo subjects and four zanamivir subjects discontinued due to adverse events which included sore throat, throat irritation, cough, headache, and rash. Serious adverse events were reported in two placebo subjects (anxiety, pneumonia) and one zanamivir subject (severe gastroenteritis, severe dehydration, headache) and were all assessed by the applicant as having no relationship to study drug. Three pregnancies were reported (two zanamivir, one placebo): two subjects reportedly elected to terminate pregnancy and the third (zanamivir group) became pregnant after finishing the study and "Prenatal test did not indicate evidence of defect." The principal laboratory events reported were decreases below threshold in bicarbonate (6% placebo, 8% zanamivir) and lymphocytes (3% placebo, 2% zanamivir).

V-B5. NAIA3005 Safety Results (FDA Comments)

Adverse event monitoring elicited a large number of reports of minor symptoms, as might be expected when detailed symptom recording is carried out over a period of weeks. Many of the adverse events were attributed to intercurrent illness; it was not clear that the

incidence of intercurrent illness would be expected to differ in the on-treatment and post-treatment periods to the extent observed (see table below), but any interpretation would be complicated by the different durations of these periods (four weeks versus one week). It is not clear how a determination of no drug relationship could be made for events such as gastroenteritis in the absence of a specific etiologic diagnosis. "Drug related" events (i.e. assessed as at least possibly drug related) included the following: ENT events were reported for 2% of each group (throat and tonsil discomfort and pain, throat and tonsil signs and symptoms, nasal signs and symptoms, vocal cord disorders), GI events for 1% of each group, lower respiratory 1% of placebo and <1% of zanamivir subjects, neurology 1% of placebo and 2% of zanamivir subjects (headache 1% in each). Post-treatment abnormalities of enzyme and LFT levels were reported for about 1% of each group, serious adverse events during treatment 1 per arm and post-treatment 1 on placebo. Discontinuations by treatment group included 3 placebo and 2 zanamivir for throat and tonsil discomfort and pain, 3 and 1 for cough (in the placebo group, also 1 asthma and 1 breathing disorder), 1 and 2 for headaches, 1 and 1 for rash.

Table V-B5a. Selected adverse events during treatment in NAIA3005

Selected adverse events during treatment (>5% in any group, or particular interest; from CSR Table 39)	Placebo (n=554)	Zanamivir (n=553)
Any event	75%	75%
Nasal signs & symptoms	41%	39%
Throat/tonsil discomfort & pain	38%	35%
Feeding problems	17%	14%
Nausea & vomiting	4%	3%
Diarrhea	3%	2%
Cough	30%	24%
Asthma	<1%	0
Constriction/obstruction, airways	0	<1%
Viral respiratory infections	<1%	0
Musculoskeletal pain	15%	12%
Muscle pain	11%	11%
Headaches	50%	47%
Malaise & fatigue	29%	29%
Temperature regulation disturbances	19%	14%
Menstruation syndromes	5%	4%

Table V-B5b. Selected adverse events after treatment in NAIA3005

Same adverse events after treatment (from CSR Table 39)	Placebo (n=554)	Zanamivir (n=553)
Nasal signs & symptoms	4%	3%
Throat/tonsil discomfort & pain	4%	3%
Feeding problems	<1%	1%
Nausea & vomiting	1%	1%
Diarrhea	1%	1%
Cough	3%	3%
Asthma	<1%	0
Viral respiratory infections	<1%	0
Musculoskeletal pain	1%	1%
Muscle pain	1%	1%
Headaches	4%	3%
Malaise & fatigue	2%	1%
Temperature regulation disturbances	3%	2%
Menstruation syndromes	1%	<1%

Table V-B5c. Laboratory values in NAIA3005 from tables 45 and 46

Event (from tables 45-47)	Placebo (n=554)	Zanamivir (n=553)
Any post-baseline		
Alkaline phosphatase>ULN	2 (<1%)	5 (1%)
ALT>2ULN	3 (<1%)	7 (1%)
AST>2ULN	1 (<1%)	4 (<1%)
Bilirubin>1.5ULN	3 (<1%)	6 (1%)
Shift from baseline		
To elevated ALT	14 (3%)	14 (3%)
To ALT>2ULN	3 (<1%)	6 (1%)
To elevated AST	10 (2%)	20 (4%)
To AST>2ULN	1 (<1%)	4 (<1%)
To elevated bilirubin	11 (2%)	8 (1%)
To bilirubin>1.5ULN	2 (<1%)	5 (1%)
To elevated alk phos	2 (<1%)	5 (1%)
To elevated CPK	29 (5%)	24 (5%)
To elevated creatinine	1 (<1%)	3 (<1%)
To elevated urea	5 (1%)	1 (<1%)

Laboratory abnormalities were reported only in very small numbers of subjects and there were not clear clinically relevant relationships to study drug. Profiles of clinical adverse events showed no clear distinction between zanamivir and placebo groups.

CRFs were received for subjects discontinuing due to adverse events and for a random sampling of other subjects. These were reviewed for additional safety concerns. Adverse events noted in the CRFs were generally compatible with those noted in the CSRs of this and other studies in the NDA submission.

V-B6. Summary of Study NAIA3005

Preliminary results from this study suggest (subject to further review) some activity of zanamivir against influenza virus in the population studied but do not permit firm conclusions about benefit that can be generalized to other population subgroups. Again, there is the suggestion that some symptoms could be related to either drug or vehicle, and there is substantial overlap between reported adverse events and symptoms associated with influenza-like viral diseases and other intercurrent illnesses that might be circulating in the population during influenza season. No major safety concerns were identified in this population.

V-C. Clinical Study NAIA2010

Volume 119 of the NDA contains the report of this pilot nursing home prophylaxis study. Zanamivir (inhaled and intranasal, twice daily for at least 14 days) was compared against rimantadine in influenza A outbreaks and no treatment in influenza B outbreaks, with no blinding. Because of the unblinded study and low occurrence of outcomes (and because there has been no submission for a prophylaxis indication at this time), no efficacy discussion is presented in this review. At the time of NDA submission, this report provided the only available safety comparison between zanamivir and a marketed anti-influenza drug. CRFs were received for six subjects withdrawn due to adverse events. These included refusal of follow-up examinations due to grief over pre-existing lung cancer diagnosis (9567, zanamivir); achiness and restless sleep (9627, rimantadine); falling episode (9568, zanamivir; according to narrative, attributed partly to drug by subject but considered not reasonably related by investigator, retrospectively noting prior history of falling); vertigo/nervousness/tremulousness (9629, rimantadine); bronchitis (9767, zanamivir, with exacerbation of underlying emphysema according to narrative, considered not reasonably related by investigator); gastrointestinal symptoms (9771, zanamivir). From this information and from the summary information shown in the table below, overall risk of adverse events could not be clearly distinguished in the different treatment groups.

Table V-C1. Selected adverse events from NAIA2010 (During Rx AE reports from CSR Table 16, >5% in any group or of particular interest, excluding reports of only one patient as every event in no-treatment group is >5%)

Adverse Event	Rimantadine (n=23)	No Rx (n=17)	Zanamivir (n=98)
Any AE	8 (35%)	10 (59%)	38 (39%)
Any ENT AE	0	1 (6%)	21 (21%)
Throat/tonsil discomfort/pain	0	1 (6%)	3 (3%)
Nasal inflammation	0	0	6 (6%)
Nasal signs & symptoms	0	0	11 (11%)
Any GI AE	1 (4%)	1 (6%)	7 (7%)
GI signs & symptoms	1 (4%)	1 (6%)	3 (3%)
Nausea & vomiting	0	0	4 (4%)
Cough	2 (9%)	0	6 (6%)
Musculoskeletal pain	1 (4%)	3 (18%)	2 (2%)
Any neurology AE	4 (17%)	3 (18%)	11 (11%)
Sleep disorders	3 (13%)	0	1 (1%)
Gait disorders	0	1 (6%)	0
Headaches	1 (4%)	0	3 (3%)
Dizziness	0	0	3 (3%)
Malaise & fatigue	1 (4%)	2 (12%)	0
Chest symptoms	1 (4%)	1 (6%)	1 (1%)
Pruritus	0	2 (12%)	0

V-D. Safety Information from Phase 1 Studies

Because many of the early studies of this drug used other delivery methods, only a few Phase 1 studies were performed with the Diskhaler system and provided information more relevant to the regimen used in phase 3 studies and the proposed marketed regimen. No major safety concerns had arisen during preliminary stages of development; potentially relevant studies were re-reviewed during evaluation of the NDA.

Study C94-009, "A study to investigate the safety, tolerability and pharmacokinetics of single and multiple doses of GG167 dry powder administered by inhalation in man" (volume 47-48), had reports of cough, headache, sore throat, chest pressure; headache was reported with both active and placebo dosing, other events more on zanamivir. Some elevations of liver enzymes and CPK were noted: these were generally mild and transient and without clear relationship to treatment (for example, peak values on a pre-study blood draw). One subject reportedly had nonconducted P waves and another developed an eczematous rash: these subjects were withdrawn from the study and both were reported to have received only placebo dosing.

The NDA submission includes a study of pulmonary function (C94-085, "A study to evaluate the effect of repeat doses of GG167 dry powder on pulmonary function and bronchial hyper-responsiveness in asthmatic subjects," volumes 74-75) in 13 subjects with relatively mild asthma, 12 of whom received active drug and lactose placebo in a

crossover design. One subject was withdrawn with elevated liver function tests (AST, ALT, and GGT); this subject reportedly had received only placebo. Combined data from all subjects did not suggest clinically significant worsening of asthma although the geometric mean PC20 (concentration of methacholine required to produce 20% decrease in FEV1) and mean morning and evening peak expiratory flow rate were slightly lower during zanamivir treatment. One subject had reduction in FEV1 at 6-9 minutes after zanamivir dosing (by 38% and 32% on days 1 and 14 of the zanamivir treatment period) that was not replicated during the placebo treatment period. According to the protocol, these FEV1 values were supposed to be obtained around the morning dose of zanamivir or placebo while the methacholine challenge test was carried out following the afternoon dose on the same day.

Study NAIA1009, "Pharmacokinetics of zanamivir (GG167) following inhaled administration in pediatric subjects with signs and symptoms of respiratory illness," provides information from single-dose administration of zanamivir by Diskhaler to 16 children aged 5 to 12 years and by nebulizer to 8 younger children aged at least 3 months (CSR in volume 51 of NDA). Six adverse events were reported (Table 10); all were rated as mild and non-serious. One adverse event (headache in a 12-year-old) was assessed as possibly drug-related and the remainder were reported as not related. The other adverse events in the age group receiving Diskhaler administration were diarrhea (1) and chills/fever (2), reported as mild, unrelated, and resolved. In the age group receiving the nebulized preparation, adverse events of bradycardia (1) and rhinorrhea and decreased pulse oximetry reading (1) were reported as mild, unrelated, and (except for the rhinorrhea) resolved before discharge. A treatment study and a family transmission study using the Diskhaler in subjects 5 years and up are in progress; limited adverse event information from these studies was made available in an amendment to the NDA and is discussed in a later section of this review.

Study NAIB1009, "A study to evaluate the safety, tolerability and pharmacokinetics of zanamivir administered intravenously as repeated doses," provides a limited amount of safety information from administration of zanamivir 600 mg twice daily for 5 days to 12 healthy male volunteers (CSR in volume 42-43 of NDA). This was a randomized, double-blind, placebo-controlled, crossover study in which each subject received 5 days of active drug and 5 days of placebo with at least one week washout period between courses. In addition to clinical and laboratory monitoring, electrocardiograms and telemetric recording were utilized. Electrocardiographic findings recorded as not clinically significant, such as "delayed intraventricular conduction, no pathology" with normal QRS duration, were reported in some subjects during pre-study recordings, pre-dose recordings, and/or either drug or placebo study periods, without clear relationship to either the timing or the content of the study infusion (similar results were recorded in single-dose infusion study NAIB1008, from which two subjects were withdrawn because of intermittent PR prolongation and infrequent unifocal ventricular ectopic beats respectively, both reported on later investigation to be present with or without drug exposure and not considered clinically significant). No subjects withdrew before completing study NAIB1009. The most frequent clinical adverse events reported on

zanamivir included "hypnagogic effects" (7 events in 5 subjects on zanamivir, 1 event on placebo), headaches (6 events in 5 subjects on zanamivir, 11 events in 4 subjects on placebo), dizziness (6 events in 2 subjects on zanamivir, one on placebo) and musculoskeletal pain (3 events in 3 subjects on zanamivir, none on placebo); none was classified as serious, and adverse events considered drug-related were comparable in frequency between treatments (12 zanamivir, 14 placebo). Only one laboratory value was classified as "potentially clinically relevant": this was a potassium of 5.9 on pre-dose screening for the second treatment period. Transaminase and GGT elevations were not found; one subject had slightly elevated bilirubin (40-41 mcM with normal <37) at time zero for each treatment period.

CRFs were provided for subjects withdrawn from phase 1 and phase 2 trials due to adverse events. Review of these did not disclose additional safety concerns.

Comment: Adverse events reported in phase 1 studies did not differ markedly from those reported in phase 3 studies; clinical and laboratory abnormalities identified in healthy subjects in general could not be clearly related to treatment and most appeared to have little clinical significance according to the information submitted. Adverse events from the small number of pediatric subjects using the Diskhaler did not appear to show any concerns that would limit the treatment studies in progress; development of a nebulized preparation for younger children has not currently been proposed except for extremely limited compassionate use purposes, and would require further characterization if pursued. The repeated occurrence of decreased FEV1 in one asthmatic subject after zanamivir but not after placebo did not, as described, appear to be temporally related to the methacholine portion of the protocol; this subject's results were reviewed by and discussed with consultant staff from the Division of Pulmonary Drug Products, and were considered to warrant attention in labeling and future study design, as well as requests for any additional information available from use of zanamivir in patients with underlying respiratory disease (discussed further in a subsequent section of this review). The five-day intravenous treatment study showed little additional evidence of toxicity using much higher doses than used in treatment trials, administered systemically, but more information would be needed if development of high-dose intravenous treatment were proposed.

VI. Challenge Studies and Other Microbiologic Issues

VI-A. Challenge Studies

There were two challenge studies using influenza B, one with drug beginning before virus inoculation and one with drug beginning after virus inoculation, and several of each type using influenza A. Intranasal (or in NAIA1010, intravenous) rather than inhaled zanamivir was used (and inoculation of virus was also intranasal), and timing of treatment varied in different studies.

Influenza B Challenge Studies:

In influenza B challenge study NAIA1005 ("A study to investigate the effect of intranasal GG167 on infection in healthy volunteers experimentally inoculated with influenza B/Yamagata/16/88 virus," volume 67, performed in U.S.), 32 volunteers received intranasal zanamivir (3.2 mg or 6.4 mg) or placebo as a nasal spray twice daily beginning about 32 hours after inoculation and continuing for 7 doses. Infection rate (by culture or antibody rise) was reported as 70% in the placebo group and 73% and 82% in the two active drug groups. According to the protocol (section 6.2), 10 subjects completing in each group should have provided 80% power to detect a 1.3 log difference in "viral titers" with α=.05. Actual enrollment was 10 in the placebo group and 11 in each active treatment group. The Efficacy Results section headed "Viral Titers" (8.3) contains p values for 38 different comparisons (including number of subjects with "positive viral titers", mean number of days with positive titer days 0-8 and 2-8, peak titer in log10TCID50/ml, and AUC, for each active treatment group vs placebo, for all subjects, all infected subjects, and all subjects with positive titer), none of them with $p<.05$ and most with $p>.3$. Several numerical estimates of viral shedding were somewhat lower in the two active drug groups than in the placebo group: for example, for "infected subjects" days 2-8 AUC was 2.9 log10TCID50•day/ml for placebo and 0.7 and 0.6 for the two active drug groups; mean number of positive days was 1.4 vs 0.8 and 0.7; mean peak titer was 1.4 vs 0.7 and 0.6. Mean sum of symptom scores (infected subjects, days 2-8) was 12.0 for placebo, 16.5 and 17.4 for the active treatment groups, again with nonsignificant p values but with numerical estimates higher in the active treatment groups than in the placebo group. No subject had any temperature over 100°F.

In study NAIA1006 ("A study to investigate the effect of intranasal GG167 on prevention of infection in healthy volunteers experimentally inoculated with influenza B/Yamagata/16/88 virus," vol. 69, performed in U.S.), zanamivir was given in 3 different regimens (1 spray BID, 2 sprays BID, 2 sprays daily) beginning 4 hours before virus inoculation. CSR section 8.5 states "In this study, all subjects who shed virus also seroconverted. All subjects with evidence of seroconversion also shed virus." Study section 8.2 states "A total of 34 subjects were included in all efficacy analyses. Twenty-six subjects had laboratory evidence of infection (either shed virus or seroconverted) and were included in analyses of "Infected Subjects". Nineteen subjects shed virus and were included in analyses of "Subjects With Positive Viral Cultures"." No analysis of "Subjects With Positive Viral Cultures" was found although 19 subjects were included in tables showing "positive viral titers" which apparently was considered equivalent (and different from antibody titers, as tabulation of "Number of subjects with Positive Viral Titers or 4-fold increase in HI Titer" included 26 subjects). Infection rate (culture or seroconversion) was modestly reduced in all zanamivir groups (9/9 placebo, zanamivir 5/9, 7/8, 5/8, p values ranging from .082 to .471 for comparison of each treatment group with placebo), number who shed virus was decreased (3, 3, and 4 in active drug groups, each with p value below .05 for comparison with 9 of 9 placebo subjects). No subject was febrile. URI symptoms were noted in 9 of 9 placebo subjects and 6/9, 6/8, 8/8 in