for ages 50-64 and ≥65, smaller for <18 and 18-34, negative for 35-49) and was not apparent in the small number of non-white subjects. In the high-risk influenza-positive population (CSR supporting table 25), median time to alleviation was shorter in the zanamivir than the placebo group for elderly subjects (4.5 vs 7.25 days) but longer in the zanamivir group for respiratory (8.75 vs 5.5 days) and cardiovascular disease subjects (7.5 vs 7 days), and also (CSR supporting table 27) for unvaccinated subjects (10 vs 7.5 days). CSR supporting tables 18 and 20 suggest that 53 placebo and 55 zanamivir subjects were vaccinated but only 36 placebo/vaccinated and 47 zanamivir/vaccinated subjects were influenza positive – although confirmation of influenza (e.g. by rapid test [redacted] was an entry requirement for vaccinated subjects. Treatment effect was more consistently noted in subjects entered 36 hours or less after onset of symptoms in this study analysis (CSR ST 28-35).

Table III-A2b. Selected outcomes in NAIA3002

Outcome	Placebo	Zanamivir	P value
All randomized subjects (ITT population)			
Median days to alleviation (ITT) (CSR Table 13)	6.0	5.5	.228
Median days to alleviation, no relief meds (ITT) (CSR Table 14)	8.0	7.0	.054
Median days to return to normal activities (ITT) (CSR Table 15)	7.5	7.25	.336
Post-treatment investigator global assessment (ITT) (CSR Table 36)	18% no symptoms, 67% mild, 15% moderate, <1% severe	21% no symptoms, 67% mild, 11% moderate, <1% severe	.131
Complications noted (ITT) (CSR Table 37)	86 (24%)	74 (18%)	.066
Antibiotics for complication (ITT) (CSR Table 37)	58 (16%)	52 (13%)	.230

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Table III-A2b. Selected outcomes in NAIA3002 (continued from previous page)

Outcome	Placebo	Zanamivir	P value
Influenza positive subjects			
Number of influenza positives (CSR Table 39)	257	312	
Median days to alleviation (influenza positive) (CSR Table 43)	6.0	5.0	.078
Median days to alleviation, no relief meds (influenza positive) (CSR Table 46)	8.0	7.25	.075
Median days to return to normal activities (influenza positive) (CSR Table 47)	7.5	7.5	.378
Post-treatment investigator global assessment (influenza positive) (CSR Table 68)	12% no symptoms, 73% mild, 14% moderate, <1% severe	19% no symptoms, 71% mild, 11% moderate, <1% severe	.029
Complications noted (influenza positive) (CSR Table 69)	22%	15%	.049
Antibiotics for complication (influenza positive) (CSR Table 69)	15%	11%	.164
Exacerbation of asthma (influenza positive) (CSR Table 69)	2 (<1%)	5 (2%)	
Follow-up throat swab culture positive (influenza positive) (CSR Table 70)	Day 3: 17/112 (15%) Day 6: 1/108 (<1%)	Day 3: 11/137 (8%) Day 6: 3/124 (2%)	.075
High-risk subjects			
Median days to alleviation (high-risk) (CSR Table 73)	6.5 (n=60)	7.5 (n=49)	.710
Median days to alleviation, no relief meds (high-risk) (CSR Table 75)	10.25	11.0	.830
Complications noted (high-risk) (CSR Table 77)	28%	35%	.612
Antibiotics for complication (high-risk) (CSR Table 77)	15%	27%	.211

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Table III-A2b. Selected outcomes in NAIA3002 (continued from previous page)

Outcome	Placebo	Zanamivir	P value
High-risk, influenza positive subjects			
Median days to alleviation (high-risk, influenza positive) (CSR Table 74)	6.0	6.25	.886
Median days to alleviation, no relief meds (high-risk, influenza +, CSR Table 76)	11.0	10.25	.491
Complications noted (high-risk, influenza positive) (CSR Table 78)	21%	33%	.324
Antibiotics for complication (high-risk, influenza positive) (CSR Table 78)	12%	25%	.210
Exacerbation of asthma (high-risk, influenza positive) (CSR Table 78)	1 (2%)	5 (14%)	
Influenza negative subjects			
Median days to alleviation (influenza negative) (from vol I, p. 290)	5.0	6.0	Not given (see post-Advisory Committee amendments)

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III-A3. NAIA3002 Efficacy Results (FDA Comments)

The overall pattern emerging from detailed examination of the efficacy analyses for this study is an inconclusive mixture of analyses yielding small differences in favor of zanamivir (generally of questionable clinical or statistical significance), other analyses showing no discernible difference between zanamivir and placebo, and a few outcomes slightly favoring placebo. In aggregate these are compatible with, but not convincingly demonstrative of, a modest treatment benefit that is difficult to quantify and may not extend to all subgroups: the study does not prove absence of benefit but cannot be used by itself to document treatment benefit and would require very substantial positive results from other studies to produce an evaluation of all studies taken together as adequately documenting efficacy.

The applicant provides in CSR section 7.4 a table titled "Summary of Significantly Different Endpoints between Treatment Groups", described as a "summary of statistically significant results in favor of zanamivir." This lists a total of eight analyses with p values less than .05, three of which are overlapping evaluations of cough (time to alleviation of cough, mean cough score days 1-5, mean cough score days 1-14) and two of which are supplemental analyses from the Supporting Tables using data censoring; the other three are average maximum daily temperature (p=.006; from Table 65: this is calculated as AUC/time and difference in point estimates is 0.1 degree C), investigator global assessment of symptoms post-treatment (see discussion of differences between phase 3 studies), and complications of influenza (see additional discussion below). Examining this list in the context of the overall study report, it was noted that CSR Tables 43-70 and Supporting Tables 3 and 4 all contain efficacy analyses in the primary (influenza

positive) population, in some instances more than one analysis per table, so that only a minority (less than one-quarter) of the presented analyses for this population achieved p values below .05 (in some instances these were highly interdependent analyses, and several of the analyses prospectively identified as most important were not among them). Thus, the usefulness of this p value for ascribing importance to a small proportion of the large number of secondary analyses appeared limited.

Analyses of individual symptoms for influenza positive subjects (median time to value of none or mild) yielded a difference between placebo and zanamivir of 1.5 days for cough; 0.5 days for sore throat, feverishness, and loss of appetite; and 0 days for headache, muscle/joint aches and pains, nasal symptoms, and weakness (CSR Tables 48-55). While none of these medians was longer on zanamivir than on placebo as might have occurred with a merely random distribution of outcomes, these results suggested minimal if any effect on several of the major constitutional symptoms of influenza. Results for individual symptoms will be discussed further in comparisons of the principal phase 3 studies below.

III-A4. NAIA3002 Safety Results (Summary of Applicant's Analysis)

Adverse events in the placebo and zanamivir groups were similar and infrequent. Medication was discontinued prematurely due to an adverse event in 6 (2%) placebo and 9 (2%) zanamivir subjects. Adverse events were also similar between zanamivir and placebo in the "high-risk" subgroup, the majority being lower respiratory events such as asthma.

III-A5. NAIA3002 Safety Results (FDA Comments)

The overall adverse event profile appeared very similar in the zanamivir and placebo groups. The optimal method of accounting for adverse events which could conceivably be associated with the lactose vehicle is unclear; however, events such as cough, sore throat, and diarrhea appear to have been reported as adverse events only in small proportions of subjects (5% or less) in any group. Another difficulty in interpretation is due to the overlap between potential adverse events and influenza manifestations: although signs (including laboratory events) or symptoms compatible with influenza could be reported as adverse events if they were believed to be more severe than anticipated, any resulting imprecision in their identification could tend to obscure treatment differences.

Adverse event reports for all subjects during treatment or in the after-treatment follow-up period (from CSR Table 79 for all adverse events, CSR Table 80 for events reported as potentially drug-related, and CSR Table 83 for adverse events leading to discontinuation of study drug) include the events summarized in Table III-A5a below. Events were selected for inclusion in this table if they were reported in at least 5% of one treatment group or if they were considered to be of special interest.

Table III-A5a. Selected adverse events in NAIA3002

Adverse event	Placebo subjects (n=365)	Zanamivir subjects (n=412)
During treatment:		
Any adverse event	136 (37%)	126 (31%)
Throat & tonsil discomfort & pain	1 (<1%)	5 (1%)
Otitis	1 (<1%)	3 (1%)
Diarrhea	17 (5%)	19 (5%)
Nausea & vomiting	19 (5%)	12 (3%)
Abnormal LFTs	1 (<1%)	3 (1%)
Bronchitis	10 (3%)	15 (4%)
Asthma	9 (2%)	7 (2%)
Dizziness	6 (2%)	7 (2%)
Headaches	6 (2%)	3 (1%)
Urticaria	2 (1%)	1 (1%)
Post-treatment:		
Throat/tonsil discomfort & pain	4 (1%)	4 (1%)
Ear signs & symptoms	1 (<1%)	4 (1%)
Nasal signs & symptoms	2 (1%)	3 (1%)
Nausea & vomiting	6 (2%)	13 (3%)
Diarrhea	5 (1%)	6 (1%)
Abnormal LFTs	2 (1%)	3 (1%)
Headaches	7 (2%)	12 (3%)
Dizziness	0	2 (<1%)
Drug-related during treatment:		
Throat/tonsil discomfort & pain	1 (<1%)	4 (1%)
Diarrhea	4 (1%)	8 (2%)
Hyposalivation	3 (1%)	6 (1%)
Abnormal LFTs	1 (<1%)	1 (<1%)
Dreams	0	2(<1%)
Disturbance of sense of taste	0	2 (<1%)
Urticaria	0	1 (<1%)
Drug-related post-treatment:	3 (1%)	7 (2%)
AE leading to drug cessation:		
Any event	8 (2%)	9 (2%)
Any GI event (all different)	1 (<1%)	4 (1%)
Urticaria	0	1 (<1%)

Laboratory values in general appeared no more likely to diverge between treatment groups on treatment than at baseline (see Table III-A5b below, values from CSR Table 87). In particular, abnormalities of hepatic and hematologic laboratory tests were not infrequent in both baseline and post-treatment assessments, but there was no clear pattern differentiating treatment groups and no clear distinction from the effects of acute viral illness.

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Table III-A5b. Laboratory abnormalities in NAIA3002

Laboratory abnormalities	NAIA3002 placebo, n=365	NAIA3002 zanamivir, n=412
ALT >normal		
Baseline	10%	17%
Post-Rx visit	21%	23%
Post-Rx visit >2xULN	4%	4%
CPK>normal		
Baseline	10%	16%
Post-Rx visit	7%	11%
Post-Rx visit >5xULN	<1%	<1%
Lymphocytes <normal		
Baseline	50%	49%
Post-Rx visit	2%	2%
Post-Rx visit <0.8xLLN	1%	<1%
Neutrophils <normal		
Baseline	3%	4%
Post-Rx visit	15%	17%
Post-Rx visit <0.8xLLN	7%	8%

Laboratory abnormalities were not always followed to resolution. In tabulations of shifts from normal to abnormal laboratory values between baseline and subsequent assays, CPK shifted (Table 89) to over 5x ULN in 3 zanamivir and 1 placebo subject (both <1%). Bilirubin shifted to over 1.5x ULN in 2 zanamivir and 0 placebo subjects, while GGT shifted to over 2.0x ULN in 16 (4%) zanamivir and 19 (5%) placebo subjects, and AST and ALT each shifted to over 2.0x ULN in 2-3% of each group. Neutrophils shifted to <0.8 LLN in 20/337 placebo subjects (6%) and 30/387 zanamivir subjects (8%); total white cell count shifted to <0.7 LLN in 3/337 placebo (<1%) and 6/387 (2%) zanamivir subjects.

Listings of subject discontinuations and investigator comments were reviewed and potentially important descriptions matched to other listings, serious adverse event (SAE) narratives in the CSR, or case report forms (CRFs) by subject numbers where possible (subject numbers with P or Z affixed refer to placebo and zanamivir groups respectively). In listings of subjects who discontinued before the end of the study (Listing 3), placebo subjects included 15 lost to follow-up, 2 consent withdrawn, 2 adverse events, one protocol violation, one non-compliance; the zanamivir group included 13 lost to follow-up, 5 adverse events, 2 consent withdrawn, 1 moving to Bali for 2 months. Premature discontinuations of medication (Listing 4) in the placebo group included 6 adverse events, 3 lost to follow-up, 2 consent withdrawn, 2 protocol violation, one noncompliance, one "inadvertingly forgot 1 dose", 1 "hospitalized, unable to use trial drug without IRB review" (subject 10207, history of COPD, hospitalized "due to influenza and increased pulmonary symptoms"); for the zanamivir group there were 9 adverse events, 2 lost to follow-up, 2 protocol violations, 2 consent withdrawn, 2 missed

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last one or two doses. Investigator comments on the trial medication (Listing 5) noted one subject as unable to operate diskhaler properly and one with 19 doses punctured from one side only (both "judged non-compliant, patient failed to successfully complete 4 days treatment (8 doses)"); two others with mention of incomplete punctures; 10977P, 10502Z, 10882Z, 12215Z stopped due to AE; 12230Z "experienced sore throat which he felt was related to study drug"; 10339Z "discontinued study drug due to sudden onset fever and chills"; 12243Z "exacerbated sore throat"; 12252Z "no longer wanted to participate in the study"; 12286Z "received only one dose of study drug, subsequently developed hives" (judged non-compliant as described above); 10470Z (85 year old man hospitalized with dehydration and mental status changes resolving over 2 days) and 10207P (summarized above) stopped due to hospitalization.

Adverse event listings (Listing 24) included several mentions of throat symptoms (dryness, pain, taste disturbance, etc.), headache, alterations in alertness (e.g. jitters, drowsiness, bad dreams), rash, chest symptoms, elevations of liver enzymes, and diarrhea which were considered possibly related to study medication and/or led to cessation of drug. These occurred in both treatment groups.

Case report forms (CRFs) were reviewed for subjects withdrawing due to adverse events and for a 10% sample of high-risk subjects. No deaths were reported. Seven CRFs were supplied for patients withdrawing from the study due to adverse events: 10232 with bronchitis and dehydration, 10455 with bronchitis and CHF, 10882 with history of asthma, sore throat, wheezing, hospitalized for meningitis (no diagnostic information given but subject appears to have completed day 28 questionnaire; influenza negative per listing 14; additional information on this subject was requested from the applicant and did not reveal a specific etiologic diagnosis but the event was characterized as a self-limited aseptic meningitis), 10977 pneumonia, 12215 decreased platelets and wbc, nausea, vomiting, diarrhea, abdominal cramps, dehydration, diagnosed as infectious bacterial enterocolitis because of improvement on cipro (cultures negative), 12250 pain in liver, 12286 hives after first dose. Eleven CRFs were supplied as a 10% sample of high risk subjects; among items of note were that 10241 (high risk because of age 72), recorded on list of subjects discontinuing medication as stopping due to "non-compliance", is described in the CRF as "unable to operate diskhaler correctly in order to dose herself"; 10454 has diarrhea noted as possibly drug related, cough and LFTS apparently noted as AE's and crossed out when CRF was edited/corrected, 10461 noted as having exacerbation of asthma and otitis, 12156 noted as taking wrong dosage initially because misinstructed, 12230 "Pt experienced sore throat which he felt was related to study drug then had difficulty swallowing after 2000 hrs dose of study drug. 4 doses of study drug taken then discontinued." [throat pain, difficulty swallowing listed as AE's but possible causality for difficulty swallowing appears to have been changed from Y to N, still hard to read; patient is not on list of discontinuations due to AE because he stopped drug but not study], 12276 LFTs attributed to disease under study. CRFs were also provided for a random sample of enrolled subjects. No major issues were identified in review of these. The data collected in the CRF may clarify some of the culture results summarized elsewhere, in that the day 1 form (First Treatment Visit) has separate check boxes for

"Sample (e.g. nasal swab) taken from the subject for culture and PCR?" and for "THROAT swab taken from the subject for viral sensitivity testing," and it is the latter that is repeated at day 3 (optionally) and day 6.

III-A6. Summary of Study NAIA3002

Overall, it was difficult to derive any convincing treatment effect from the principal primary and secondary analyses in study NAIA3002. The point estimate for differences between zanamivir and placebo in median time to the primary endpoint was marginal (at the lower limit of differences that might be considered clinically meaningful), with a p value above .05 despite the large size of the study so that a one-day difference in median time to primary endpoint could not be concluded with any reasonably high level of confidence, and with little support for magnitude of effect from secondary endpoints as the time to alleviation without use of relief medications showed a similar p value with a smaller point estimate, the grouped high-risk subjects and the influenza-negative subjects showed a negative point estimate, and the time to return to normal activities showed no difference. Time to alleviation with use of relief medications had been prospectively considered as an important secondary endpoint because of the anticipated possible confounding effects of symptom relief medications and the difficulty of avoiding such confounding within the limits of feasible study design; among the other evaluations prospectively considered as having potential importance were temperature and investigator's assessments (considered as potentially more objective, or providing a different perspective, than symptom recordings) and reconsideration of the influenza positive population with separate evaluation of those positive only on PCR. Mean temperature showed a difference of marginal magnitude. Median time to afebrile status in influenza positive subjects (CSR Supporting Table ST40) was reported as having a p value of .012 but the point estimate was 1.5 days for both treatment groups, with the largest difference in the proportion of subjects reported as reaching afebrile status by day 0.5 (36% of zanamivir and 22% of placebo subjects). The investigator's global assessment at day 6 favored the zanamivir group with a p value of .029 but with differences reflecting only a few percent more subjects characterized as "mild" or better rather than "moderate" or "severe" in the zanamivir group compared with the placebo group. Restricting the influenza positive population to those positive by culture or serology yielded the same point estimates with a slightly lower p value than the primary analysis. Numerous other analyses, including individual-symptom analyses for all symptoms except cough, showed very small or no differences between treatment groups when point estimates and p values were considered together. Thus, although absence of effect was not proven, treatment effects if present appeared to be marginal, and a few of the subgroup analyses actually yielded point estimates favoring placebo, reinforcing the impression of a study that, although large and well-powered, was inconclusive in its results.

The safety profile of study treatment did not show major differences between the zanamivir group and the placebo group. Most events were characterized as mild and not treatment-limiting. Evaluation of causality was complicated by the substantial overlap

between reported adverse events and characteristics of influenza-like illness itself. Some of the symptoms reported as possibly drug-related could reasonably be associated with inhalation of powder, which occurred in both treatment groups. Laboratory abnormalities appeared largely consistent with acute viral infection although there was insufficient information to evaluate possible drug effects on duration of some of these abnormalities. The possibility of very-low-frequency treatment differences in some adverse events could not be evaluated from a database of this size.

III-B. Clinical Study NAIB3002

Protocol NAIB3002 carried the same title as NAIA3002, and information was provided in parallel to DAVDP, but the study was not carried out under IND. NAIB3002 and NAIA3002 were originally proposed by the applicant as the two principal phase 3 studies in support of an indication for zanamivir for treatment of influenza A and B. The study report is located in volumes 109 through 113 in NDA 21-036.

III-B1. NAIB3002 Study Design

See under NAIA3002 above for description of general study design. NAIB3002 failed to enroll its projected sample size and the applicant originally indicated an intention to continue it in a second influenza season, then elected to close the study and submit the study report as final.

III-B2. NAIB3002 Efficacy Results (Summary of Applicant's Analysis)

A total of 356 subjects were enrolled in 11 countries (Belgium 5, Denmark 22, Finland 80, France 73, Germany 21, Italy 12, Netherlands 2, Norway 34, Spain 1, Sweden 82, U.K. 24), of whom 182 were randomized to placebo and 174 to zanamivir. These and the following numbers are taken from Clinical Study Report (CSR) Tables 1-8. Of the total enrollment, 32 subjects (9%) were designated as "high-risk". In the placebo group, 3 discontinued the study prematurely (lost to follow-up); in the zanamivir group, 4 discontinued prematurely (2 adverse events, one lost to follow-up, one "other"). In the placebo group, 3 discontinued study medication early (2 adverse events, one "other"), compared with 4 in the zanamivir group (2 adverse events, 1 protocol violation, 1 "other"). Protocol violations were identified for 12 (7%) placebo and 6 (3%) zanamivir subjects, the most common being no post-treatment visit and "Fewer than two other major symptoms" (4 subjects each). The placebo group was slightly older than the zanamivir group (mean age 38.8 vs 35.6 years, median 38 vs 34); 55% of placebo subjects and 52% of zanamivir subjects were female; almost all subjects (99% in each group) were classified as White. In each group, 22% were noted as taking concurrent anti-infective/immunological medications, mostly penicillins, while 5% and 6% were noted as taking beta-agonists. Four percent or 14 subjects (5% placebo, 3% zanamivir) had received current season influenza vaccine. Of those vaccinated, 8 of 9 placebo subjects and all 5 zanamivir subjects were reported as influenza positive (CSR Table 9).

Sources of influenza diagnosis are summarized in the following table (data from CSR Table 10). Overall influenza symptom scores at baseline showed some variability, but distributions of none/mild vs moderate/severe scores were reasonably balanced between treatment groups.

Table III-B2a. Influenza diagnosis in NAIB3002

Influenza diagnosis	Placebo	Zanamivir
Total subjects	182	174
Positive for influenza A	133 (73%)	132 (76%)
Positive for influenza B	8 (4%)	4 (2%)
Influenza positive, type unknown	--	--
Positive by culture	111/181	112/172
Positive by PCR	122/182	120/174
Positive by serology	110/174	106/166

Selected outcome measures are summarized in the following table. In sensitivity analyses (CSR supporting tables 1-8), mean and median times to alleviation were at least 2 days longer in placebo than zanamivir groups for ITT, influenza positive, high-risk, and high-risk influenza-positive categories, whether times were calculated censoring patients with incomplete data or assigning them a time to alleviation near the end of follow-up, and each of these comparisons in the total ITT and influenza-positive populations yielded a p value of .002 or less. Restricting the definition of "influenza positive" to positive culture and/or serology yielded unchanged medians and p value for time to alleviation (supporting table 10), and only an extremely small number of subjects (5 placebo, 4 zanamivir) were positive only on PCR. In subgroup analyses (CSR supporting tables 16 and 21), treatment effect in influenza positive subjects did not vary appreciably by gender or vaccination status but was principally seen in age groups 35 years and older and was not apparent in the extremely small number (2 in each treatment group) of non-white subjects. In the high-risk influenza-positive population (CSR supporting table 25), median time to alleviation was shorter in the zanamivir than the placebo group for elderly subjects (11 vs >26.5 days) and those with respiratory disease (6.5 vs 10.75 days) but longer in the zanamivir group for cardiovascular disease subjects (21 vs 16.5 days); a similar pattern was seen for high-risk ITT subjects (CSR supporting table 24), while median time to alleviation was also longer on zanamivir (CSR supporting table 26 and 27) for the small number of high-risk vaccinated subjects (10.5 vs 9.5 days, 5 and 3 subjects respectively).

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Table III-B2b. Selected outcomes in NAIB3002

Outcome	Placebo	Zanamivir	P value
All randomized subjects (ITT population)			
Median days to alleviation (ITT) (CSR Table 13)	7.5	5.0	<.001
Median days to alleviation, no relief meds (ITT) (CSR Table 14)	8.25	5.5	<.001
Median days to return to normal activities (ITT) (CSR Table 15)	8.5	6.75	.023
Post-treatment investigator global assessment (ITT) (CSR Table 36)	25% no symptoms, 55% mild, 18% moderate, 2% severe	33% no symptoms, 57% mild, 9% moderate, 2% severe	.025
Complications noted (ITT) (CSR Table 37)	34%	23%	.037
Antibiotics for complication (ITT) (CSR Table 37)	18%	12%	.189
Influenza positive subjects			
Number of influenza positives (CSR Table 39)	141	136	
Median days to alleviation (influenza positive) (CSR Table 43)	7.5	5.0	<.001
Median days to alleviation, no relief meds (influenza positive) (CSR Table 46)	8.5	5.5	<.001
Median days to return to normal activities (influenza positive) (CSR Table 47)	8.5	7.0	.025
Post-treatment investigator global assessment (influenza positive) (CSR Table 68)	25% no symptoms, 52% mild, 21% moderate, 2% severe	32% no symptoms, 59% mild, 7% moderate, 2% severe	.020
Complications noted (influenza positive) (CSR Table 69)	33%	24%	.125
Antibiotics for complication (influenza positive) (CSR Table 69)	17%	11%	.207
Exacerbation of asthma (influenza positive) (CSR Table 69)	3	0	
Follow-up throat swab culture positive (influenza positive) (CSR Table 70)	Day 3: 2/54 (4%) Day 6: 0/54	Day 3: 1/57 (2%) Day 6: 0/57	Not given

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Table III-B2b. Selected outcomes in NAIB3002 (continued from previous page)

Outcome	Placebo	Zanamivir	P value
High-risk subjects			
Median days to alleviation (high-risk) (CSR Table 73)	11.5 (n=19)	9.0 (n=13)	.178
Median days to alleviation, no relief meds (high-risk) (CSR Table 75)	11.5	9.0	.076
Complications noted (high-risk) (CSR Table 77)	58%	31%	.250
Antibiotics for complication (high-risk) (CSR Table 77)	26%	0	.115
High-risk influenza positive subjects			
Median days to alleviation (high-risk, influenza positive) (CSR Table 74)	11.5	9.25	.21
Complications noted (high-risk, influenza positive) (CSR Table 78)	61%	33%	.264
Antibiotics for complication (high-risk, influenza positive) (CSR Table 78)	28%	0	.120
Exacerbation of asthma (high-risk, influenza positive) (CSR Table 78)	3 (17%)	0	
Influenza negative subjects			
Median days to alleviation (influenza negative) (from vol 1, p. 293)	7.0	5.25	

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III-B3. NAIB3002 Efficacy Results (FDA Comments)

This study was originally projected to enroll about 500 subjects. Thus, final enrollment was about 71% of the planned quantity. In teleconference discussions following submission of the NDA, the applicant indicated that the decision to finalize and submit the study with this enrollment was based on the observation of a late increase in influenza leading to increased enrollment late in the season, and that preliminary analyses were completed several months later. The number of "high risk" subjects enrolled is extremely small (Table 41: 19P [9≥65, 10 respiratory, 3 CV]; 13Z [4≥65, 8 respiratory, 3 CV]), despite the pre-defined intent to recruit 25% "high risk" subjects in this study as well as in NAIA3002. Review of treatment results by study site (CSR Supporting Tables 22 and 23) did not suggest that a few centers had contributed disproportionately to the efficacy results; however, most centers enrolled small numbers of subjects and the point estimates for treatment effect varied markedly among centers. Given the smaller enrollment and similar study design, the finding of positive results with low p values in NAIB3002 for numerous analyses that yielded inconclusive results in NAIA3002 was striking. It was also noted that the influenza-negative subgroups in NAIB3002 had a shorter median time to alleviation on zanamivir than on placebo, and it was unclear whether this could be due

to chance, to false-negative influenza diagnoses, or to some other reason(s); additional analyses of influenza-negative subgroups are summarized later in this review.

III-B4. NAIB3002 Safety Results (Summary of Applicant's Analysis)

Adverse events were infrequent and similar between placebo and zanamivir recipients. Two zanamivir and no placebo subjects discontinued the study prematurely due to adverse events; two zanamivir and two placebo subjects discontinued medication prematurely due to adverse events. Serious adverse events were reported for two subjects (abdominal discomfort and pain, temperature regulation disturbance in a placebo subject; pneumonia and lower respiratory failure in a zanamivir subject). Two pregnancies were reported in placebo recipients, one of whom experienced a "non-serious hemorrhage" during pregnancy. Laboratory results were similar between treatment groups.

III-B5. NAIB3002 Safety Results (FDA Comments)

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

Table III-B5a. Selected adverse events in NAIB3002

Adverse event	Placebo subjects (n=182)	Zanamivir subjects (n=174)
During treatment:		
Any adverse event	63 (35%)	44 (25%)
Sinusitis	4%	2%
Pharyngitis	3%	2%
Any ENT event	10%	7%
Diarrhea	4%	2%
Nausea/vomiting	3%	2%
Abnormal LFTs	1%	2%
Bronchitis	5%	2%
Headache	2%	1%
Dizziness	0	1%
Post treatment:		
Sinusitis	3%	3%
Nasal inflammation	1%	2%
Bronchitis	1%	5%
Cough	1%	2%
Headache	2%	1%
Dizziness	1%	0
Migraine	0	1%
Urticaria	0	1% (1)

Adverse events considered possibly drug-related were reported in 12 (7%) subjects in each treatment group, with no predominant pattern (CSR Table 80). Adverse events

leading to drug discontinuation (CSR Table 83) included, for placebo, one angina pectoris and one nausea/vomiting; for zanamivir, one "gastrointestinal spasms" and one "lower respiratory failure" (described further below).

The most common laboratory abnormalities (from CSR Table 87) included those shown in the following table.

Table III-B5b. Laboratory abnormalities in NAIB3002

Laboratory abnormalities	NAIB3002 placebo n=182	NAIB3002 zanamivir n=174
ALT >normal		
Baseline	11%	11%
Post-Rx visit	15%	14%
Post-Rx visit >2xULN	2%	2%
CPK>normal		
Baseline	4%	5%
Post-Rx visit	4%	4%
Post-Rx visit >5xULN	0	0
Lymphocytes <normal		
Baseline	75%	79%
Post-Rx visit	22%	13%
Post-Rx visit <0.8xLLN	8%	4%
Neutrophils <normal		
Baseline	7%	10%
Post-Rx visit	26%	27%
Post-Rx visit <0.8xLLN	15%	15%

Laboratory shifts from baseline (Table 88) showed slightly more increases in bilirubin on zanamivir (4% Z vs <1% P; but none of these to >1.5x ULN from Table 89), GGT rises in 10% of zanamivir and 6% of placebo recipients (but 4% vs 9% for shifts to values over 2xULN in table 89), glucose elevations 16% Z and 10% P, PMN decrease 22% Z and 24% P, total white blood cell decrease 8% Z and 14% P.

Listing 5, investigators' comments on medications, included one subject with 13 blisters "not perforated properly" (patient "judged noncompliant" because of failure to complete 4 days of therapy), and three others with at least one blister not perforated properly or completely. Listing 24 indicates at least possible causality for several reports of dry mouth or sore throat, taste disturbance, diarrhea, increased LFTs. These occurred in both placebo and zanamivir recipients.

CRFs were received for two subjects discontinuing the study prematurely due to adverse events (both on zanamivir according to listing 3). Subject 9534 discontinued due to an event handwritten on the CRF as "abdominal [illegible word, possibly 'spasms']" coded as not reasonably related to study medication. Subject 9572 is described as having severe

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("end-stage") underlying COPD and emphysema with right cardiac failure at baseline, and was discontinued from the study apparently on day 3 due to "threatening respiratory failure" coded as not reasonably related to study medication, with a narrative note that telephone contact with the hospital later indicated the patient was recovering well (from the description in the day 1 visit form, it is not clear why this patient was considered a reasonable candidate to complete an outpatient treatment course at entry). Three CRFs were received as a 10% random sample of high-risk patients; one of these (with underlying asthma as the high-risk condition, in the placebo group) had a report of pregnancy thought to have begun "shortly after finishing the treatment period", and the CRF notes type of contraception as "none" with "no plans of becoming pregnant" as an additional note. No additional issues were identified in the random sample of all enrolled subjects. In NAIB3002 the CRF included an additional form for the first treatment visit "Viral culture" to indicate whether this was a nasal wash, nasal aspirate, nasopharyngeal and throat swab in same tube, throat swab, or nasopharyngeal swab; as in NAIA3002, this query regarding the initial diagnostic specimen was distinct from the query regarding a throat swab obtained for viral sensitivity.

III-B6. Summary of Study NAIB3002

This study showed a difference between treatment groups in time to the primary alleviation endpoint that would generally be considered clinically meaningful. The finding of treatment differences was reasonably resilient to use of various secondary endpoints and subgroup analyses. Safety did not appear markedly different in the two treatment groups.

III-C. Clinical Study NAIB3001

Study NAIB3001 is entitled "A double-blind, randomized, placebo-controlled, parallel-group, multicenter study to investigate the efficacy and safety of inhaled zanamivir administered twice daily in the treatment of influenza A and B viral infections." This study was carried out in the Southern Hemisphere. It was not originally proposed as a pivotal phase 3 study. The protocol was submitted in IND [redacted] as a "Non-US, Non-IND Phase III Protocol for Australia" with a covering letter stating "The purpose of this submission is to provide you with a copy of the Phase III protocol that is currently being conducted in Australia. [redacted]" In subsequent correspondence (March and May 1998, as summarized in previous sections of review), the applicant proposed to submit this study as one of the two principal phase 3 studies in support of the treatment indication or as a study providing additional information for the treatment indication. The study report is located in volumes 97 through 101 in NDA 21-036.

III-C1. NAIB3001 Study Design

The study design was similar to that of NAIA3002 and NAIB3002 described in previous sections of this review, with several salient exceptions. For example, subjects were required to be symptomatic for no more than 36 hours before study entry and were not required to have objectively elevated temperature at entry if "feverishness" was present. Time to alleviation without relief medications was not part of the prospective analysis but was added at FDA request. The study was planned (Section 3.1 of CSR) to enroll 360 subjects "with a target of >50% 'High Risk' patients"; the high risk categories were also defined slightly differently from NAIA3002 and NAIB3002, to include metabolic and endocrine disorders and immunocompromised patients in addition to those with chronic respiratory or cardiovascular disease and those aged 65 years and over. The dose and duration of treatment (zanamivir or placebo, two inhalations twice daily for five days, each inhalation containing 5 mg zanamivir in the active drug group and lactose powder in both the active drug and placebo groups) were the same as in NAIA3002 and NAIB3002, but symptom recording was not continued beyond the first two weeks. Vaccinated subjects could be enrolled but "study staff were advised to maintain a 2 week window between vaccination and entry into the study (this was based on evidence to suggest that most people develop their optimal immune response within 2 weeks)."

The protocol (as provided in Vol. 101, p. 96 of volume, p. 11 of protocol) indicates that symptoms will be recorded four times a day for the first five days and twice a day days 6-14. The sample diary card originally supplied in the NDA submission (Vol 101, p. 252) differs from the protocol in the number of recordings requested and the scale on which symptoms were recorded. Following inquiries about this discrepancy, the applicant stated the wrong diary card had been submitted and provided a replacement diary card corresponding to the scoring described in the protocol. Division of Scientific Investigations (DSI) staff performing site inspections confirmed that the card format corresponding to the protocol was the format for actual study data seen during inspection. Unlike other phase 3 trials, the protocol for NAIB3001 contained a provision "It is important the patient assesses their own symptoms, but a carer may fill out the Diary Card on behalf of the patient." DSI reported nurses sometimes performed this function.

III-C2. NAIB3001 Efficacy Results (Summary of Applicant's Analysis)

A total of 455 subjects were enrolled in 3 countries (414 Australia, 12 New Zealand, 29 South Africa), of whom 228 were randomized to placebo and 227 to zanamivir. These and the following numbers are taken from Clinical Study Report (CSR) Tables 1-8. Of all randomized subjects, 76 (17%) were classified as "high risk". In the placebo group, 18 (8%) discontinued the study prematurely (4 adverse event, 3 "consent withdrawn", 10 lost to follow-up, 1 protocol violation); in the zanamivir group, 13 (6%) discontinued prematurely (5 "consent withdrawn", 7 lost to follow-up, 1 "other"). In the placebo group, 14 (6%) discontinued study medication early (6 adverse events, 3 "consent withdrawn", 5 "other"), compared with 13 (6%) in the zanamivir group (4 adverse events, 4 "consent withdrawn", 1 lost to follow-up, 4 "other"). The placebo group had a higher

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proportion of females (54% vs 41%) and was slightly older than the zanamivir group (mean 37.6 vs 36.3 years, median 37.3 vs 34.6); 95% of subjects (93% placebo, 96% zanamivir) were classified as White. As in NAIA3002 and NAIB3002, smoking status was approximately balanced between treatment groups. Twenty-eight percent in the placebo group and 23% in the zanamivir group were noted as taking concurrent anti-infective/immunological medications, mostly penicillins, macrolides, cephalosporins and tetracyclines, while 15% and 14% were noted as taking beta-agonists. Six percent (12 subjects or 5% placebo, 14 subjects or 6% zanamivir) had received current season influenza vaccine. Sources of influenza diagnosis are summarized in the following table (data from CSR Table 9). Overall influenza symptom scores at baseline showed some variability, but distributions of none/mild vs moderate/severe scores were reasonably balanced between treatment groups.

Table III-C2a. Influenza diagnosis in NAIB3001

Influenza diagnosis	Placebo	Zanamivir
Total subjects	228	227
Positive for influenza A	109 (48%)	105 (46%)
Positive for influenza B	51 (22%)	56 (25%)
Positive by "virology" [from combination of CSR Table 9 and CSR Supporting Table 13, this appears to include all subjects with positive culture and/or "quick test"]	139/227	144/227
Positive by serology [four subjects positive for both A and B]	109/202	102/205

Selected outcome measures are summarized in the following table. In sensitivity analyses (CSR supporting tables 5, 7, 9, 11), mean and median times to alleviation ranged from 0.96 days to 3.25 days longer in placebo than zanamivir groups for ITT, influenza positive, high-risk, and high-risk influenza-positive categories, when times were calculated by censoring patients with incomplete data or by assigning them a time to alleviation near the end of follow-up, and each of these comparisons in ITT, influenza-positive, and high-risk populations yielded a p value less than .05 (the influenza-positive high-risk population had p values up to .16-.17 but only 52 subjects in the two treatment groups combined). Restricting the definition of "influenza positive" to positive culture and/or serology yielded median time to alleviation of 6.5 days in the placebo group and 4.75 days in the zanamivir group (p=.008, CSR Supporting Table 14). In subgroup analyses (CSR supporting tables 18 and 22), treatment effect in influenza positive subjects was seen in female (7.5 vs 4 days) but not male (5 vs 5 days) subjects, was observed in most age groups (smallest difference 0.5 days for ages 18-34, differences 1.75 days and upward in other age groups) and in both "white" and "other" ethnic groups, and was not observed in the very small number of vaccinated subjects (median time to alleviation 4 days for 7 placebo subjects, 4.5 days for 8 zanamivir subjects). In the high-risk ITT and influenza-positive populations (CSR supporting tables 26 and 27), median time to alleviation was shorter in the zanamivir than the placebo group for all high-risk categories examined (respiratory, cardiovascular, elderly, endocrine/metabolic, immunocompromised). Among subjects with baseline temperature at least 37.8° C,

treatment effect was enhanced (ITT median time to alleviation 6.5 vs 4.5 days, p<.001, CSR Table 13; influenza-positive time to alleviation 6.5 vs 4.5 days, p<.001, CSR Table 45), while no effect was seen in those with baseline temperature less than 37.8° C (ITT median time to alleviation 5.5 vs 5.5 days, p=.705, CSR Table 14; influenza-positive time to alleviation 5.0 vs 5.0 days, p=.777, CSR Table 46). Median time to eradication of symptoms was greater than 12.5 days for both treatment groups (ITT and influenza positive, placebo and zanamivir) but the p value was reported as .046 for ITT (CSR Table 15) and .013 for influenza positive (CSR Table 49). Treatment effect was similar in magnitude for 214 subjects with influenza A (6.5 vs 4.5 days) and 107 subjects with influenza B (6.0 vs. 4.5 days, CSR Tables 47 and 48).

Table III-C2b. Selected outcomes in NAIB3001

Outcome	Placebo	Zanamivir	P value
All randomized subjects (ITT population)			
Median days to alleviation (ITT) (CSR Table 12)	6.5	5.0	.011
Median days to alleviation, no relief meds (ITT) (CSR Supporting Table 1)	9.0	7.0	.085
Median days to return to normal activities (ITT) (CSR Table 24)	9.0	7.0	<.001
Post-treatment investigator global assessment (ITT) (CSR Table 38)	no symptoms 16%, mild 68%, moderate 14%, severe 1%	no symptoms 17%, mild 72%, moderate 11%, severe <1%	.180
Complications noted (ITT) (CSR Table 39)	29%	22%	.135
Antibiotics for complication (ITT) (CSR Table 39)	26%	23%	.508
Influenza positive subjects			
Number of influenza positives (CSR Table 40)	160	161	
Median days to alleviation (influenza positive) (CSR Table 44)	6.0	4.5	.004
Median days to alleviation, no relief meds (influenza positive) (CSR Supporting Table 2)	8.5	6.5	.033
Median days to return to normal activities (influenza positive) (CSR Table 58)	9.0	7.0	<.001
Post-treatment investigator global assessment (influenza positive) (CSR Table 72)	13% no symptoms, 70% mild, 15% moderate, 2% severe	18% no symptoms, 71% mild, 11% moderate	.054
Complications noted (influenza positive) (CSR Table 73)	30%	24%	.243
Antibiotics for complication (influenza positive) (CSR Table 73)	28%	26%	.580

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Table III-C2b. Selected outcomes in NAIB3001 (continued from previous page)

Outcome	Placebo	Zanamivir	P value
High-risk subjects			
Median days to alleviation (high-risk) (CSR Table 76)	8.0, n=39	5.5, n=37	.048
Median days to alleviation, no relief meds (high-risk) (CSR Supporting Table 3)	>12.5	6.5	.028
Complications noted (high-risk) (CSR Table 78)	46%	14%	.004
Antibiotics for complication (high-risk) (CSR Table 78)	41%	16%	.025
High-risk influenza positive subjects			
Median days to alleviation (high-risk, influenza positive) (CSR Table 77)	8.3	5.0	.161
Influenza negative subjects			
Median days to alleviation (influenza negative) (from vol 1 p. 287)	7.0	6.75	

III-C3. NAIB3001 Efficacy Results (FDA Comments)

Some variability was noted in exploratory analyses of NAIB3001 results. Overall, however, the principal analyses and numerous secondary analyses yielded estimates of treatment effect that would generally be considered relevant and statistically supported. Line listings were reviewed for a sampling of subjects identified during biostatistical review as having return of symptoms to a level not meeting alleviation criteria after the initial time of alleviation identified in the applicant's analysis. In these 28 records, points of note included the following (these are not mutually exclusive, so some records may have fitted more than one of these categories). Eleven subjects had only one symptom at one time point showing an increase after initial satisfaction of the alleviation criteria. Six subjects appeared still to be taking relief medications when symptom fluctuation was recorded. Six had no temperature of 37.8 or higher in the data listing (although it was not known whether there might have been any other study-entry temperature measurements not present in the line listing). Two appeared to have cough that fluctuated throughout the study period, and two appeared to have fairly prolonged asymptomatic periods followed by some symptoms recorded in the last few days of the recording period. No clear recurrence of fever was noted, most subjects did have elevated temperature early in the study with subsequent improvement, and most had symptom patterns compatible with general improvement over time.

Overall, inspection of these line listings appeared to reinforce the (previously suspected) importance of taking relief medications into account in the definition of alleviation, having some objective criterion (e.g. temperature) for entry, and interpreting missing values with caution. Another previously recognized problem in this study is the lack of symptom recording after the first two weeks, which reduces the proportion of subjects

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with an observed time of sustained alleviation by any definition. After allowing for these issues, there remain a number of subjects who had isolated "recurrence" type values, and a few who had repeated scores suggesting meaningful persistence or reappearance of symptoms that should be taken into account as clinically significant. Any treatment-related imbalance in such events would further indicate the caution that must be used in assessing analyses of the primary endpoint. In part because of these concerns, and at the recommendation of the statistical reviewer, additional analyses were requested from the applicant including time to meeting alleviation criteria without any subsequent symptom rise or without any subsequent symptom rise lasting more than one diary card recording: these will be summarized and discussed below for all three principal phase 3 treatment studies.

Two of the largest sites in NAIB3001 were inspected by the Division of Scientific Investigations (DSI). Preliminary discussions with DSI included consideration of the importance of randomized double-blinded methodology and systematic symptom recording for studies of diseases in which symptomatic relief is a major goal of therapy, and the potential risk of obscuring treatment differences if symptom classification was variable or imprecise. Issues raised by review team members included the possibility that a few subjects had been classified as stopping treatment due to "consent withdrawn" when withdrawal was actually associated with clinical symptoms (see further discussion under FDA comments on safety analysis below), and discrepancies between symptom scoring categories in the CSR and those in the sample diary card provided in the original NDA submission. DSI staff did not recommend against use of the data from this study and did not recommend additional inspections. During site inspections they checked the diary card format and reported that the actual card used were consistent with the categories used in data analysis for the CSR (see Study Design section above). As part of the overall effort to take subjectivity of symptom recording into account in analyses of all studies, the applicant was asked to perform additional analyses such as breakdown of treatment effect by timing of study entry (which will be discussed further below).

In this study, median time to alleviation was longer on placebo than on zanamivir in female but not male subjects for the primary efficacy endpoint in the influenza-positive population. Male subjects did have somewhat longer median times to alleviation on placebo than on zanamivir for the ITT population primary alleviation endpoint (6 vs 5 days, ST 16), the ITT population time to alleviation without ongoing use of relief medications (7.75 vs 7 days, ST 17), and the influenza positive population time to alleviation without ongoing use of relief medications (7 vs 6.25 days, ST 19). Evaluation of gender effects across studies in discussed further in a later section of this review.