III-C4. NAIB3001 Safety Results (Summary of Applicant's Analysis)

Adverse events were infrequent, and similar in placebo and zanamivir subjects. Seven serious adverse events were reported, three in zanamivir subjects and four (one considered possibly drug-related) in placebo subjects. Of "high-risk" placebo subjects, 56% reported adverse events compared with 38% of "high-risk" zanamivir subjects, mostly in the lower respiratory tract. Laboratory values were similar across treatment groups.

III-C5. NAIB3001 Safety Results (FDA Comments)

Adverse event reports for all randomized subjects during treatment (from CSR Table 79) included the following. Events in this table were selected because they were reported for at least 5% for one group or were considered to be of special interest.

Table III-C5a. Selected adverse events in NAIB3001

Adverse event	Placebo subjects (n=228)	Zanamivir subjects (n=227)
During treatment:		
Any adverse event	98 (43%)	83 (37%)
Any ENT event	17 (7%)	30 (13%)
Sinusitis	3 (1%)	10 (4%)
Ear signs & symptoms	2 (1%)	6 (3%)
Any GI event	20 (9%)	11 (5%)
Diarrhea	10 (4%)	2 (1%)
Abnormal LFTs	2 (1%)	0
Any lower respiratory	50 (22%)	29 (13%)
Bronchitis	17 (7%)	7 (3%)
Cough	13 (6%)	8 (4%)
Any neurology event	8 (4%)	9 (4%)
Headaches	2 (1%)	4 (2%)
Dizziness	1 (<1%)	3 (1%)
Urticaria	0	2 (1%) (drug related)

Post therapy events included ENT infections (2% zanamivir vs 1% placebo), throat and tonsil discomfort and pain (2% vs 1%), sinusitis (3 subjects or 1% vs 1 subject), nasal signs and symptoms (3 subjects vs 0). Among events identified as possibly drug related (Table 80) were ENT events, headache, and dizziness. For any ENT event during therapy frequency was 13% zanamivir vs 7% placebo, post therapy 8% vs 4%, drug related ENT events during therapy 4% zanamivir vs 2% placebo and post therapy 2% vs 0; any neurologic event considered drug-related during therapy 3% zanamivir vs 1% placebo. Adverse events in high risk subjects (Table 89) included asthma (8% zanamivir, 15% placebo), bronchitis (5% zanamivir, 10% placebo), ENT events (5% in each group).

Common laboratory abnormalities included those in the following table (data from CSR Table 85).

Table III-C5b. Laboratory abnormalities in NAIB3001

Laboratory abnormalities	NAIB3001 placebo n=228	NAIB3001 zanamivir n=227
ALT >normal		
Baseline	21%	23%
Post-Rx visit	35%	38%
Post-Rx visit >2xULN	6%	8%
CPK>normal		
Baseline	13%	6%
Post-Rx visit	13%	5%
Post-Rx visit >5xULN	<1%	0
Lymphocytes <normal		
Baseline	45%	48%
Post-Rx visit	<1%	0
Post-Rx visit <0.8xLLN	<1%	0
Neutrophils <normal		
Baseline	4%	4%
Post-Rx visit	23%	19%
Post-Rx visit <0.8xLLN	16%	10%

Laboratory values also included several reports of hyperkalemia attributed by investigators to delay in specimen processing, which were more frequent in zanamivir subjects (4% vs 2%). Bilirubin above the normal range was noted at baseline for 4% of each treatment group; at the post-treatment measurement for 4 (2%) of placebo and no zanamivir recipients (>1.5x ULN for one placebo recipient); and at any post-baseline visit for 9 (4%) of placebo and 3 (1%) of zanamivir recipients (>1.5x ULN in 3 placebo and 1 zanamivir recipient). GGT above the normal range was noted at baseline for 15% of placebo and 11% of zanamivir recipients; at the post-treatment measurement for 27% and 28% (>2x ULN for 7% on placebo and 5% on zanamivir); and at any visit post baseline for 39% on placebo and 36% on zanamivir (>2x ULN for 24 or 11% of placebo and 14 or 6% of zanamivir subjects). Shifts of ALT, AST, or GGT to high, CPK to high, and neutrophils to low occurred in both placebo and zanamivir recipients and were commonly attributed to the underlying viral syndrome; not all abnormalities were followed to resolution.

Listing 22 yielded several reports of diarrhea, dizziness, headache, taste disturbance, chest tightness or pleuritic pain, cough, nose or throat dryness or soreness, and asthma exacerbations considered to have at least possible causal relationships to study drug (either zanamivir or placebo). Two reports of hives, one of "boils" and one of exacerbation of herpes simplex, all in zanamivir recipients, were also considered to have

at least a possible causal relationship.

From listing 4 supplemented by information from listing 29, adverse events leading to discontinuation of study therapy occurred in placebo recipients (subjects 8363, 8680, 8337, 8368, 8686, 8280, 8281, 8626: itchy rash, collapse/hypotension/arm twitching [not considered causally related], vasovagal collapse [apparently venipuncture related from additional review], cough, headache, throat irritation, chest tightness, rash) and zanamivir recipients (8701, 8785, 8403, 8373, 8274, 8316: irritated throat and coughing fits, concern about lung damage, migraine, headache, chest tightness, sore throat). Subject 8492 (placebo) had withdrawal of consent listed as the reason for discontinuing medication, but the investigator's comments in listing 29 indicate that she stopped because of symptoms which the investigator attributed to muscle strain from coughing.

Listing 29 also contains investigators' comments about completeness of study medication administration. These comments may refer to missed doses, deliberate stopping of medication, or incomplete delivery due to problems with the device. There are 9 comments which appear to refer specifically to incompletely punctured medication blisters suggesting that the subject tried to take a dose but did not get the device to operate as intended.

CRFs were submitted for 10 subjects withdrawn from the study due to adverse events. No salient alterations to information already reviewed were identified; the subject discontinued because of hypotension and arm twitching was noted to have presented to his local physician for follow-up and was believed to have influenza-related dehydration as the precipitating factor for his adverse event. Seven CRFs were received as a random sampling of high-risk subjects. These contain a "high risk assessment" page which could not be located in the withdrawal CRFs, and which has checkboxes for respiratory disease, cardiovascular disease, renal failure, and age 65 or over plus a hand-written "other (please specify)" line. Of the high-risk subject CRFs, the CRF for subject 8298 in fact has a check in the "no" box for high-risk classification but the subject is elsewhere recorded as having asthma and having been on medication for asthma (not clear whether "regular"), and an exacerbation of asthma appears to have been entered as a complication, crossed out, and entered as an adverse event. The CRF for subject 8300 has the box for "chronic respiratory disease requiring regular medication" checked and crossed out, and "mild asthma" entered on the "other" line. The CRF for subject 8420 notes an apparent vaso-vagal episode with onset about 10 minutes after the first dose of study medication, with recovery over a further 10 minutes; this was cross-checked against listing 22 (adverse events) and found in the placebo group as an event of moderate severity that was considered potentially related to study drug but did not lead to stopping treatment or to study withdrawal. The CRF for subject 8559 has "yes" for high-risk classification checked and crossed out, and "asthma" entered and crossed out on the "other" line with a note that is difficult to read but appears to state "no medication until pt has flu!" The CRFs submitted as a random sample of all subjects contained a "High Risk Assessment" page with the same checkboxes described above (with the "no" box duly checked). In this sampling of CRFs, a note of "recurrence of flu symptoms" on day 14 was found for

subject 8721: this was checked against listing 22 (adverse events) and found in the placebo group as an adverse event rated "severe" and lasting 5 days (no additional details were located).

III-C6. Summary of Study NAIB3001

This study showed a treatment effect which was modest, and less consistent than the results of NAIB3002, but appeared reasonably stable to use of various supporting methods for secondary analyses including different endpoint definitions and subgroup analyses. This study showed some gender imbalance both in treatment assignment and in treatment effect, which will be discussed further in the following section. Like the other phase 3 treatment studies, recruitment of high risk subjects appears to have fallen short of the number intended. In addition, the CRF review suggests some potential for confusion in the definition of "high risk" subjects for this study, in terms of the general categories used and the interpretation of the categories for individual subjects, and results for the "high risk" subgroup may require some caution in interpretation. In particular, it appeared that some patients with relatively mild asthma (possibly less severe than the criteria for chronic respiratory disease used to define high-risk patients in the other phase 3 studies) may have been included in the "high risk" analyses. Adverse event reports suggested some excess of events such as ENT symptoms in the zanamivir group, but no major safety concerns were identified.

III-D. Comments on Three Principal Phase 3 Studies Considered Together

Principal Efficacy Analyses and Secondary Endpoints

Looking at efficacy results from the three principal phase 3 studies together showed some discrepancies between the North American study and the other two studies in major results of the applicant's analyses. Some of these are summarized in the following tables, with numbers abstracted from the preceding sections of the review except where otherwise indicated.

Table III-D1. Difference between placebo and zanamivir, primary endpoint, primary and selected secondary populations

	NAIB3001 (Southern Hemisphere)	NAIB3002 (Europe)	NAIA3002 (North America)
Median days to alleviation (flu +)			
Placebo	6.0 days	7.5 days	6.0 days
Zanamivir	4.5 days	5.0 days	5.0 days
Difference	1.5 days	2 days	1.0 days
Number of subjects	321	277	569
p-value	.004	<.001	.078
Median days to alleviation (all randomized subjects)			
Placebo	6.5 days	7.5 days	6.0 days
Zanamivir	5.0 days	5.0 days	5.5 days
Difference	1.5 days	2.5 days	0.5 days
Number of subjects	455	356	777
p-value	.011	<.001	.228
Median days to alleviation (high-risk)			
Placebo	8.0 days	11.5 days	6.5 days
Zanamivir	5.5 days	9.0 days	7.5 days
Difference	2.5 days	2.5	-1.0 days
Number of subjects	76	32	109
p-value	.048	.178	.710
Median days to alleviation (high-risk, flu +)			
Placebo	8.3 days	11.5 days	6.0 days
Zanamivir	5.0 days	9.25 days	6.25 days
Difference	3.3 days	2.25 days	-0.25 days
p-value	.161	.21	.886
Median days to alleviation (flu negative)			
Placebo	7.0 days	7.0 days	5.0 days
Zanamivir	6.75 days	5.25 days	6.0 days
Difference	0.25 days	1.75 days	-1.0 days
p-value (from 5/10/99 amendment discussed below)	.486	.551	.712

Despite larger numbers enrolled, NAIA3002 appeared to have less favorable point estimates and larger p values for each of these groups. Because of concerns that some subjective components of endpoint definition (for example, dependence on a transition from "moderate" to "mild" in symptom scoring) could obscure the interpretation of results, additional endpoints in the original submission were examined (Table III-D2 below). Endpoints with "no relief meds" are times to alleviation calculated as for the

primary endpoint except that the subject must not have recorded use of the standard relief medications (acetaminophen and cough suppressant) supplied in the study at the time alleviation criteria were met and in the succeeding 24 hours. A similar pattern across studies was observed.

Table III-D2. Difference between placebo (P) and zanamivir (Z), selected secondary endpoints

	NAIB3001 (Southern Hemisphere; n=455, Flu + 321, high-risk 76)	NAIB3002 (Europe; n=356, flu + 277, high-risk 32)	NAIA3002 (North America; n=777, flu + 569, high-risk 109)
Median days to alleviation, no relief meds (flu +)	P 8.5 days, Z 6.5 days, difference 2.0 days, p=.033	P 8.5 days, Z 5.5 days, difference 3.0 days, p<.001	P 8.0 days, Z 7.25 days, difference 0.75 days, p=.075
Median days to return to normal activities (flu +)	P 9.0 days, Z 7.0 days, difference 2.0 days, p<.001	P 8.5 days, Z 7.0 days, difference 1.5 days, p=.025	P 7.5 days, Z 7.5 days, difference 0 days, p=.378
Median days to alleviation, no relief meds (high-risk)	P >12.5 days, Z 6.5 days, difference >6.5 days, p=.028	P 11.5 days, Z 9.0 days, difference 2.5 days, p=.076	P 10.25 days, Z 11.0 days, difference –0.75 days, p=.830

Effects on individual symptoms also were not uniform across studies, as shown in the following table. In particular, the near-exclusive contribution of cough to these treatment differences in NAIA3002 was not replicated in the other studies.

Table III-D3. Treatment differences in time to improvement of individual symptoms

Median days to alleviation (i.e. to score of mild or less) of individual symptoms (flu +)	NAIB3001 (CSR Tables 50-57)	NAIB3002 (CSR Tables 48-55)	NAIA3002 (CSR Tables 48-55)
Headache	P 1.5, Z 1.0, p=.139	P 2.0, Z 1.5, p=.079	P 1.5, Z 1.5, p=.947
Sore throat	P 1.0, Z 1.0, p=.898	P 1.5, Z 1.0, p=.467	P 2.0, Z 1.5, p=.641
Feverishness	P 2.0, Z 1.5, p=.011	P 2.5, Z 1.5, p<.001	P 2.0, Z 1.5, p=.227
Myalgia (muscle/joint aches and pains in 3002)	P 2.0, Z 1.5, p=.025	P 2.0, Z 1.5, p=.004	P 2.0, Z 2.0, p=.646
Cough	P 3.8, Z 3.0, p=.271	P 4.0, Z 3.0, p=.010	P 4.5, Z 3.0, p<.001
Nasal congestion (nasal symptoms in 3002)	P 3.0, Z 3.0, p=.630	P 3.5, Z 3.0, p=.571	P 3.5, Z 3.5, p=.871
Weakness	P 3.0, Z 3.0, p=.019	P 3.5, Z 2.5, p=.003	P 2.5, Z 2.5, p=.473
Loss of appetite	P 2.0, Z 1.5, p=.066	P 2.5, Z 2.0, p=.067	P 2.0, Z 1.5, p=.312

The subgroup analyses for NAIB3001 suggested a gender difference in treatment effect (greater for female than male subjects). Re-examination of these analyses for the other studies showed that point estimates of treatment effect were slightly larger for male than female subjects in NAIA3002 and identical for female and male subjects in NAIB3002; thus, there was no systematic evidence of a reproducible gender difference across studies, and gender differences did not appear likely to account for the differing study results.

Table III-D4. Treatment effect by gender in principal phase 3 studies

Median days to alleviation (flu +)	NAIB3001 (ST 18; Female 148 or 46%; Male 173 or 54%)	NAIB3002 (ST 16; Female 147 or 53%; Male 130 or 47%)	NAIA3002 (ST 16; Female 279 or 49%; Male 290 or 51%)
Female, placebo	7.5	8.5	6.5
Female, zanamivir	4	6	5.5
Male, placebo	5	6.5	5.75
Male, zanamivir	5	4	4.5
Difference between placebo and zanamivir	Female 3.5 days, Male 0 days, All subjects 1.5 days	Female 2.5 days, Male 2.5 days, All subjects 2.5 days	Female 1.0 days, Male 1.25 days, All subjects 1.0 days

Additional FDA analyses (the following are from the analyses by FDA statistical reviewer as presented in the briefing document for the Advisory Committee meeting; all analyses made available by either FDA or applicant personnel were taken into consideration) were carried out to confirm and explore results noted in the NDA submission and to address the questions regarding the results in the different studies. The subject's overall assessment of symptoms as severe at entry was predictive of a longer time to alleviation than in those with moderate symptoms, but the proportion self-classified as severe, moderate, or mild at entry did not differ between studies and there was not a consistent effect on treatment response. Higher temperature at entry was suggested as associated with greater treatment effect in each study, but there were not study-related differences in entry temperature that would explain the study-related differences in treatment effect. Several alternative descriptors of symptom intensity and time course were examined, including the overall symptom rating (subjects indicated whether their overall symptoms were severe, moderate, mild, or absent at the given time point), a summary score constructed by adding the scores for each of the principal symptoms, and a summation of the total days with any febrile temperature recorded. For each of these, the difference between zanamivir and placebo was greatest in NAIB3002 and much less in NAIA3002, with NAIB3001 intermediate between the other two. Thus, these analyses did not change the initial impression with regard to different treatment effects between the principal Phase 3 treatment studies. Duration of symptoms at entry into NAIA3002 did not appear to have a major effect on the estimate of treatment effect, although the applicant presented analyses suggesting that subjects entered after 36 hours might have a smaller effect than those entered earlier (additional analyses of symptom duration at entry will be discussed in a subsequent section). Gender, age, race, vaccination status, influenza strain, and smoking status did not show any consistent relationships with treatment effect that appeared likely to explain the differences between studies. Use of relief medications (acetaminophen and cough syrup) was highest in NAIA3002, lowest in NAIB3002, and intermediate in NAIB3001: this difference suggested that medications used to treat acute symptoms might have some role in obscuring treatment effect, but no firm conclusions about the magnitude or importance of this effect can be drawn. There was anecdotal information that Southern Hemisphere subjects might have greater pre-existing familiarity with the delivery device, but no data on this issue that could be directly applied to interpretation of results from the specific

subjects in these studies. Overall, the differences between studies were not conclusively explained, although some possible avenues for further exploration could be identified.

Investigator's global assessment

The investigator's global assessment of symptoms at the post-treatment visit was also compared across studies, and results are shown in Table III-D5 below. This was prospectively considered to be a secondary analysis of importance because it provided a different perspective for assessment from the subjective symptoms recorded on diary cards. Although each study showed some shift toward milder scores in the zanamivir group, the majority of subjects in both groups were categorized as "mild". Differences appeared to reflect only a small percentage of subjects shifted from the "moderate or severe" to "mild" or "mild" to "no symptoms" categories. The largest effect was again in NAIB3002 where 23% of placebo subjects but only 9% of zanamivir subjects were considered to have moderate or severe symptoms in the post-treatment assessment.

Table III-D5. Investigator's global assessment in principal phase 3 studies

	NAIB3001 (Southern Hemisphere)	NAIB3002 (Europe)	NAIA3002 (North America)
Post-treatment investigator global assessment (influenza positive, placebo)	13% no symptoms, 70% mild, 15% moderate, 2% severe	25% no symptoms, 52% mild, 21% moderate, 2% severe	12% no symptoms, 73% mild, 14% moderate, <1% severe
Post-treatment investigator global assessment (influenza positive, zanamivir)	18% no symptoms, 71% mild, 11% moderate	32% no symptoms, 59% mild, 7% moderate, 2% severe	19% no symptoms, 71% mild, 11% moderate, <1% severe
P value for comparison of treatment groups	.054	.020	.029

Analyses accounting for symptom recurrence/recrudescence

Because some subjects who satisfied the protocol-specified definition of alleviation (sustained for 24 hours) had subsequent return of at least one symptom or temperature recording above the level meeting the alleviation definition, analyses reflecting more durable or profound symptom diminution were requested.

Additional analyses received from the applicant in the submission of January 18, 1999, included the following.

Table III-D6. Difference between placebo (P) and zanamivir (Z), additional symptom measurements

	NAIB3001 (Southern Hemisphere; n=455, Flu + 321, high-risk 76)	NAIB3002 (Europe; n=356, flu + 277, high-risk 32)	NAIA3002 (North America; n=777, flu + 569, high-risk 109)
Median days to alleviation (flu+), no subsequent return of any symptom above level satisfying alleviation definition	P 9.0 days, Z 7.0 days, difference 2.0 days (p=.078)	P 9.0 days, Z 6.75 days, difference 2.25 days (p=.006)	P 8.0 days, Z 8.0 days, difference 0 days (p=.931)
Median days to alleviation	P 7.5 days, Z 5.5 days,	P 8.5 days, Z 5.5 days,	P 6.5 days, Z 6.0 days,

(flu+), no subsequent return of any symptom above level satisfying alleviation definition for more than one diary card entry	difference 2.0 days (p=.008)	difference 3.0 days (p<.001)	difference 0.5 day (p=.291)
Median days to eradication of symptoms, flu+ (major symptoms recorded as none, t<37.8)	Both treatment groups >12.5 days, p=.013	P >26.5 days, Z 12.0 days (p=.063)	P 18.5 days, Z 12.5 days (p=.141)
Median number of days with any symptom score moderate or severe, flu+	P 7 days, Z 6 days (p=.053)	P 8 days, Z 6 days (p<.001)	P 6 days, Z 6 days (p=.064)

Intent-to-treat and non-high-risk analyses

In general, despite somewhat smaller treatment effects on some measures, analyses of all randomized subjects did not suggest dramatically different conclusions from those using influenza positive subjects, consistent with the fact that in these studies the clinical criteria for entry (plus rapid screening tests used in some instances) were reasonably predictive of influenza (321/455 or 70% with at least one diagnostic test positive for influenza in Southern Hemisphere study NAIB3001, 277/356 or 78% in European study NAIB3002, 569/777 or 73% in North American study NAIA3002). Some of these results, identified as all randomized subjects or intent-to-treat (ITT) analyses, are summarized in the discussions of individual studies. Selected additional intent-to-treat analyses from the submission of January 18, 1999, are summarized in the following table.

Table III-D7. Difference between placebo (P) and zanamivir (Z), additional symptom measurements

	NAIB3001 (Southern Hemisphere; n=455, Flu + 321, high-risk 76)	NAIB3002 (Europe; n=356, flu + 277, high-risk 32)	NAIA3002 (North America; n=777, flu + 569, high-risk 109)
Median days to alleviation (ITT), no subsequent return of any symptom above level satisfying alleviation definition	P 9.5 days, Z 8.0 days, difference 1.5 days (p=.098)	P 9.5 days, Z 6.75 days, difference 2.75 days (p=.003)	P 8.0 days, Z 8.5 days, difference –0.5 days (p=.546)
Median days to alleviation (ITT), no subsequent return of any symptom above level satisfying alleviation definition for more than one diary card entry	P 8.25 days, Z 6.5 days, difference 1.75 days (p=.020)	P 8.5 days, Z 5.5 days, difference 3.0 days (p<.001)	P 6.5 days, Z 6.5 days, difference 0 day (p=.565)
Median days to eradication of symptoms, ITT (major symptoms recorded as none, t<37.8)	Both treatment groups >12.5 days, p=.046	P >26.5 days, Z 11.5 days (p=.017)	P 14.0 days, Z 12.25 days (p=.423)
Median number of days with any symptom score moderate or severe, ITT	P 7 days, Z 6 days (p=.092)	P 7 days, Z 6 days (p<.001)	P 6 days, Z 6 days (p=.482)

Because North American study NAIA3002 had the largest number of subjects classified as high-risk (though high-risk recruitment fell short of the pre-defined objective in all

three studies), and to determine whether recruitment of high-risk subjects affected the overall analyses, an analysis of influenza positive non-high-risk subjects in that study was also requested, and received in the submission of January 18, 1999.. The difference between medians for the primary endpoint was 1.0 day (6 days on placebo, 5 days on zanamivir), p=.068; for time to alleviation without ongoing relief medications, the difference was 1.0 (7.5 days on placebo and 6.5 days on zanamivir), p=.139.

Adverse event profiles

Overall, the adverse event profiles of zanamivir and placebo have been very similar in the principal Phase 3 treatment studies. A few subjects have reported cough, chest tightness, sore throat, headache, dizziness, nasal symptoms, or gastrointestinal symptoms that were considered possibly related to study drug administration. In general, there were not striking differences between such reports with zanamivir and with placebo. Because the placebo consisted of inhaled lactose which was also received by active drug recipients, the possibility of association with the proposed product cannot be ruled out, but few subjects reported severe symptoms or discontinued drug due to these events. In addition to inhalation effects, the possible effect of the lactose vehicle in the setting of lactose maldigestion was discussed both during protocol development and during review; the applicant's proposal that the amount of lactose in the standard dose is not large enough to be a salient concern was supported by literature review (e.g. J Am Diet Assoc 1996;96:243-246), by discussions with internal consultants regarding Chemistry concerns for other drugs using lactose as an excipient, and by labeling of previously approved lactose-based inhalation drugs. Both for clinical adverse events and for laboratory abnormalities (discussed further below), there is substantial overlap between reported events and abnormalities that may occur during acute viral illness; this overlap may also contribute to the difficulty of making causal assessments. The possibility of severe adverse events of low frequency cannot be evaluated from the current size of the safety database, and little information is available regarding safety in individuals with severe or acutely unstable illness, so continued surveillance is warranted with any wider use of the drug.

Concerns about the possibility of adverse events in patients with underlying chronic respiratory disease arose from phase 1 study results and from efficacy results in the high-risk subgroups rather than from reported adverse events per se in the principal phase 3 studies. Additional information was requested to clarify some issues in this special population and will be discussed further in later sections of this review.

Complications

Differences between treatment groups in the percentages of subjects categorized as experiencing complications were small (favoring zanamivir) in the overall influenza positive populations of all three studies. For the high-risk population, NAIA3002 recorded more complications in the zanamivir group than the placebo group, while the other two studies continued to show more complications on placebo than zanamivir.

Table III-D8. Difference between placebo (P) and zanamivir (Z), % with complications or antibiotics noted

	NAIB3001 (Southern Hemisphere; n=455, Flu + 321, high-risk 76)	NAIB3002 (Europe; n=356, flu + 277, high-risk 32)	NAIA3002 (North America; n=777, flu + 569, high-risk 109)
Percent with complications or receiving antibiotics for complications (flu +)	Complications 30% P, 24% Z, p=.243; Antibiotics 28% P, 26% Z, p=.580	Complications 33% P, 24% Z, p=.125; Antibiotics 17% P, 11% Z, p=.207	Complications 22% P, 15% Z, p=.049; Antibiotics 15% P, 11% Z, p=.164
Percent with complications or receiving antibiotics for complications (high-risk)	Complications 46% P, 14% Z, p=.004; Antibiotics 41% P, 16% Z, p=.025	Complications 58% P, 31% Z, p=.250; Antibiotics 26% P, 0% Z, p=.115	Complications 28% P, 35% Z, p=.612; Antibiotics 15% P, 27% Z, p=.211
Percent with complications or receiving antibiotics for complications (high-risk, flu +)	[not found in study summary]	Complications 61% P, 33% Z, p=.264; Antibiotics 28% P, 0% Z, p=.120	Complications 21% P, 33% Z, p=.324; Antibiotics 12% P, 25% Z, p=.210

Evaluation of complications across studies was slightly complicated by the fact that check-boxes for complications were not uniform on the case report forms (details here are from the day 6 post-treatment visit forms in the sample CRFs). All three studies had check boxes for Pulmonary complications including pneumonia, exacerbation of COPD, bronchitis, respiratory failure, and other; ENT infections including sinusitis, otitis, pharyngitis, and other; and Cardiovascular including CHF, angina, MI, arrhythmia, and other. The two 3002 studies also included exacerbation of asthma as a check box under Pulmonary (in NAIB3001, this would have to be free-text entered spontaneously by the investigator, most likely under Other Pulmonary) and a section for Other Complications separate from the organ-system sections, while NAIB3001 included an Endocrine section listing diabetic ketoacidosis and other. NAIB3001 had a question "Did the patient require any antibiotics?" as a yes/no checkbox at the bottom of the complications page; also on this form, the section for ENT infections was headed only "infections" and the tables in the CSR included a category of "chest infections" which was not a checkbox (it was not clear how or whether this category overlapped with pneumonia or bronchitis).

Some complications of influenza (such as pneumonia or respiratory failure) would usually be regarded as more serious than others (such as sinusitis or pharyngitis). Therefore, it appeared reasonable to examine occurrence of individual types of complication in addition to the aggregate analyses.

Table III-D9. Occurrence of specified complications

Complication	NAIB3001 placebo	NAIB3001 zanamivir	NAIB3002 placebo	NAIB3002 zanamivir	NAIA3002 placebo	NAIA3002 zanamivir
ALL FLU+	CSR Table 73 (n=160)	CSR Table 73 (n=161)	CSR Table 69 (n=141)	CSR Table 69 (n=136)	CSR Table 69 (n=257)	CSR Table 69 (n=312)
Pneumonia	4 (3%)	2 (1%)	5 (4%)	0	4 (2%)	4 (1%)
COPD exacerbation	1 (<1%)	0	0	0	1	0
Asthma exacerbation	Not a checkbox & not tabulated	Not a checkbox & not tabulated	3 (2%)	0	2 (<1%)	5 (2%)
Bronchitis	19 (12%)	6 (4%)	9 (6%)	11 (8%)	15 (6%)	15 (5%)
Respiratory failure	0	0	0	0	0	0
Other pulmonary	8 (5%)	5 (3%)	3 (2%)	2 (1%)	3 (1%)	5 (2%)
Any cardio-vascular	1	0	1	1	0	1
Sinusitis	2 (1%)	9 (6%)	11 (8%)	6 (4%)	17 (7%)	14 (4%)
Otitis	7 (4%)	5 (3%)	2 (1%)	1	6 (2%)	9 (3%)
Pharyngitis	4 (3%)	2 (1%)	5 (4%)	3 (2%)	4 (2%)	4 (1%)
Chest infection (not a checkbox for any study)	7 (4%)	8 (5%)	Not a checkbox & not tabulated	Not a checkbox & not tabulated	Not a checkbox & not tabulated	Not a checkbox & not tabulated
Other infection	4 (3%)	5 (3%)	Not a checkbox & not tabulated	Not a checkbox & not tabulated	Not a checkbox & not tabulated	Not a checkbox & not tabulated
Other ENT infection	Not a checkbox & not tabulated	Not a checkbox & not tabulated	5 (4%)	3 (2%)	5 (2%)	6 (2%)
DKA	0	0	Not a checkbox & not tabulated	Not a checkbox & not tabulated	Not a checkbox & not tabulated	Not a checkbox & not tabulated
Other endocrine	0	1	Not a checkbox & not tabulated	Not a checkbox & not tabulated	Not a checkbox & not tabulated	Not a checkbox & not tabulated
Other complications	Not a checkbox & not tabulated	Not a checkbox & not tabulated	16 (11%)	13 (10%)	13 (5%)	2 (<1%)

NAIB3001 did not include a separate tabulation for influenza positive, high-risk subjects; therefore, in the following table, listings are high-risk influenza-positive for NAIA3002 and NAIB3002, and all high-risk for NAIB3001.

Table III-D10. Specified complications in high-risk subjects (NAIB3001) or in high-risk influenza-positive subjects (NAIA3002 and NAIB3002)

Complication	NAIB3001 placebo	NAIB3001 zanamivir	NAIB3002 placebo	NAIB3002 zanamivir	NAIA3002 placebo	NAIA3002 zanamivir
High-risk flu+ for 3002, all high-risk for 3001	CSR Table 78 (n=39)	CSR Table 78 (n=37)	CSR Table 78 (n=18)	CSR Table 78 (n=12)	CSR Table 78 (n=43)	CSR Table 78 (n=36)
Pneumonia	2	1	1	0	2	1
COPD exacerbation	1	0	0	0	1	0
Asthma exacerbation	Not a checkbox & not tabulated	Not a checkbox & not tabulated	3	0	1	5
Bronchitis	4	2	3	2	1	4
Respiratory failure	0	0	0	0	0	0
Other pulmonary	4	0	2	0	0	2
Any cardio-vascular	1	0	1	0	0	0
Sinusitis	1	1	1	0	2	2
Otitis	1	0	0	1	0	2
Pharyngitis	0	1	0	0	0	1
Chest infection (not a checkbox for any study)	5	0	Not a checkbox & not tabulated	Not a checkbox & not tabulated	Not a checkbox & not tabulated	Not a checkbox & not tabulated
Other infection	4	0	Not a checkbox & not tabulated	Not a checkbox & not tabulated	Not a checkbox & not tabulated	Not a checkbox & not tabulated
Other ENT infection	Not a checkbox & not tabulated	Not a checkbox & not tabulated	1	0	0	1
DKA			Not a checkbox & not tabulated	Not a checkbox & not tabulated	Not a checkbox & not tabulated	Not a checkbox & not tabulated
Other endocrine			Not a checkbox & not tabulated	Not a checkbox & not tabulated	Not a checkbox & not tabulated	Not a checkbox & not tabulated
Other complications	Not a checkbox & not tabulated	Not a checkbox & not tabulated	5	1	3	1

For some of the respiratory diagnoses (particularly exacerbation of asthma), there was again a suggestion of some differences across studies, as also suggested by the overall results from efficacy analyses and aggregate occurrence of complications. However, numbers were small for any individual complication type and no firm conclusions could be derived with regard to either increases or decreases in specific complications associated with treatment assignment.

Center Effects

In NAIA3002 it did not appear that a few centers drove the outcome (ST23); the number of centers was large and the number of subjects per center relatively small, with little potential for one center to contribute disproportionately to the outcome. In NAIB3001, there was a smaller number of centers and several centers each enrolled relatively large proportions of the study population; in particular, one center appeared to have the potential for making a somewhat dominating contribution to the overall study outcome (ST25) and was inspected. In NAIB3002 (ST23), of 29 centers with at least one subject randomized to each treatment group, the influenza positive population showed at least one day treatment effect (considered as median time to the primary alleviation endpoint in the placebo group minus the median time to the primary alleviation endpoint in the zanamivir group) in 20; of 6 centers randomizing at least 10 subjects, treatment effects were 2.0, -1.0, -2.25, 10.25, >12.0, 6.25. Overall, it appeared unlikely that events at individual centers would affect the total study results unduly, but there was substantial variability in point estimates of effect among centers, suggesting some instability of estimates derived from small numbers of subjects (as was also true in other studies where point estimates were derived for small subgroups, such as the by-country analyses of a large phase 2 study described in a later section of this review).

Separate High-Risk Groups

In addition to the possibly disparate components of the "complication" definition, the definitions of "high-risk" differed in the different studies and all of the "high-risk" definitions encompassed subjects with different risk factors which cannot be assumed to have a uniform effect on the course of influenza or its response to treatment. Furthermore, review of case report forms suggested the possibility that high-risk definitions might in some instances be applied differently by different investigators, so that uniformity in the average severity of underlying disease of these subgroups in different studies could not be assumed with confidence. The following table summarizes the applicant's analyses of time to the primary protocol-defined endpoint for the component groups of the "high-risk" category in each of the principal phase 3 studies. There may be some overlap in composition of high-risk subgroups because it was possible for a subject to have more than one high-risk diagnosis or attribute. In part because of concerns about differences between studies and between components of the high-risk subgroups, additional analyses, including analyses by available descriptors of underlying respiratory disease, were requested from the applicant and will be presented and discussed below.

Table III-D11. Treatment effect in specified high-risk subgroups

Treatment effect (placebo (P) – zanamivir (Z), difference in median days to alleviation, flu+)	NAIB3001 (Southern Hemisphere) (CSR ST 27)	NAIB3002 (Europe) (CSR ST25)	NAIA3002 (North America) (CSR ST25)
High-risk category			
Respiratory	P 7 days, Z 5.5 days, difference 1.5 days (n=41)	P 10.75 days, Z 6.5 days, difference 4.25 days (n=17)	P 5.5 days, Z 8.75 days, difference -3.25 days (n=36)
Cardiovascular	P 8.5 days, Z 1.5 days, difference 7.0 days (n=3)	P 16.5 days, Z 21 days, difference -4.5 days (n=6)	P 7 days, Z 7.5 days, difference -0.5 days (n=19)
Elderly	P 13 days, Z 2.75 days, difference 10.25 days (n=9)	P >26.5 days, Z 11 days, difference >15.5 days (n=12)	P 7.25 days, Z 4.5 days, difference 2.75 days (n=37)
Endocrine/metabolic	P 13 days, Z 4 days, difference 9 days (n=6)		
Immune compromise	P 4.5 days, Z 3 days, difference 1.5 days (n=2)		

While the small numbers preclude any clear conclusions, there was a positive point estimate for treatment effect in elderly subjects in each of these studies, while the respiratory subgroup had a negative point estimate in NAIA3002 and the very small cardiovascular subgroup had a negative point estimate in two of the three studies. Based on these analyses, it appeared important to consider specific "high-risk" diagnoses, as well as different study enrollments, in evaluation of overall efficacy results.

Because patients with underlying reactive airways disease may be at risk for acute worsening of the underlying disease in the setting of an acute respiratory tract infection such as influenza, and because there is theoretical potential for additional exacerbation of airway hyperreactivity by an inhaled medication (a concern also raised by single subject results in a phase 1 study discussed in a later section of this review) and also for altered distribution (and therefore possibly altered efficacy) of an inhaled drug in the setting of acute bronchospasm, additional efforts were made to maximize the amount of information that could be derived from these studies regarding safety and efficacy in the setting of underlying respiratory disease. Enrollment of such patients in the principal Phase 3 treatment trials appears to have been at the investigator's discretion in that recruitment of "high-risk" patients was to be encouraged but subjects judged likely to need hospitalization were to be excluded, and it is difficult in practice to ascertain the actual spectrum of severity of subjects entered with underlying respiratory disease. In response to a request for clarification on this subject, the applicant provided an analysis comparing subjects receiving one drug for asthma versus subjects receiving more than one asthma drug, which indicated that the "more severe" subjects by this criterion had a smaller (or absent) treatment effect. There were too few non-asthma patients classified as high-risk respiratory to permit any firm conclusions about this subgroup. The following results (from the submission of January 22, 1999) were presented only as an aggregate

analysis of patients classified as "high-risk respiratory" in all three principal treatment studies.

Table III-D12. Time to alleviation for subcategories of subjects with respiratory disease

Median days to alleviation, influenza positive "high-risk respiratory" subjects from principal Phase 3 treatment studies	Placebo	Zanamivir
All (n=94)	6	6.5
Non-asthma (n=7)	>12.5	>12.5
"Mild/Moderate" (Single asthma medication, n=37)	8	7.25
"Severe" (More than one asthma medication, n=50)	5	5.5
Median days to alleviation, all randomized "high-risk respiratory" subjects from principal Phase 3 treatment studies		
All (n=132)	7	6.25
Non-asthma (n=11)	8.75	11.5
"Mild/Moderate" (Single asthma medication, n=56)	8	6
"Severe" (More than one asthma medication, n=65)	6	5.75

Lower respiratory adverse events

To further pursue questions arising about possible effects on respiratory disease in data in the original NDA submission for the principal phase 3 treatment studies, adverse events in the lower respiratory tract were also tabulated.

Table III-D13. Lower respiratory adverse events during treatment

AE during Rx (all subjects, CSR Table 79 for each study)	NAIB3001 placebo n=228	NAIB3001 zanamivir n=227	NAIB3002 placebo n=182	NAIB3002 zanamivir n=174	NAIA3002 placebo n=365	NAIA3002 zanamivir n=412
Any lower respiratory	50 (22%)	29 (13%)	20 (11%)	8 (5%)	37 (10%)	32 (8%)
Bronchitis	17 (7%)	7 (3%)	10 (5%)	4 (2%)	10 (3%)	15 (4%)
Asthma	7 (3%)	3 (1%)	3 (2%)	0	9 (2%)	7 (2%)
Pneumonia	3 (1%)	1 (<1%)	5 (3%)	2 (1%)	4 (1%)	5 (1%)
Cough	13 (6%)	8 (4%)	2	1	6 (2%)	3 (1%)
Chest sounds	3 (1%)	1 (<1%)	1	0	2 (1 %)	2 (<1%)
Lower respiratory hemorrhage	1 (<1%)	1 (<1%)			2	1
Breathing disorders	3 (1%)	3 (1%)			2	1
Viral respiratory infections					2	0
Lower respiratory signs & symptoms	3 (1%)	2 (1%)	1	0	2	0
Lower respiratory infections	6 (3%)	7 (3%)	0	1	0	1
Sputum					0	1
Chronic obstructive airways disease					1	0
Lower respiratory failure			0	1		
Bacterial respiratory infections	1 (<1%)	1 (<1%)			0	1
Tracheitis	1 (<1%)	0				

Table III-D14. Lower respiratory adverse events after treatment

AE after Rx (all subjects)	NAIB3001 placebo	NAIB3001 zanamivir	NAIB3002 placebo	NAIB3002 zanamivir	NAIA3002 placebo	NAIA3002 zanamivir
Any lower respiratory	20 (9%)	12 (5%)	6 (3%)	13 (7%)	15 (4%)	11 (3%)
Bronchitis	4 (2%)	3 (1%)	1 (1%)	9 (5%)	9 (2%)	5 (1%)
Asthma	0	1 (<1%)			2	2
Pneumonia	3 (1%)	1 (<1%)	2 (1%)	0	2	2
Cough	5 (2%)	4 (2%)	1	4 (2%)	3	3
Viral respiratory infections	1	1	1	0		
Lower respiratory signs & symptoms	1	1				
Lower respiratory infections	5 (2%)	1 (<1%)	1	0		
Bacterial respiratory infections	0	1				
Tracheitis	1	0				
Pleuritis					1	0

Table III-D15. Lower respiratory adverse events in high-risk subjects during treatment

AE during Rx (high risk, CSR Table 89 for NAIB3001, CSR Table 84 for other studies)	NAIB3001 placebo n=39	NAIB3001 zanamivir n=37	NAIB3002 placebo n=19	NAIB3002 zanamivir n=13	NAIA3002 placebo n=60	NAIA3002 zanamivir n=49
Any lower respiratory	14 (36%)	6 (16%)	6 (32%)	1 (8%)	13 (22%)	12 (24%)
Bronchitis	4 (10%)	2 (5%)	3	0	2 (3%)	5 (10%)
Asthma	6 (15%)	3 (8%)	3	0	8 (13%)	6 (12%)
Pneumonia	0	1	0	1	1 (2%)	2 (4%)
Cough	2	0			1	0
Chest sounds			1	0	0	1
Viral respiratory infections					1	0
Lower respiratory signs & symptoms	1	0	1	0	1	0
Lower respiratory infections	4 (10%)	0				
Lower respiratory failure			0	1		

Table III-D16. Lower respiratory adverse events in high-risk subjects after treatment

AE after Rx (high-risk)	NAIB3001 placebo	NAIB3001 zanamivir	NAIB3002 placebo	NAIB3002 zanamivir	NAIA3002 placebo	NAIA3002 zanamivir
Any lower respiratory	7 (18%)	1 (3%)	2 (11%)	2 (15%)	4 (7%)	4 (8%)
Bronchitis			0	2	1 (2%)	3 (6%)
Asthma					2	1
Pneumonia	2 (5%)	1 (3%)	1	0	1	1
Cough	2 (5%)	0				
Lower respiratory infections	2 (5%)	0	1	0		
Tracheitis	1	0				

Again, no definite conclusions could be drawn from small numbers of individual events. The proportion of subjects (and of high-risk subjects) with any lower respiratory adverse event during treatment was lower on zanamivir than placebo in two studies and about the same across treatment groups in the third. Post-treatment patterns were more variable and appeared in large part to reflect the distribution of a small number of reported bronchitis events. It might be hoped that treatment of influenza could be associated with a reduction in lower respiratory adverse events, and there was some suggestion that this might be the case for some event categories in some studies, but there was not enough consistency across studies to suggest that pooled analyses could be used with confidence.

Laboratory abnormalities

Comparisons of laboratory abnormalities showed some variability in the three principal phase 3 studies. Mild laboratory abnormalities were relatively common in both placebo and zanamivir groups, and in many instances appeared consistent with acute viral illness, although the patterns showed some differences between studies. No definite conclusions could be drawn about possible treatment-related differences, although low-frequency treatment effects could not be ruled out and the possibility of toxicities that might become more apparent with wider use could not be dismissed. Overall, differences between studies were more striking than differences between treatments within each study.

Table III-D17. Summary of principal laboratory abnormalities in phase 3 studies

Laboratory abnormalities (CSR Table 85 for NAIB3001, Table 87 for other studies)	NAIB3001 placebo n=228	NAIB3001 zanamivir n=227	NAIB3002 placebo n=182	NAIB3002 zanamivir n=174	NAIA3002 placebo n=365	NAIA3002 zanamivir n=412
ALT >normal						
Baseline	21%	23%	11%	11%	10%	17%
Post-Rx visit	35%	38%	15%	14%	21%	23%
Post-Rx visit >2xULN	6%	8%	2%	2%	4%	4%
AST>normal						
Baseline	19%	20%	8%	6%	8%	13%
Post-Rx visit	31%	32%	7%	6%	18%	13%
Post-Rx visit >2xULN	4%	5%	1%	0	2%	2%
GGT>normal						
Baseline	15%	11%	19%	15%	11%	11%
Post-Rx visit	27%	28%	23%	23%	17%	15%
Post-Rx visit >2xULN	7%	5%	11%	5%	7%	5%
Bilirubin>nl						
Baseline	4%	4%	4%	6%	4%	5%
Post-Rx visit	2%	0	1%	3%	<1%	2%
Post-Rx visit >1.5xULN	<1%	0	<1%	0	<1%	<1%
Glucose>nl						
Baseline			23%	26%	18%	13%
Post-Rx visit			13%	15%	14%	14%
Post-Rx visit >1.3xULN			4%	2%	4%	5%
Calcium<nl						
Baseline	5%	4%	34%	42%	3%	5%
Post-Rx visit	7%	2%	33%	33%	3%	3%
Post-Rx visit <.95LLN	<1%	0	3%	6%	<1%	<1%
CPK>normal						
Baseline	13%	6%	4%	5%	10%	16%
Post-Rx visit	13%	5%	4%	4%	7%	11%
Post-Rx visit >5xULN	<1%	0	0	0	<1%	<1%

(table continued on next page)

Table III-D17. Summary of principal laboratory abnormalities (continued from previous page)

Laboratory abnormalities (CSR Table 85 for NAIB3001, Table 87 for other studies)	NAIB3001 placebo n=228	NAIB3001 zanamivir n=227	NAIB3002 placebo n=182	NAIB3002 zanamivir n=174	NAIA3002 placebo n=365	NAIA3002 zanamivir n=412
HCT<normal						
Baseline	9%	4%	5%	3%	8%	5%
Post-Rx visit	18%	8%	7%	5%	10%	8%
Post-Rx visit <0.93 (M) or 0.91 (F) xLLN	2%	<1%	2%	0	6%	5%
HGB<normal						
Baseline	1%	<1%	3%	1%	3%	2%
Post-Rx visit	2%	2%	4%	1%	4%	4%
Post-Rx visit <0.85(M) or 0.83(F) xLLN	0	0	0	0	<1%	0
PLT<normal						
Baseline	11%	13%	9%	4%	6%	4%
Post-Rx visit	10%	7%	2%	6%	3%	2%
Post-Rx visit <0.6xL LN	0	<1%	<1%	0	<1%	0
WBC<normal						
Baseline	7%	5%	15%	17%	6%	8%
Post-Rx visit	14%	10%	22%	15%	14%	16%
Post-Rx visit <0.7xLLN	1%	<1%	1%	1%	<1%	2%
Lymphocytes <normal						
Baseline	45%	48%	75%	79%	50%	49%
Post-Rx visit	<1%	0	22%	13%	2%	2%
Post-Rx visit <0.8xLLN	<1%	0	8%	4%	1%	<1%
Neutrophils <normal						
Baseline	4%	4%	7%	10%	3%	4%
Post-Rx visit	23%	19%	26%	27%	15%	17%
Post-Rx visit <0.8xLLN	16%	10%	15%	15%	7%	8%