treatment groups (section 8.1) and noted for 2 or more days in 9 of 9 placebo and 4/9, 3/8, 6/8 in the active treatment groups (section 8.6), the latter comparisons showing p<.05 for the two BID treatment groups against placebo.

Influenza A challenge studies:

In study NAIA1002 ("A study to investigate the effect of intranasal GG167 (GR121167X) initiated at various intervals post inoculation on infection in healthy volunteers when inoculated with influenza A/Texas/91(H1N1) virus," vol. 59, n=56, performed in U.S.), intranasal zanamivir was started 6 times per day at 26 or 50 hr post H1N1 inoculation, or twice daily beginning 32 hr post inoculation, all compared against placebo (groups 1,2,3,4 respectively). Mean days of viral shedding were reported as 1.3, 2.4, 0.8, and 3.3 for the respective groups (the two zanamivir regimens started at 26 and 32 hours after inoculation had p<.05 compared with placebo, while the group starting at 50 hours did not). Occurrence of URI (69-92%), and of cough (31-33%) and myalgia (38-42%) separately, was similar across treatment groups. Mean sums of symptom scores were numerically somewhat lower in the treatment groups, with p<.05 only for the twice-daily group starting treatment at 30 hours (for symptoms on days 2-8). There is a suggestion that fever >99.9F may have been reduced when zanamivir was started at 26 or 32 hours but not at 50 hours (1/12 volunteers in group 1, 7/13 in group 2, 1/13 in group 3, 4/15 in group 4).

In study NAIA1001 ("A study to investigate the effect of intranasal GG167 (GR121167X) in infection in healthy male volunteers when experimentally inoculated with influenza A/Texas/91 (H1N1) virus," vol. 56-57, n=48, performed in U.S.), intranasal zanamivir six times daily was started 4 hours before (Group 1) or 26 hours after (Group 2) H1N1 inoculation. Two placebo groups were combined for analyses. Positive cultures were obtained in 0/16 Group 1, 8/13 Group 2, and 11/17 placebo subjects, and evidence of infection (by culture or serology) in 1/16, 9/13, and 12/17 (each of these, and also viral titer AUC and mean days of shedding, reported p<.001 for Group 1 but not Group 2 compared with placebo). Fever was reported for 0/16, 0/13, and 6/17 (p<.05 for each active group compared with placebo), URI symptoms in 5/16, 6/13, and 11/17 (these, and incidence of cough and myalgia individually, were not reported as differing significantly). AUC for days 2-8 (section 8.2) was reported as 0.7 for group 2 and 6.0 for pooled placebo (p=.038), mean days with positive titer 0.5 and 2.2 (p=.026), mean peak viral titer 0.7 and 2.8 (p=.047).

In NAIA1003 (vol. 62, n=31, performed in U.S.), only drug administration before virus exposure was utilized (intranasal zanamivir starting 4 hr before H1N1 inoculation, two or six times daily). Measures of viral shedding, seroconversion, summary symptom scores were reduced but 3/10 six-times-daily and 2/10 twice-daily zanamivir subjects had URI (only one had fever) vs 7/10 placebo (4 had fever).

In NAIA1004 (vol. 64, n=31, performed in U.S.), only drug administration before virus exposure was utilized (intranasal zanamivir as drops or spray, starting 4 hr before H1N1

inoculation). Shedding and seroconversion were somewhat reduced, fever was documented in 2/6 placebo and no other subjects (8-9 per group, three groups with active drug), and there was little consistency in symptom patterns.

In NAIA1008 (vol. 71, n=47, performed in U.S.), only drug administration before H1N1 virus exposure was utilized. A single dose of zanamivir 2 days before viral inoculation did not have a salient effect, dosing started 4 days before inoculation was accompanied by reduced shedding, while the relationship between treatment and symptoms was variable, and too few placebo subjects developed fever to permit useful comparisons.

NAIA1010 ("Evaluation of the safety and efficacy of zanamivir administered intravenously as repeated doses to healthy male volunteers inoculated with influenza A/Texas/91 (H1N1) virus," vol. 73, n=16, performed in U.S., also see J Infect Dis 1999;180:586-593 published shortly after the NDA review period) used IV zanamivir and H1N1. Treatment started 4 hours before inoculation (600 mg zanamivir twice daily for 5 days, or placebo). One zanamivir subject was excluded from efficacy analysis because he shed a different strain. With that subject excluded, no other zanamivir subjects shed virus and only one seroconverted, vs 8/8 and 8/8 on placebo; fever was reduced from 7/8 to 1/7; although most zanamivir subjects reported at least one symptom at some time, the number meeting 2-symptom URI definition on 2 or more days was 8/8 placebo and 0/8 zanamivir; these comparisons reached p values below .05. Adverse events were generally compatible with influenza-like symptoms, headache was common (75% in placebo group and 50% in zanamivir group), and two serious adverse events (overall discomfort and severe headache) were both in the placebo group. Post-treatment transaminase elevations were reported in more zanamivir than placebo subjects (5/8 vs 1/8 AST, 5/8 vs 3/8 ALT), but these were reported as not exceeding 2xULN; the study report suggests that these were not drug-related because opposite changes in GGT were seen, but laboratory shifts in Tables 9 and 10 show only one placebo subject with elevated GGT (vs no zanamivir subjects), although mean and median were higher for placebo (table 8). Two subjects were also noted to have shifts to elevated triglycerides in the zanamivir group. A previous safety and tolerability study of intravenous dosing with a similar regimen (but in the absence of influenza) had not suggested hepatic abnormalities (see study NAIB1009 above under Adverse Events from Phase 1 Studies).

Comments on challenge studies:

Overall, these studies suggest that zanamivir treatment starting before virus inoculation is associated with reductions in viral shedding and with more modest reductions in symptoms of viral-like illness. Zanamivir started after virus inoculation had more variable results, with more convincing effects in influenza A studies than in the one applicable influenza B study (but with less suggestion of effect when started beyond a narrow time window after inoculation that may be more analogous to post-exposure prophylaxis than to treatment of established disease). Application of results from these studies to clinical situations is limited because of issues such as timing and route of exposure relative to treatment and use of laboratory influenza strains; however, these

results do provide supporting evidence of activity of zanamivir against influenza virus in humans. Study NAIA1010 is of interest for at least two additional reasons. Firstly, although the zanamivir dose employed is much larger than in any of the other prophylaxis or treatment studies, it suggests that administration via inhalation is not essential for activity of zanamivir. Secondly, in combination with the report of study NAIB1009, it provides a limited amount of safety data for systemic exposure vastly exceeding that likely to be achieved with the inhalation regimens that have been studied, with little evidence of major clinically evident safety concerns but with results suggesting the advisability of careful laboratory as well as clinical monitoring if regimens involving comparable levels of systemic exposure are pursued for future development.

VI-B. Influenza A versus Influenza B

In vitro studies were reported as showing no clear difference in activity of zanamivir against influenza A and influenza B in MDCK-cell-based assays (Microbiology Summary in volume 1 of NDA). In murine studies (section 2.2.4.1), the ED_{AUC10} (dose reducing viral titer AUC by a log) for zanamivir administered beginning before viral inoculation was reported as 0.027 mg/kg for influenza A/Singapore/1/57 and 0.079 mg/kg for influenza B/Victoria/102/85 using intranasal administration, and 108 mg/kg for influenza A/Singapore/1/57 and >400 mg/kg for influenza B/Victoria/102/85 using intraperitoneal administration. In ferrets, the ED_{AUC10} for zanamivir administered beginning before viral inoculation was reported as 0.32 mg/kg for influenza A/Mississippi/1/85 and 0.59 mg/kg for influenza B/Victoria/102/85 using intranasal administration.

Challenge studies with influenza A and influenza B are summarized above. The following table summarizes A vs B breakdowns from clinical trial results using the standard phase 3 endpoint (for NAIA2005 and NAIB2005, these were *post hoc* analyses in the submission dated January 20, 1999; for other studies, these are taken from the CSRs). For NAIA/B2008, the only analysis available for this review uses the combined placebo group, and the treatment was inhaled plus intranasal zanamivir. In NAIB2007 (Southern Hemisphere study with only 5 days' symptom recording, thus not expressible in terms of median time to alleviation because fewer than 50% of subjects reached the endpoint), alleviation by day 4 was 22% of 105 placebo subjects and 34% of 103 inhaled zanamivir subjects for influenza A, and 38% of 8 placebo subjects and 63% of 8 inhaled zanamivir subjects for influenza B (CSR Tables 52-53).

Table VI-B1. Median days to alleviation by standard Phase 3 definition, influenza A and influenza B

Study	Influenza A (placebo)	Influenza A (zanamivir)	Influenza B (placebo)	Influenza B (zanamivir)
NAIA2005 (placebo vs inhaled zanamivir)				
N	31	24	9	13
Median days	4.5	3.75	6.0	4.0
NAIB2005 (placebo vs inhaled zanamivir)				
N	22	20	27	28
Median days	6.25	2.5	4.5	4.25
NAIA/B2008 (combined placebo groups vs bid inhaled + intranasal zanamivir; CSR Tables 54 & 55)				
N	222	220	15	17
Median days	7.0	5.5	8.0	5.5
NAIB3001 (CSR Tables 47 & 48)				
N	109	105	51	56
Median days	6.5	4.5	6.0	4.5
NAIB3002 (CSR Tables 44 & 45)				
N	133	132	8	4
Median days	7.5	5.0	14.0	7.5
NAIA3002 (CSR Tables 44 & 45)				
N	251	307	5	3
Median days	6.0	5.5	13.5	4.5

Comment: Results from challenge and animal studies using a limited number of strains and showing only modest differences must be interpreted with great caution. The drug-after-virus challenge study with influenza B suggested somewhat less activity than several influenza A challenge studies but may have been limited by characteristics of the viral strain (for example, no subjects developed fever so effect on this outcome could not be evaluated). It is unclear whether the approximately 2- to 4-fold differences in ED_{AUC10} between single strains of influenza A and B in the drug-before-virus animal study could be at all clinically relevant, but noteworthy that these differences were observed using two different species (and two routes of administration in mice) and two strains of influenza A. Clinical trials to date have not shown any consistent difference in effect of zanamivir against naturally acquired influenza A and B, but the number of influenza B

infections has been small and it is not possible to rule out a difference based on the information currently available. Given the possibility of less activity against influenza B from the very limited comparisons in challenge and animal studies, more information about clinical outcomes in influenza B would be desirable as part of future efforts to determine optimal uses and reasonable expectations for zanamivir therapy. However, the aggregate results suggest that, in multiple preclinical and clinical settings, zanamivir has shown *in vivo* activity against both influenza A and influenza B with point estimates repeatedly favoring the active drug, although statistical significance and magnitude of effect in individual studies are variable and a confident quantitative estimate of the extent of activity may be difficult to derive from the available information.

VI-C. Resistance emergence and assay issues

Zanamivir resistance has been reported to emerge during *in vitro* studies, and may involve mutations in the hemagglutinin gene, the neuraminidase gene, or both (please see the Microbiology review for additional discussion of this and the *in vitro/in vivo* influenza A and B issues mentioned above). Some resistant isolates emerging after *in vitro* passage are described by the applicant as zanamivir-dependent (raising the question of whether zanamivir-dependent mutants could have any relevance for re-treatment or for coordinated treatment and prophylaxis in outbreak settings). In the evaluation of resistance, different assays have been used, including measurement of the ability of zanamivir to inhibit the viral neuraminidase as well as assays of receptor binding and of viral replication: some isolates may exhibit resistance using one assay while remaining susceptible when another assay is used, and the relationship between each of these assays and potential clinical events remains to be fully determined.

The number of subjects with pre- and post- or during-treatment isolates examined in the clinical treatment trials is less than 60 so far, and at least two of these have demonstrated diminished susceptibility using the plaque reduction assay. Although preserved susceptibility of the neuraminidase has been noted in such instances, the clinical significance of such isolates is not fully understood. Most of the paired samples examined from clinical trials reflect only very short periods of zanamivir exposure (*e.g.* 1 or 2 days), many of them do not reflect the proposed marketed regimen of zanamivir, and most of those from phase 3 studies were examined only with an assay of enzyme activity and not with any cell-culture-based assay. The small number of on-treatment or post-treatment isolates available for examination was attributed by the applicant to the antiviral activity of zanamivir; however, the yield of positive cultures has been very low in the placebo group (15% of day 3 cultures in NAIA3002 and 4% of day 3 cultures in NAIB3002), and the applicant has noted that throat swabs, which were used to obtain these cultures, had a "significantly lower" isolation rate than nasal washings used in some of the earlier studies.

Emergence of resistance (with a neuraminidase enzyme resistant to zanamivir inhibition) has also been noted in an immunocompromised patient who received two weeks of

nebulized zanamivir therapy for influenza B (JID 1998;178:1257-1262). Multiple viral isolates from this patient were analyzed; a mutation in the hemagglutinin gene was first identified after 8 days of zanamivir, and a mutation in the neuraminidase gene after several additional days of zanamivir exposure.

Therefore, while the data thus far suggest that emergence of resistance is not a routine rapid event during zanamivir therapy, it has been observed both *in vitro* and in naturally acquired human infection, and further surveillance is needed to determine the actual risks and consequences of treatment-emergent viral mutations. Because mutations in both hemagglutinin and neuraminidase genes contribute to resistance on the basis of available data, and it is unknown what findings may emerge with wider use, different methods of *in vitro* testing may need to be considered for the optimal collection of information relevant to resistance emergence.

VI-D. Viral Shedding

Information on viral shedding in the three principal phase 3 treatment studies has been summarized above. Concerns about the method of sampling (throat swabs, shown to be less sensitive than nasal washings) were discussed with the applicant. Additional information about quantitative virology will be discussed in a later section. Please see the Microbiology review for additional comments on microbiologic issues.

VII. Safety Update, and Summary of Death Reports from Original Submission

The Safety Update was dated January 29, 1999. This contained only SAE (serious adverse event) and death information, stating that "Other information (such as withdrawals due to adverse events and laboratory abnormalities) are not provided as no new information is forthcoming from completed summaries. This information from ongoing studies has not been entered into the database and is therefore not available." Thus, it contains no information from the ongoing study in subjects with underlying respiratory disease; the applicant had been informed that such information would be useful to risk/benefit evaluations in this important patient subgroup, and results from additional requests will be discussed further below. The safety update contains one new report of a death in follow-up to a previously reported SAE in NAIB3004, the Lithuanian nursing home prophylaxis study. This describes a patient with multiple problems who had shortness of breath, chest pain, and dyspnea "for a long time" and about one week after completing blinded study drug had left chest pain, right upper flank pain, dyspnea, and hypertension; was hospitalized "for an exudative pleural effusion, possible lung cancer, acute cholecystitis with gallbladder stones and jaundice," and it was noted subsequently that "An X-ray examination confirmed the diagnosis of pneumonia, pleural effusion and probable lung cancer." The patient was initially discharged from the hospital but later readmitted, and it is reported that he died approximately two and a half months after study completion. The report notes "The investigator considered that there

was not a reasonable possibility that pleural effusion, acute cholecystitis and possible lung cancer were related to the study medication." Because the etiologic and temporal relationships between the patient's respiratory symptomatology, any events intercurrent with drug administration, any influenza-related event that may have occurred (not determinable from summary), pneumonia, and proximate causes of death are not evaluable from the narrative supplied, more information on this patient was requested from the applicant.

In re-assessing ISS section 8, ISS case narratives, and the safety update, it appears that three deaths were reported in controlled clinical trials in the inhaled dry powder zanamivir development program up to this point, all from ongoing nursing home prophylaxis studies (no death reports from the clinical trials of inhaled dry powder zanamivir treatment for influenza). In addition to the patient from study NAIA3004 summarized above, one was a patient hospitalized for leg amputation due to peripheral artery disease two days after starting prophylactic rimantadine, who died with pneumonia about two weeks after surgery. A second was an 83 year old patient who developed upper respiratory symptoms after 8 days of prophylactic zanamivir, progressed to pneumonia with a culture positive for influenza A, and was said to have improvement in respiratory distress followed by continued deterioration and death.

There were five deaths reported in patients receiving zanamivir on an emergency or compassionate use basis (one adult with a diagnosis of influenza pneumonia unresponsive to rimantadine; a 4-year-old with leukemia hospitalized with pneumonia for two weeks before beginning zanamivir; an 11-month-old diagnosed with influenza B pneumonia during hospitalization for congenital cataract; a 4-year-old with influenza B infection post bone marrow transplant for acute lymphocytic leukemia; an 18-month-old with juvenile chronic myelocytic leukemia diagnosed with influenza B unresponsive to ribavirin post bone marrow transplant). These cases of compassionate use of zanamivir have generally specified a nebulized preparation rather than the lactose-based dry powder developed for this NDA; in keeping with the usual context for compassionate use requests, most of these patients have been extremely ill and considered at very high risk of death before receiving zanamivir, and none of the reports has suggested a specific link between the drug and the outcome. One death was reported from an ongoing NIAID study of nebulized zanamivir in hospitalized patients: this was described as a 93 year old man who developed pneumonia 24 days after completion of zanamivir treatment, and died from cerebrovascular accident and pneumonia considered unrelated to study drug.

Overall, the reported deaths have appeared to reflect underlying disease and have not provided any specific evidence of otherwise unsuspected safety problems. One patient is reported to have died with influenza A pneumonia following prophylactic use of zanamivir, and additional comparative information from ongoing studies will be important to forming any conclusions about the ability of zanamivir to prevent major adverse outcomes of influenza.

VIII. Other Data, Use, and Interpretation Issues

VIII-A. Chemistry

The original NDA did not contain some components of information that had been discussed during pre-NDA deliberations as necessary to support proposed specifications and expiration dating. The applicant indicated that this information would be contained in a later amendment. At the time of the major amendment dated March 2, 1999, which prompted extension of the review timeline, it was determined that information was still lacking; this was projected for submission in June, within a few weeks of the deadline date for the extended review timeline. Additional discussions between FDA Chemistry reviewers and the applicant led to resolution of outstanding issues through review of submitted information together with agreements regarding phase 4 commitments; please see the Chemistry review for full information.

VIII-B. Pharmacology/Toxicology

Discussions with Pharmacology/Toxicology reviewers did not disclose major issues related to the dosing regimen, duration of treatment, and patient population proposed in this NDA. An increase in lymphomas in one carcinogenicity study was reported not to meet criteria for significant concern; however, to support longer-term use of zanamivir in future applications, the applicant was asked to conduct immunotoxicology studies as a phase 4 commitment. Juvenile animal inhalation toxicology studies were also requested as a phase 4 commitment to support use of the drug in younger target populations in future applications. Please see the Pharmacology/Toxicology review for additional information.

VIII-C. Microbiology

Clinical and microbiologic review have been closely related in the evaluation of this application, especially with reference to the implications of susceptibility testing methods and viral shedding data for interpretation of clinical results. Microbiology issues are addressed in greater detail in section VI above; please see the Microbiology review for full information.

VIII-D. Biopharmaceutics

Biopharmaceutics and pharmacokinetics issues related to this review included the appropriate interpretation of pulmonary distribution studies and studies of systemic exposure. From discussion with Biopharmaceutics reviewers and also with consulting staff from the Division of Pulmonary Drug Products, it was concluded that no studies had been submitted that would adequately support a claim of topical activity according to usual expectations, but that the relevance of systemic exposure from inhaled drug was unclear for efficacy evaluations (though potentially more important for safety considerations). Dosing issues with regard to renal impairment were raised in the initial

NDA submission, with a statement from the sponsor (draft labeling in volume 1) that "significant decreases in renal clearance ... and significant increases in half-life and systemic exposure were observed" and that "no reduction in dose is recommended...." Pharmacokinetic results from subjects with impaired renal function were discussed at several stages during review with Biopharmaceutics reviewers, who indicated that most patients with mild or moderate renal impairment were unlikely to receive more exposure to zanamivir from the proposed marketed dosing regimen than the exposure received by several hundred subjects in NAIA/B2008 who received inhaled plus intranasal zanamivir four times daily (this was considered to represent a level of exposure at least as great as that received by subjects with mild to moderate renal impairment), and indeed that the two small intravenous-dosing studies (NAIA1009, described under Phase 1 Studies above, and NAIA1010, described under Challenge Studies above) represented far higher systemic exposure than the proposed marketed regimen would administer even to patients with very severe renal insufficiency. As noted in the sections above, neither the QID dosing regimen in NAIA/B2008 nor the safety data from NAIA1009 and NAIA1010 had identified major dose-related toxicities, although it was considered that collection of additional safety data would be advisable if there were plans to develop very-high-exposure regimens comparable to the intravenous regimens used in NAIA1009 and NAIA1010. Given that over 400 subjects with naturally occurring influenza-like illness received the QID inhaled/intranasal regimen in NAIA/B2008, while the intravenous dosing regimen had been administered to a far smaller number of subjects who did not have influenza-like illness on entry (and received a viral challenge in NAIA1010 but not NAIA1009), the conclusion of these interdisciplinary discussions was that there were no definite safety issues that might mandate dose adjustment for renal insufficiency, and no exposure-vs-efficacy data that would permit concluding that lower doses would be effective in renal insufficiency, but that there was not enough information to draw definitive conclusions about whether any safety issues might appear at systemic exposures comparable to those expected for severe renal insufficiency with the proposed marketed dosing regimen. Therefore, a consensus was reached that the label should indicate a lack of safety and efficacy information in the presence of severe renal insufficiency (in addition to the more general statement in the Precautions section that safety and efficacy have not been demonstrated in patients with high-risk underlying medical conditions).

VIII-E. Further examination of statistical issues

As statistical issues are integrally related to clinical evaluation of efficacy, many of these are addressed in other sections of this review. As already described, it was noted during statistical review that some subjects recorded some symptoms as moderate or greater at time points after the pre-defined primary endpoint had been reached. A number of records in which this occurred were examined as outlined under NAIB3001 above, and symptom courses appeared generally compatible with influenza. Additional analyses taking this observation into account were requested from the applicant and are summarized in additional discussions of the treatment studies, above and below.

In general, analyses of symptoms across all recording days (or at least days 1-14) yielded numerically smaller treatment differences than comparisons of median times to a stated endpoint, as would be predicted when the latter part of the study period (when symptoms have spontaneously subsided in the majority of no-active-treatment patients and treatment groups are expected to become similar in studies of a largely self-limited disease) is averaged together with the time period of acute symptomatology. The protocol-defined primary endpoint, which was defined such that it represented time to first occurrence of a defined period of diminished symptoms, allowed the possibility of subsequent symptom fluctuation. Symptoms above the threshold for the primary endpoint reportedly may have occurred after the primary endpoint was reached in a larger proportion of zanamivir than placebo recipients, but (in a supplemental analysis by the applicant) in a similar proportion of diary card timepoints in the two treatment groups. This appeared compatible with effects that might be predicted if symptoms after the primary endpoint were randomly distributed among all post-endpoint recording timepoints and zanamivir recipients (because of reaching the endpoint earlier) had the opportunity for a larger number of post-endpoint recording timepoints per subject than placebo recipients.

The question of which components of influenza-like symptomatology are most important clinically, and which components are affected by drug treatment, was also raised. It was agreed that there could be interest in exploring relationships between different components of recorded symptomatology with possible discussion of the implications for future study designs. It was not clear that any broadly generalizable conclusions about relative importance of different symptoms could be derived from the study datasets, nor that treatments could be judged on the basis of whether they were associated in post-hoc analyses with differences in specific symptom components ranked by other post-hoc analyses. Differences in means were also noted to be numerically smaller than differences in medians for some time-to-event analyses expected to have skewed distributions. The applicant was asked for analyses using different types of symptom scores over time to explore the appearance of results from the NDA studies when analyzed by methods more similar to some of the measurements used historically in studies of other influenza drugs, while acknowledging that none of these measures could be objectively determined to be preferable given the subjective and self-limited nature of the symptoms of influenza in most instances and the questionable relevance of various numerical transformations of categorical symptom descriptions: multiple different approaches to secondary analyses yielded varying point estimates and p values but overall continued to show substantial treatment effects in NAIB3002, more modest treatment effects in NAIB3001, and very modest or no treatment effect in NAIA3002.

The acceptability of different methods of diagnosing influenza positivity, and different definitions of the population for analysis (in particular, intent-to-treat versus influenza positive), were also subjects of discussion. The statistical team indicated that attempts to reproduce the applicant's analyses using the same data and methods generally produced the same results, although only selected analyses were so examined; attention was focused on the appropriateness of different approaches. Intent-to-treat and influenza positive analyses are summarized in the discussions of individual studies above, and

generally yielded similar patterns across studies but often smaller treatment effects with intent-to-treat analyses than influenza-positive analyses. This would be predicted from the assumption that zanamivir would offer no benefit to patients with influenza-like clinical illness not caused by influenza virus, but is of limited use for clinical practice because the expected effect in an intent-to-treat population could vary greatly in different seasons and populations associated with variation in the proportion of influenza-like illness actually attributable to influenza. Treatment effects in influenza-positive populations defined by different diagnostic tests were examined in some detail because of the imperfect nature of all diagnostic modalities (culture methods may have been relatively insensitive, seroconversion requires a post-randomization on-treatment antibody measurement, and other diagnostic tests were not well standardized or uniform across studies). The following table was provided by the FDA statistical reviewer for the Advisory Committee briefing document and shows no marked relationship between treatment assignment and likelihood of seroconversion, nor between diagnostic method and treatment effect, in any of the principal phase 3 treatment studies.

Table VIII-E1. Relationship between diagnostic tests and treatment effect

Study	NAIB3001 (Southern Hemisphere)	NAIB3002 (Europe)	NAIA3002 (North America)
Culture positive			
Time to alleviation, placebo (median days to alleviation)	6.0	7.5	6.0
Time to alleviation, zanamivir (median days to alleviation)	4.5	5.0	5.0
Direct test positive (e.g. immunofluorescence in SH, PCR in others)			
Time to alleviation, placebo (median days to alleviation)	6.0	7.5	6.0
Time to alleviation, zanamivir (median days to alleviation)	4.0	5.0	5.0
Percent of placebo subjects with convalescent serology results	89%	95%	81%
Percent of zanamivir subjects with convalescent serology results	90%	95%	84%
Percent of all placebo subjects with seroconversion	48%	60%	46%
Percent of all zanamivir subjects with seroconversion	45%	61%	51%
Percent of culture-positive placebo subjects with seroconversion	65%	77%	69%
Percent of culture-positive zanamivir subjects with seroconversion	59%	77%	65%
Seroconversion-positive subjects			
Time to alleviation, placebo (median days to alleviation)	6.0	7.5	6.0
Time to alleviation, zanamivir (median days to alleviation)	4.5	5.0	5.0

VIII-F. Inhalation drug use and other pulmonary issues

Two drugs with similar lactose-based inhalation devices and blister-packaged medication (Flovent Rotadisk, a corticosteroid, and Serevent Diskus, a beta-adrenergic agonist) are

marketed for treatment of asthma. Their approved labeling lists headache and ENT and respiratory symptoms among the more common adverse events that have occurred with administration of either active drug or placebo in clinical trials, and some gastrointestinal events occurring at lower frequency. These drugs are described in their approved labeling as not indicated for treatment of acute symptomatic asthma exacerbations. A third product, Ventolin Rotacaps, is a beta-adrenergic agonist marketed for treatment of acute bronchospasm using a lactose-based dry powder inhalation system with a different type of device into which a gelatin capsule containing the powder is inserted. The approved label for this product contains warnings concerning the possibility of paradoxical bronchospasm, and the possibility of inhaling capsule fragments if the capsule is damaged by handling; the adverse event list for clinical trial subjects aged 12 and over includes cough (5%) and central nervous system (2%) and gastrointestinal (2%) events.

Consultation with the Division of Pulmonary Drug Products was requested early in the review process because of that Division's familiarity with previously approved drugs using the dry powder inhaler delivery system, and frequent interactions with DPDP were maintained throughout. Specific concerns arising from this consultation included the potential for problems with use of the delivery system in the acute influenza setting as compared with chronic maintenance treatment of asthma; possible differences in safety and efficacy associated with underlying pulmonary disease of varying severity; and the need for appropriate labeling language to address such issues. Discussions with Division of Pulmonary Drug Products reviewers are reflected where appropriate in other sections of this review including considerations of safety and efficacy in high-risk subjects, inhalation device use and instructions, and labeling language and phase 4 commitments.

VIII-G. Inspections

The Division of Scientific Investigations (DSI) inspected study sites in Australia and the United States. Preliminary discussions with DSI staff included review team concerns about the diary cards in NAIB3001 and some of the recordings of reasons for discontinuation as summarized in the discussion of that study above, as well as general issues of patient instruction and device usage. Site inspection comments were taken into detailed consideration in requests to the applicant summarized in other sections of this review, such as confirmation of the use of appropriate diary card categories for the Clinical Study Reports and performance of secondary analyses stratified by baseline characteristics of subjects at study entry. DSI did not report any findings that suggested salient compromise of randomization, blinding, or validity of the data as recorded, and did not recommend additional inspections. The Inspection Summary received from DSI noted that "Although minor problems were noted, overall, the data generated appear to be acceptable in support of the pending NDA application. No follow-up action is necessary."

VIII-D. Use, Instructions, and DDMAC Issues

Discussions with the Division of Drug Marketing, Advertising, and Communications (DDMAC) were initiated at early stages in the review process with regard to patient instructions for use of the drug/device/delivery system. A formal consult request was also made during review of a proposed label comprehension study (see section XII-C).

The principal study reports included a few investigators' comments from each study indicating that subjects returned incompletely punctured medication blisters. These comments suggested that the subject tried to take a dose of study drug but did not get the device to operate as intended, and there were occasional comments stating specifically that the subject was unable to use the device properly during self-dosing. Because subjects in these studies were selected for ability to use the device and took the first dose under supervision and instruction at the study site, even a few such comments may raise concern about whether acutely ill patients who might have only the written instructions, without pre-selection or supervision, can be assumed to be able consistently to use the drug/device system effectively from the first dose onward. Other drugs on the market with similar administration systems are used on a more chronic basis and the effect of a learning curve on their efficacy may be smaller, while the likely importance of starting effective therapy soon after symptom onset to achieve maximal treatment effect may render even a brief learning period detrimental to efficacy in the treatment of acute influenza. Thus, the concern is not whether most people are capable of learning to use the delivery system but whether it can be confidently anticipated that potential patients will be able to use it immediately in the setting of acute illness.

The original NDA submission contained text instructions for patients as part of the proposed draft labeling, but it was not clear how instructions were intended to be presented to patients, and an inquiry to the applicant produced a verbal response indicating that such instructions were under development. A "mock-up" of an illustrated patient instruction leaflet was submitted January 27, 1999, and a "draft of the final version" was submitted on February 3, 1999. In addition, in response to another request the applicant submitted a brief report from an ease-of-use study conducted by a marketing research firm with 32 subjects and multiple versions of proposed patient instructions. According to the study report, some subjects had difficulty identifying the right spots to grasp and squeeze in disassembling the device to load it, puncturing medication blisters completely, and keeping the device level to avoid spilling the drug. While it was stated that the majority rated the device as somewhat or very easy to use, this question was asked without regard to any need for practice, and some subjects reportedly added a comment that the first time they encountered the instructions it would "take time" to follow them. The study report further commented that all subjects appeared healthy and alert at the time of their marketing interview, and that "Having the flu while trying to follow the instructions could impair concentration, vision, and clarity of mind to some extent." The study did not include any subjects who were over 65 or under 21 years of age or were "sick with the flu"; no information about education or literacy level was provided. The recruiting instructions specified that potential subjects "may not have

strong accents": therefore, although it was stated that three subjects were Hispanic, it is unlikely that there was major representation of potential patients whose primary language was not English.

The applicant also provided several publications referring to use of the Diskhaler or other dry powder inhaler devices (telephone facsimile communication from applicant, February 18, 1999). These described use in non-acute situations by patients already accustomed to use of inhalation medications. Of these, two articles published by the applicant described evaluation of first use of the Diskhaler. Of asthmatic patients with at least three months' inhaled steroid maintenance who received written instructions plus a video demonstration and used a demonstration Diskhaler device once, 67% were "comfortable or very comfortable" with its use, rising to 79% and 83% after 2 and 8 weeks of experience (J Asthma 1997;34:249-253). Of 326 asthmatic patients on prior inhalation therapy without recent asthma exacerbations, 58.6% "could use the Diskhaler successfully" at the first attempt with written instructions, rising to 86.2% at the second attempt and 93.6% at the third attempt (Eur J Clin Res 1992;3:45-50). Thus, some patients in these populations may have experienced some difficulty with initial use of the Diskhaler, although the majority were able to learn to use the device and expressed satisfaction with it after the initial learning period.

Discussions were carried out with the applicant regarding the issue of patient education and assessment of its effectiveness, which appeared potentially to require further examination to optimize use of this drug delivery system in this setting of short-term treatment for acute symptomatic disease. Preliminary comments on the patient instructions were provided, and inquiries were made about plans for study of patients' ability to use the system with the instructions provided under conditions of clinical practice.

IX. Pediatric Information

The original NDA submission included limited safety and pharmacokinetic information from a small single-dose study in children aged 3 through 12 (see summary of study NAIA1009 under Adverse Events in Phase 1 Studies above). The applicant has initiated a treatment study in children and a study of effect on transmission within families, from which serious adverse event information was included in the amendment dated May 10, 1999 (see below). Adolescents (age 12 and up) were included in the principal phase 3 studies submitted for the treatment indication. It was judged that some pediatric data had been provided in support of the present application and additional pediatric data are being collected, so that a base of relevant information will be available regarding use in the pediatric age group. Additional study of use of the delivery system by children was outlined in a Written Request under Pediatric Exclusivity provisions.

X. Drugs Previously Approved for Influenza Treatment

The two previous approvals of drugs for treatment of influenza do not serve for direct comparisons to the zanamivir application because they took place over widely separated time periods characterized by changes in clinical and regulatory climates and expectations for design and application of clinical trials. However, it would be inappropriate to ignore them completely, as they provide the principal illustrations of approaches to study of influenza and the problems encountered in such studies, as well as the basis for current public health recommendations. From the reviews which could be located (as some of the older ones cannot), principal points concerning studies of treatment of acute influenza illness will be summarized briefly here.

X-A. Amantadine

According to the Medical Officer's Review at the time amantadine labeling was changed from "symptomatic management" to "treatment" of influenza A (December 1979), this change was based on viral shedding data from two studies. One was a study in 54 college students who received amantadine, rimantadine, or placebo (a later publication, JAMA 1981;245:1128-1131, appears to refer to the same study); according to the review, at 48 hours 9/12 placebo, 3/11 amantadine, and 6/16 rimantadine subjects were shedding virus (log10 TCID 1.6, 0.5, 0.4). The second study (principal investigator, Knight; also included in 1976 review for symptomatic management) did not show a decrease in viral titers.

The "symptomatic management" review for amantadine involved consideration of both "symptomatic management" and prophylaxis (broadening the prophylaxis indication to all influenza A). The review (August 1976) refers to a prophylaxis approval in October 1966, a June 1968 submission for treatment and prevention that was not approved because of insufficient efficacy, and an April 1970 resubmission that also was not approved; these reviews could not be located. Focusing on the symptomatic management

indication (the drug was already marketed for prophylaxis at that time), the central evaluation of efficacy appears to have been based on five prison studies (approximately 20 to 75 subjects per study, males aged 17 to 63 years). Safety and efficacy were said to be based on seroconverters only. Antipyretic/analgesic medications were given only if the investigator believed them to be medically indicated, and few subjects appear to have received them (two subjects in one study, one subject in another study, none in the remaining three studies). Criteria for efficacy specified in the review were rate of clinical improvement (rapid, medium, slow), duration of fever, and number of subjects becoming afebrile. Approximately 18 signs and 21 symptoms were recorded; details of scoring were not readily recoverable. Principal analyses stated as showing significance in most of these studies (it is not clear when or how these were specified) were by categorization of rapid, medium, and slow responders. Rapid response was defined as "a) Temperature drop to 100F or less within and including the first 24 hours with b) 50% or more clearing of symptoms within the first 36 hours and no increase of symptoms to 50% or more of any previous high in this 36-hour period." Medium resolution was defined as "a) Temperature drop to 100F or less from 24 to 36 hours, and b) symptoms are not cleared 50% or more in the 36-hour period." Slow resolution was defined as "No temperature drop to 100F or less in first 36 hours or more and sustained there (100F). Symptoms may or may not be markedly cleared by this time."

Time to 50% improvement in signs/symptoms was stated to be shorter on amantadine in some studies but not statistically significant; absolute numbers were difficult to find but one of the studies reportedly showed mean time to 50% improvement of 36.6 hours in the amantadine group and 56 hours in the placebo group (difference of 19.4 hours). Temperature decrease was also stated to be faster on amantadine but not uniformly significant. Two additional studies were submitted but not contributory. One in a psychiatric hospital enrolled only 13 subjects of whom two were confirmed as influenza A. One in a geriatric facility enrolled 35 subjects, 28 with confirmed influenza A, of whom 9 amantadine and 8 placebo recipients had initial fever and were considered evaluable; there was said to be more rapid defervescence on amantadine between 17 and 70 hours but no significant difference in signs and symptoms or mean duration of fever between treatment groups. Two publications (JAMA 1970;211:1149-1156 and Bull WHO 1969;41:671-676) contain some of the same data as the review (and as each other); treatment difference in duration of fever at least 99F in four of the studies is given as 19.2, 32.3, 23.2, and 26 hours, each with a p value less than .05.

Five studies cited as "supportive" appear to have been reviewed from publications. One was a prison study (29 males ages 22-42) in which symptom reduction and time to defervescence were similar across treatment groups but time to "sustained" temperature reduction was less on amantadine. One was a study in otherwise healthy young adults that reported improvements in expiratory flow rate following treatment of influenza were greater on amantadine than placebo. Three were foreign studies enrolling both adults and children. One Japanese study (n=132) reported decrease in febrile course on amantadine. Two were UK studies (n=153 and n=66). The first reported no significant difference in symptoms but mean time to defervescence of 46.6 hours on amantadine and 75.1 hours

on placebo (difference of 28.5 hours); the second included two separate influenza outbreaks, reporting borderline decreases in fever duration which were "significant" when combined, no definite difference in symptoms between treatment groups, significant difference in time spent in bed (2.58 days on amantadine, 3.44 days on placebo, difference of 0.86 days). Four other studies were mentioned as "inadequate" in the review.

IX-B. Rimantadine

The review of rimantadine appears to have taken place from 1986 to 1988, followed by time lapses due to further discussion of resistance issues (including a CDC/NIH/FDA/industry meeting in 1990) and to a change in applicant, before approval in 1993. An initial Medical Officer's Review (dated May 28, 1987) recommended (p. 61) approval for prophylaxis and for therapy of uncomplicated influenza A in children, adults, and the elderly; a subsequent Medical Officer's Review (dated December 3, 1987) recommended (p. 116) approval for prophylaxis but not for therapy of established influenza A infection; the Division Director's memorandum (November 2, 1988, p. 7) recommended approval for prophylaxis in adults and children and for therapy in adults but not children. The review of treatment efficacy considered the prior amantadine studies, as well as rimantadine prophylaxis studies submitted at the same time, as supportive. Seven treatment studies were reviewed. Many of these used total sign and symptom scores of variable composition, not always available to the reviewer at the time. Evaluations appear to have been based only on subjects with influenza confirmed by culture or serology.

One study was the same study of 54 college students (45 with confirmed influenza: 14 amantadine, 19 rimantadine, 12 placebo) cited in the amantadine review. This used the 100 mg bid rimantadine dosing that was eventually approved. Amantadine symptom scores were better than either of the other treatment groups at day 2, and both active treatments had better scores than placebo at day 3; the proportion shedding virus was smaller on rimantadine than placebo on day 3; each active treatment group showed time to 50% reduction in symptom score one day shorter than the placebo group. The review (p. 45 of MOR dated December 3, 1987) additionally comments that "By day 4, 5 (28%) of the 16 patients in the rimantadine group were shedding virus as contrasted to 3 (21%) of the 9 patients in the amantadine group and 4 (33%) of the 12 in the placebo group. These latter percentages are not that divergent...." Two studies were in male prisoners given no antipyretics (one of these had amantadine, rimantadine, and placebo arms, and it is unclear whether there is overlap with the amantadine studies): these used a dose of 150 mg rimantadine bid, and showed treatment effects in time to 50% improvement of 1 day and 0.7 days. One of these enrolled 22 subjects (9 rimantadine and 9 placebo evaluable for efficacy) and the other enrolled 71 in the placebo and rimantadine groups (24 rimantadine and 46 placebo evaluable for efficacy out of 24 randomized to rimantadine and 47 to placebo; study also included 24 subjects randomized to amantadine). Symptom scores by day generally showed greater decreases in the rimantadine group than the placebo group but with p values below .05 on only an "intermittent" basis. In one of

these studies, the rimantadine group had a mean temperature of 98.5 on day 4 which rose subsequently; in the other, there was a 17 hour difference in time to temperature less than 100. The largest difference between treatment groups in temperature on a by-day basis in these two studies was 1.1 degrees F.

Two studies of rimantadine treatment were in pediatric subjects and compared rimantadine against acetaminophen. One found no difference in signs and symptoms; the other reported an early improvement (days 2 and 3) in symptoms and viral shedding followed by increases in shedding and symptoms and isolation of resistant virus from some subjects. Rimantadine is not approved for treatment in children. These studies have been published and it is noteworthy that the first (J Med Virol 1987;21:249-255) showed a greater number of children shedding virus on days 3 and 4 than on day 2 in the rimantadine group, and mean temperature in the rimantadine group at 88, 92, and 96 hours appeared by visual estimation from the published graph to be greater than 99 and higher than at any other time after 36 hours; the second (Pediatrics 1987;80:275-282) showed higher mean symptom scores in the rimantadine group on days 4 and 5 than on days 2 and 3, a higher percentage shedding virus on days 6 and 7 than on day 5, and higher mean titers of virus recovered on days 4, 5, and 6 than on day 3, and also showed each of these measurements first falling below and then rising above the placebo group. A sixth study enrolled only 5 subjects with confirmed influenza per treatment group (the reviewer considered 3 of the 5 rimantadine subjects inappropriate because of excessive or unknown duration of symptoms before study entry). A seventh, in nursing home residents, appears to have been reviewed in interim form with incomplete data (principally for safety in the initial review, with a separate review addressing interim efficacy data), and showed some differences in temperature course but no statistically confirmed differences in symptoms (although a "trend" was noted, and opinions about overall evaluation differed among reviewers in reviews dated July 24, 1987, December 3, 1987, and a review of an update dated November 14, 1988), complications, or activity between rimantadine and placebo groups; the primary analysis was noted to differ between the protocol and the study report. It was noted that 2 deaths occurred in this study, attributed to "influenza A" and "influenza A and pneumonia," both in the rimantadine group.

XI. Advisory Committee Discussion

This application was presented at a meeting of the Antiviral Drug Advisory Committee on February 24, 1999. The Committee voted against recommending approval at that time although a number of panelists indicated that additional information could alter their conclusions. Concerns raised and discussed at the meeting included the following. There was some overlap between issues raised regarding recommendations for approval and for potential future post-marketing studies.

A number of panelists felt that the treatment effects demonstrated with zanamivir were too small to provide a clear-cut benefit: this was based in part on evaluation of symptom

scores averaged over a 14-day period and considered as analogous to symptom scoring in chronic diseases. The issue of symptom recurrence or rebound after the primary endpoint was discussed, and differing opinions were expressed regarding the most appropriate primary endpoint for studies of influenza treatment.

Substantial concern was voiced over the lack of definite treatment effect in NAIA3002 and the fact that this study was performed in a North American population. There were questions about whether studies performed elsewhere could be considered on a comparable basis.

Concerns were raised that the amount of virologic information presented by the applicant was small and that more quantitative virology should be presented. Past amantadine/rimantadine studies were mentioned as a comparative example.

A desire for more information concerning patients with underlying respiratory disease, and also for more information in very-high-risk patients, was expressed. There were recommendations that emergence of resistance and transmission of influenza within families be addressed in greater detail, as well as questions regarding relationship between treatment effect and subgroup characteristics such as age and duration of symptoms at treatment initiation.

Concerns were expressed that the intended population would not be able to use the device/delivery system appropriately under conditions of acute infection on the basis of written instructions. There were also concerns that prescribing practice might not be limited to the most appropriate patient subgroups.

In the weeks following the Advisory Committee meeting, discussions took place between the review team and the applicant regarding issues discussed at the Advisory Committee meeting and the possibility of providing additional information, analyses, and proposals to address those issues. Chemistry issues were also under active discussion during this time period. A Chemistry, Manufacturing, and Controls amendment to the NDA was received and determined to be a major amendment extending the review timeline. Additional information provided by the applicant in several of the subsequent submissions will be summarized briefly below.

XII. Additional Information Submitted Following Advisory Committee Meeting

In response to the discussions of issues that took place during and in the weeks following the Advisory Committee meeting, the applicant provided a series of submissions addressing clinical and microbiology concerns and some specific requests from the review team for additional information, analyses, or proposals (distinct from the ongoing CMC submissions and from labeling language discussions which were carried on concurrently). The review team summarized in a letter of March 17, 1999, requests and suggestions for information that might assist in addressing open issues. Selected points from some of the ensuing submissions will be summarized below.