

XII-A. Amendment dated April 2, 1999

This three-volume amendment was submitted in response to the request for any available information on other approvals, expert reports, labeling in other jurisdictions, inspection findings, etc. The submission contains a copy of review information from Sweden (serving as the reference member state for the European Union mutual recognition process), and expert reports by several Glaxo Wellcome employees which overlap substantially with information elsewhere in the NDA. No information is included from the Australian review, although zanamivir approvals by both Australia and Sweden were announced in February 1999. In the Swedish review, an application was also stated to be under review in New Zealand.

Selected points from the Swedish review include the following. The application had apparently included both treatment and prophylaxis indications, and the information in support of prophylaxis was considered inadequate at this time for reasons including lack of efficacy and safety data in elderly and high-risk patients, lack of efficacy data applicable to influenza B, and lack of information on emergence of resistance particularly with once-daily dosing. The overall safety evaluation indicated "There are no safety concerns related to zanamivir" while noting that data in high risk, elderly, and asthmatic patients were limited, information was lacking for children, immunosuppressed patients, and those with severe underlying respiratory disease, and preclinical testing showed an excess of lymphomas in one animal study that was considered not to be meaningful. Questions were raised concerning limited resistance data (neuraminidase test results were said not always to agree with results of sequencing or ferret testing, and it was noted after communication with the applicant that susceptibility assays were performed after unblinding of studies), lack of benefit in subjects afebrile at study entry, limited information on influenza B and on subtype H1N1 of influenza A, the possibility of nose and throat adverse events associated with lactose inhalation, and variable results of intent-to-treat analyses (better than influenza positive in some studies, less favorable than influenza positive in some studies, enriched by pre-screening with rapid diagnostics at some centers). The primary efficacy endpoint for the treatment studies was considered appropriate. Negative results in NAIA3002 were commented upon at length, with a note that "only trends" in favor of a treatment effect were seen but that some analyses, such as censoring of influenza positive subjects with missing data without evidence of reaching the primary endpoint or analyses only of those with positive culture or serology, produced p values below .05. Questions were conveyed to the applicant on a number of points related to NAIA3002 including possible differences from the other studies in viral subtype and resistance, use of relief medications, fever at entry, and ability to handle the device. Comments on the applicant's responses to questions indicate that some but not all questions were resolved; allusions to information likely to become available in the near future make several references to a treatment study NAI30012 being conducted in elderly subjects, which does not appear to be part of the submissions yet seen by this division. The overall database, including the initial submission and the applicant's

responses to questions and comments, was considered to provide adequate documentation for a treatment indication but not for a prophylaxis indication at this time.

XII-B. Amendment dated April 7, 1999

Quantitative virology and resistance monitoring

The review team had requested a summary of quantitative virology results available from the zanamivir treatment studies. The following mean virus titers and percent virus recovery were provided for groups receiving inhaled zanamivir (without intranasal zanamivir) and placebo groups in the same studies. Units were not provided but are assumed to be probably log₁₀ TCID₅₀. No results were provided from NAIB3002 which was known from previous submissions to have 4% virus recovery in the placebo group and 2% in the zanamivir group at day 3. Although not explained in the submissions, from inquiry during a teleconference it was understood that "Day 1" was pre-treatment (as also suggested by language in the CRFs). Values represent nasal washes for NAIA2005 and NAIB2005 and throat swabs for NAIA3002; the submission states that nasal washings "are the best samples for quantitative virology" and it had previously been noted that throat swabs were much less sensitive.

Table XII-B1. Quantitative virology results, mean titer and % positive: selected studies, inhaled zanamivir (from tables on pages 5 and 6 of covering letter of April 7 submission)

Day	NAIA2005 placebo	NAIA2005 zanamivir	NAIB2005 placebo	NAIB2005 zanamivir	NAIA3002 placebo	NAIA3002 zanamivir
1	2.93 (82%)	4.44 (93%)	4.4 (100%)	3.28 (89%)	BLQ (41%)	BLQ (60%)
2	4.57 (82%)	4.04 (86%)	4.14 (94%)	3.35 (79%)		
3			1.83 (56%)	2.29 (63%)	BLQ (15%)	BLQ (8%)
4	2.11 (53%)	1.96 (43%)	0.67 (31%)	1.38 (47%)		
5			0.19 (19%)	0.57 (21%)		
6	0.57 (18%)	0.06 (14%)	BLQ (12%)	0.39 (11%)	BLQ (<1%)	BLQ (2%)
8	BLQ (0%)	BLQ (0%)				

Comment: While there was some suggestion of decrease in percent positive on zanamivir in NAIA3002 (and in the data from NAIB3002 previously reviewed), this was not clearly supported by the phase 2 study results, and the applicant's analysis of NAIA3002 in a previous submission indicated no statistically significant difference between treatment groups. It was not clear how a sample with 60% positive cultures could have a mean titer below the limit of quantitation. The applicant's discussion suggests that orally inhaled drug is not expected to produce any decrease in nasal shedding of virus ("we would expect to see reductions in virus shedding from the nose comparable to those seen with placebo but greater reductions in virus shedding from the throat in the treated group"), in contrast to expectations with systemic treatment; this suggestion may be of concern with regard to risks of continued viral transmission in an outbreak situation, regarding which more information may be obtained from ongoing studies.

BEST POSSIBLE COPY

The data summarized here show progressive declines over time in both the proportion culture-positive and the quantitative titers. Thus, these values did not suggest "rebound" such as might occur with rapid evolution of resistance, although no precise conclusions about resistance emergence (or its absence) could be drawn as already discussed.

Proposals for further studies of quantitative virology, and a brief description of plans for resistance surveillance, were also outlined in this submission. The applicant proposed to perform both nasal washings and throat swabs in a future substudy, and to monitor resistance using their neuraminidase enzyme activity assay. In a teleconference on May 14, 1999, the review team reinforced the importance of using culture samples which do not minimize the likelihood of recovering virus, and of having a cell-culture-based resistance assay in order to be able to propose any conclusions about risk (or absence) of resistance. In response to a request for information on plans to investigate antigenic variation and potential short-term investigations, the applicant indicated that post-zanamivir viral isolates have generally had fewer hemagglutinin sequence changes than involved in antigenic drift, but also indicated that preliminary investigations involving ferret antisera have been initiated. The review team requested more information on proposals for resistance monitoring.

Rises in Symptoms after Reaching Primary Endpoint

The review team had specifically requested an analysis of proportion of post-endpoint diary cards containing a sign or symptom higher than that permitted to satisfy the initial endpoint criteria. The applicant provided this for the influenza positive subjects in NAIA3002 (6% in each treatment group), NAIB3001 (8% in each group), and NAIB3002 (8% placebo, 4% zanamivir) and also indicated that of the influenza positive subjects in NAIA3002, 5% of placebo subjects and 4% of zanamivir subjects recorded a moderate or severe overall symptom score at some point after reaching the primary endpoint (21% and 20% in NAIB3001, 7% and 3% in NAIB3002). Proportion of influenza-positive subjects with a post-primary-endpoint rise in symptoms lasting more than one diary card entry was presented for the three principal phase 3 studies as follows:

Table XII-B2. Proportion of subjects with post-endpoint symptom rise lasting more than one diary card entry

Proportion with rise	NAIA3002	NAIB3001	NAIB3002
Placebo	11%	21%	17%
Zanamivir	14%	15%	10%

Comment: Although presented as similar across groups, it is of note that the placebo group has numerically more rises in NAIB3001 and NAIB3002 and the zanamivir group has more rises in NAIA3002. However, it is expected that subjects in the treatment group that tends to reach the primary endpoint sooner may have a larger number of diary cards after the primary endpoint, so that randomly distributed subsequent symptoms (such as

sporadic headaches not related to influenza or its treatment) might be recorded by a higher proportion of subject in that treatment group because they have more total timepoints available for such a recording; therefore, it is meaningful to consider the proportion of post-endpoint diary cards with higher-level symptoms as well as the proportion of subjects with these symptoms recorded.

High-risk subjects

The applicant presented a treatment-by-study interaction analysis with a p value of 0.128 as a demonstration that "there is no specific contraindication to pooled subgroup analysis, across protocols" in the principal phase 3 studies. Analysis of complications and antibiotic use was presented as already outlined in the original NDA submission. Time to primary endpoint for the aggregate high-risk subgroup in NAIA/B2008 (inhaled plus intranasal zanamivir) was presented showing shorter median times on zanamivir than placebo for the entire group and for the North American component.

Comment: The absence of a statistical interaction is not generally considered to prove homogeneity across studies, especially in the context of the many differences between studies (especially in subgroup analyses) already discussed. Because the high-risk subgroup includes far fewer subjects than prospectively planned and represents several underlying diagnoses within each study, and because initial analyses suggested differences in outcome between underlying diagnoses (*e.g.* elderly compared to respiratory or cardiovascular disease) and between studies, a pooled analysis could not be confidently considered as representing a single treatment effect applicable to all components of the populations included. Most of the studies with "high risk" population analyses available suggest some treatment benefit in this aggregate subgroup, but it is difficult to derive any statement about expectations for specified subpopulations because of the lack of consistency between studies and between diagnosis-defined groupings: if results for an aggregate "high risk" analysis are driven by one subcomponent of the "high risk" population, it is appropriate to avoid suggesting that these results can be generalized to another subcomponent with clearly different characteristics.

Additional exploratory analyses

The applicant submitted several additional analyses in patient groups defined somewhat differently from the many analyses previously presented. Some of the results are shown below. In addition, the number of days with temperature 38.3 or above was stated to be greater on placebo than zanamivir with a p value of <.001 in NAIA3002. Other exploratory analyses included an analysis of time with fever or cough greater than mild (comment: this is a *post hoc* construct based on a combination of the individual symptom scores reported to show the greatest suggestion of treatment effect in previous analyses of NAIA3002, and cannot be documented to have acquired any independent validity on this basis; other analyses with $p < .05$ at this point, after multiple analyses have already been

performed, must be interpreted with caution; they are compatible with some treatment effect but cannot be assumed to be "statistically significant").

Table XII-B3. Selected additional analyses of time to primary endpoint

Median days (flu +)	Placebo	Zanamivir	P
NAIA3002, excluding protocol violators	6.0	5.0	.014
NAIA3002, US sites	6.0	5.0	.043
NAIA2005, US sites	7.0	3.75	.012

In the large phase 2 study NAIA/B2008 (inhaled plus intranasal zanamivir or placebo, BID or QID), analyses of the two separate placebo groups were presented: placebo BID had slightly longer times to primary endpoint than placebo QID for the ITT and influenza positive populations and slightly shorter for the high-risk subgroup (reference to Table 26, provided for another purpose, indicates that high-risk North American subjects again had longer time to endpoint on placebo BID than placebo QID). Placebo QID had a somewhat higher proportion of subjects reporting adverse events during treatment (37% vs 29%), including higher occurrence of gastrointestinal (11% vs 7%) and lower respiratory (9% vs 4%) adverse events, but these were distributed among a heterogeneous assortment of specific adverse event terms and there was not a clear pattern of relationship to treatment groups. Comment: These analyses are compatible with the concern that some adverse events may be associated with lactose vehicle inhalation, but do not show a large excess of any specific adverse events, or any systematic effect on duration of illness, with more frequent administration of the placebo preparation.

XII-C. Amendment dated April 14, 1999

This amendment was submitted in response to the review team's concerns regarding the ability of acutely ill influenza subjects to promptly and accurately follow the device/delivery system instructions in the absence of instruction and supervision from a health care professional. The amendment contains a draft protocol entitled "A prospective study of consumer comprehension of the patient instructional leaflet for Relenza (zanamivir for inhalation)," in which it is proposed to survey healthy subjects in shopping malls for ease of use after they have had an opportunity to assemble the device first with the written instructions and then with a demonstration from a health care professional. This protocol was reviewed both by DAVDP reviewers and consultatively by DDMAC, and comments on the protocol and the patient instructions were provided to the applicant by telephone facsimile. In the teleconference of May 14, it was reiterated that there are concerns about use of the patient instructions in the setting for which they are designed, that telephone facsimile comments had been provided based on those concerns, and that the study should be seen as an opportunity to demonstrate that a more convincing treatment effect might be achievable with improved instructions.

BEST POSSIBLE COPY

XII-D. Amendment dated April 23, 1999

This two-volume amendment contains additional analyses and other responses. Selected points are summarized below. Again it should be noted that multiple exploratory analyses have been performed, these submissions represented only results that were selected for presentation, and summary and comments in this review will be limited to a selection appearing appropriate for further consideration on the basis of how the data may add to understanding of the NDA and/or address issues that appeared to be of concern at the Advisory Committee meeting.

The covering letter to the April 23, 1999, amendment contains the applicant's proposal for training of healthcare providers, as alluded to by the applicant at the Advisory Committee meeting and as encouraged in later discussions with the review team. As presented here, the proposal is limited to general statements, for example that marketing representatives will demonstrate the product in physicians' offices and at conventions and will make copies of the patient instructions available, and that the applicant will send a "pharmacy mailer" and be "prepared to demonstrate the device to pharmacists." Any information on specific content of educational activities, and any information differentiating the current plans from usual marketing, is lacking. In the teleconference of May 14, 1999, the applicant was again invited to provide a proposal for content of a healthcare provider training program.

Subgroup analyses of the primary endpoint by age, temperature, severity, and duration-of-illness categories that could be applied uniformly across studies had been discussed as a means of exploring the totality of evidence for identification of groups that might have greater or lesser benefit. For age, grouped exploratory analyses of subjects aged 50 and over compared to younger adults were prompted partly by the fact that the 50-64 age group is considered sufficiently high-risk by public health authorities to be under consideration as a potential target for immunization, in addition to older persons; and because very few persons 65 and over had been enrolled in treatment studies but the 50-64 and 65-and-over groups had appeared somewhat similar on initial analyses. For temperature, a cutoff approximating 101°F was selected for exploratory analyses partly because this corresponds to a common understanding of meaningful fever, and because it thus provided a clinically relevant cutoff that could be applied to analyses of studies that excluded persons with baseline temperature below a stated threshold as well as those that did not; this was also reported to be approximately the median baseline temperature for the principal phase 3 treatment studies and was therefore considered likely to provide reasonable numbers of subjects for analysis in each subgroup. Some of these analyses were presented in this submission and selected outcomes are summarized below. Graphs of time to alleviation for the primary endpoint and for time to "alleviation with no use of relief medications" were also presented in this submission. The frequency histograms of time to alleviation suggest an excess of subjects reaching the primary endpoint in the zanamivir group during the first few days of recording, an impression compatible with the frequency histograms provided by the FDA statistical reviewer for the Advisory

Committee briefing document which grouped times to alleviation differently (by full rather than half days). Unless otherwise indicated, numbers below refer to influenza positive subjects.

Table XII-D1. Principal phase 3 treatment studies, influenza positive population, time to principal alleviation endpoint

Influenza +	NAIB3001 Placebo	NAIB3001 Zanamivir	NAIB3002 Placebo	NAIB3002 Zanamivir	NAIA3002 Placebo	NAIA3002 Zanamivir
Age 12-17 (n)	6.5 (7)	4.0 (11) p=.302	4.5 (8)	4.0 (15) p=.948	5.0 (30)	4.5 (35) p=.514
Age 18-49 (n)	6.0 (121)	5.0 (125) p=.023	5.75 (102)	5.0 (101) p=.037	6.0 (166)	5.0 (219) p=.311
Age ≥50 (n)	6.25 (32)	4.0 (25) p=.999	14.5 (31)	6.75 (20) p=.006	7.0 (61)	4.5 (58) p=.126
Baseline T≤38.2C (n)	5.0 (94)	5.0 (103) p=.309	6.5 (53)	5.0 (51) p=.117	5.5 (97)	5.0 (127) p=.082
Baseline T≥38.3C (n)	6.5 (66)	4.0 (56) p<.001	8.0 (88)	5.5 (85) p=.001	6.0 (151)	5.0 (174) p=.337
Baseline severe (n) (investigator assessment)	9.0 (53)	4.0 (62) p<.001	9.25 (30)	5.0 (36) p<.001	7.5 (74)	6.0 (93) p=.106
Baseline not severe (n)	5.0 (107)	5.0 (99) p=.769	6.5 (111)	5.0 (100) p=.027	5.5 (183)	5.0 (219) p=.286

The analysis of baseline severity in this submission uses the investigator's global assessment of severity. An analysis by subject's assessment of severity at baseline, provided by the FDA statistical reviewer for the Advisory Committee briefing document, is reproduced below and does not show a comparable relationship to effect estimate.

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY

Table XII-D2. Subject-rated baseline severity and treatment effect

Subject's assessment of severity at study entry	NAIB3001	NAIB3002	NAIA3002
"Moderate" at entry – placebo (time to alleviation)	6.0	5.0	5.0
"Moderate" at entry – zanamivir (time to alleviation)	4.5	5.0	4.0
Difference	1.5	0.0	1.0
"Severe" at entry – placebo (time to alleviation)	6.5	8.5	6.5
"Severe" at entry – zanamivir (time to alleviation)	5.0	5.5	5.5
Difference	1.5	3.0	1.0
"Moderate" at entry – placebo (time to alleviation without relief medications)	5.5	5.5	7.0
"Moderate" at entry – zanamivir (time to alleviation without relief medications) •	4.5	5.0	5.0
Difference	1.0	0.5	2.0
"Severe" at entry – placebo (time to alleviation without relief medications)	8.5	9.5	8.5
"Severe" at entry – zanamivir (time to alleviation without relief medications)	5.5	6.0	9.0
Difference	3.0	3.5	-0.5

A breakdown by entry into the study within 36 hours versus more than 36 hours after symptom onset was included in the submission of April 23, 1999; this analysis was not performed for NAIB3001 because entry criteria required no more than 36 hours of symptoms or for NAIB3002 because the information reportedly was not collected. In NAIA3002, median time to alleviation was given as 6.0 days on placebo and 5.0 days on zanamivir for those entering by 36 hours ($p=.051$) and 5.0 days on placebo and 4.25 days on zanamivir for those entering after 36 hours. Small numbers of subjects from phase 2 studies were reported as showing reduced (or negative) treatment effect if entered after 36 hours; however, NAIB2007 appeared to show a greater treatment effect in those entered after than before 36 hours, as did the QID treatment group in NAIA/B2008. A new analysis of North American versus European centers in NAIA2008 is provided which shows a greater treatment effect in North American centers (1.5 days, $p=.176$, versus 1.0 day, $p=.107$, for European centers, and 1.5 days, $p=.033$, for combined analysis of BID zanamivir in influenza-positive subjects) in contrast to previous analyses with different ways of looking at placebo groups and/or geographic breakdowns, but no benefit in influenza-positive subjects 50 and over, less effect of BID treatment with higher baseline

BEST POSSIBLE COPY

temperature, and little if any benefit of QID treatment (except on time to return to normal activities). Information on entry before or after 24 hours, available more generally across studies, was provided in a later submission (May 21, 1999) and will be summarized below. Other breakdown information from phase 2 treatment studies is summarized in the following tables; estimates were unstable and interpretations were limited by very small numbers in many subgroups.

Table XII-D3. Subgroup analyses of phase 2 studies

Median days to endpoint	NAIA2005 Placebo	NAIA2005 ZI	NAIA2005 ZI2	NAIB2005 Placebo	NAIB2005 ZI	NAIB2005 ZI2
Age 12-17 (n)						
Age 18-49 (n)	4.5 (33)	4.0 (33)	3.5 (30)	4.5 (45)	3.5 (46)	3.5 (49)
Age ≥50 (n)	6.75 (6)	3.5 (3)	7.75 (4)	5.5 (4)	>26.5 (2)	3.0 (5)
Baseline T ≤38.2C (n)	4.5 (27)	3.0 (23)	3.5 (28)	4.0 (33)	3.5 (34)	3.5 (35)
Baseline T ≥38.3C (n)	5.5 (13)	4.5 (13)	2.5 (6)	8.5 (16)	3.0 (14)	3.5 (19)
Baseline severe (n) (investigator assessment)	6.0 (11)	6.5 (6)	3.5 (9)	8.5 (6)	3.5 (9)	3.5 (11)
Baseline not severe (n)	4.0 (29)	3.5 (31)	3.5 (25)	4.0 (43)	3.0 (39)	3.5 (43)
Return to normal activities	3.5	2.5	2.5	4.5	4.5	3.5

(table continued on next page)

BEST POSSIBLE COPY

APPEARS THIS WAY
ON ORIGINAL

Table XII-D3. Subgroup analyses of phase 2 studies (continued from previous page)

Median days to endpoint	NAIB2007 Placebo*	NAIB2007 Z1,Z12	NAIA/B2008 P BID	NAIA/B2008 Z BID	NAIA/B2008 P QID	NAIA/B2008 Z QID
Age 12-17 (n)	20% (5)	43%,25% (7,8)	>8.5 (9)	4.0 (23)	>8.5 (8)	6.0 (24)
Age 18-49 (n)	23% (101)	36%,40% (97,98)	7.0 (91)	5.5 (185)	5.0 (97)	5.0 (185)
Age ≥ 50 (n)	25% (12)	44%,27% (9,11)	6.0 (16)	8.0 (33)	>8.5 (19)	6.0 (32)
Baseline T _≤ 38.2C (n)	21% (87)	37%,43% (71,84)	7.0 (83)	5.0 (175)	5.5 (90)	5.0 (173)
Baseline T _≥ 38.3C (n)	29% (31)	40%,25% (40,32)	8.0 (33)	7.0 (63)	6.5 (33)	6.25 (66)
Baseline severe (n) (investigator assessment)	21% (48)	33%,35% (46,51)	7.5 (59)	6.0 (105)	5.5 (58)	6.0 (110)
Baseline not severe (n)	24% (70)	40%,39% (67,66)	6.5 (57)	5.5 (136)	5.5 (66)	5.0 (131)
Return to normal activities	52%	58%,56%	6.5	5.5	6.5	5.5

*For NAIB2007, % of group recorded as reaching endpoint (primary endpoint changed retrospectively because too few subjects reached it during symptom recording to calculate medians).

Summaries of temperature, activity score, and summed symptom scores by day were also presented in this amendment. The following table summarizes and collapses data from the presentation of activity scores. It suggests treatment differences throughout most of the treatment course in NAIB3001 and NAIB3002 with minimal or no difference between treatments in NAIA3002; but no clear "rebound" during or immediately after treatment was noted in any of the three studies (there were minor fluctuations in reported activity during the second week after most subjects appeared to have passed the acute phase of illness and recovery in each treatment group), and in NAIA3002 there was the suggestion that distributions (excess of subjects performing most or all normal activities, and deficit of subjects performing few or none of their normal activities) were in the direction of zanamivir at almost all on-treatment and post-treatment time points (despite a slight difference favoring placebo at baseline).

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY

Table XII-D4. Activity scoring, adapted from April 23, 1999, submission (%s are from number of diary card scores listed for 2 categories at each end of scale; middle "some" score is not listed; p-value is applicant's p value for treatment comparison of overall distribution of that day's scores for flu + subjects)

Normal activities performed (% of diary cards)	NAIB3001 placebo	NAIB3001 zanamivir	NAIB3002 placebo	NAIB3002 zanamivir	NAIA3002 placebo	NAIA3002 zanamivir
Day 0						
None/v. few	72%	75%	83%	81%	80%	85%
Most/all	10%	8%	4%	9%	6%	4%
p-value		.513		.434		.147
Day 1						
None/v. few	63%	55%	75%	69%	64%	61%
Most/all	13%	16%	10%	11%	11%	12%
p-value		.254		.127		.595
Day 2						
None/v. few	44%	38%	57%	44%	38%	34%
Most/all	26%	31%	17%	23%	28%	25%
p-value		.056		.016		.430
Day 3						
None/v. few	29%	22%	46%	28%	28%	17%
Most/all	41%	43%	28%	42%	45%	45%
p-value		.238		.002		.153
Day 4						
None/v. few	22%	10%	27%	19%	15%	13%
Most/all	52%	68%	39%	53%	57%	60%
p-value		<.001		.010		.102
Day 5						
None/v. few	10%	9%	21%	13%	11%	9%
Most/all	63%	75%	50%	64%	67%	69%
p-value		.007		.019		.309
Day 6						
None/v. few	8%	7%	16%	11%	7%	8%
Most/all	72%	83%	64%	77%	74%	74%
p-value		<.001		.011		.803
Day 7						
None/v. few	8%	6%	15%	11%	6%	5%
Most/all	78%	86%	70%	83%	79%	82%
p-value		.003		.018		.730

(continued on next page)

BEST POSSIBLE COPY

Table XII-D4. Activity scoring (continued from previous page)

Normal activities performed (% of diary cards)	NAIB3001 placebo	NAIB3001 zanamivir	NAIB3002 placebo	NAIB3002 zanamivir	NAIA3002 placebo	NAIA3002 zanamivir
Day 8						
None/v. few	8%	3%	19%	11%	5%	4%
Most/all	81%	92%	69%	85%	82%	85%
p-value		.005		.003		.936
Day 9						
None/v. few	7%	5%	13%	7%	5%	3%
Most/all	80%	90%	76%	84%	86%	89%
p-value		.002		.042		.446
Day 10						
None/v. few	6%	6%	12%	6%	6%	4%
Most/all	84%	91%	74%	86%	86%	91%
p-value		.016		.022		.545
Day 11						
None/v. few	5%	6%	13%	5%	5%	3%
Most/all	86%	93%	75%	89%	88%	93%
p-value		.014		.005		.568
Day 12						
None/v. few	4%	5%	12%	6%	4%	4%
Most/all	86%	92%	78%	88%	90%	92%
p-value		.014		.005		.324
Day 13						
None/v. few	7%	3%	9%	5%	3%	4%
Most/all	88%	94%	82%	89%	92%	92%
p-value		.004		.008		.837

Mean temperature and symptom scores by day are summarized below. These appear to include only subjects with diary cards available for the given time points; it was not clear from the submission how twice-daily symptom recordings were used to calculate the day's score or how the first few recordings were handled for subjects entered at different times of day. Two symptom scores were used: a sum of the subject's scores for headache, sore throat, feverishness, myalgia, and cough (5-symptom score) and a sum of the subject's scores for these five plus nasal symptoms, weakness, loss of appetite, and "overall" influenza score (8-symptom plus overall score). Applicant's p values are given; according to the submission, temperature and symptom measurements were compared using analysis of covariance with the baseline measurement as a covariate. Symptoms were expressed as a percentage of the total score obtainable if all symptoms included in

BEST POSSIBLE COPY

the sum received their maximum severity score. Both means and medians were provided; examination did not yield any obvious differences in interpretation.

Comment: There are many cautions to be observed in interpreting any calculations using symptom scores, as they arbitrarily assign equal weights to different symptoms and assume that the categorically defined diary-card scores correspond to equally spaced numerical scores. Thus, it is difficult to ascribe and interpretation with clear clinical relevance to numerical results with any combination of symptom scores (or with the "overall" score converted to a numerical measurement). In this setting, these calculations also do not show uniform results across studies and are obviously just a few among many *post hoc* analyses, but are useful if clearly understood as exploratory evaluations in the context of broadly analogous evaluations in the amantadine/rimantadine studies. In general, there is an impression that the mean symptom score fell below 50% of mean baseline score about a day earlier on zanamivir than placebo in the principal phase 3 treatment studies, influenza positive population. Phase 2 studies with smaller enrollment had more variable effects, but also did not show an evident pattern of rebound; symptom scores by day in NAIA/B2008 appeared broadly consistent with some treatment effect for North American, European, and all centers combined, BID and QID, though p values were variable and none of these groups received the proposed marketed regimen.

Table XII-D5. Temperature and symptom scores by day and treatment; NAIB3001, influenza positive

Day (NAIB 3001, flu +)	Mean T (P)	Mean T (Z)	p value	Mean 5-Sx score (P)	Mean 5-Sx score (Z)	P value	Mean 8-Sx score (P)	Mean 8-Sx score (Z)	p value
0	38.3	38.2	.670	62.6	59.7	.315	66.5	64.8	.161
1	37.9	37.8	.241	50.3	48.1	.458	56.3	54.0	.232
2	37.6	37.3	<.001	41.9	36.5	.036	48.0	43.0	.020
3	37.3	37.1	.005	34.4	27.9	.004	40.1	34.1	.005
4	37.0	36.9	.024	26.5	20.5	.005	31.8	26.6	.010
5	36.8	36.7	.305	21.5	16.5	.006	25.9	21.8	.019
6	36.8	36.7	.344	19.4	15.1	.034	22.9	18.8	.033
7	36.7	36.7	.406	17.5	13.2	.035	21.1	16.5	.019
8	36.8	36.6	.005	15.9	12.1	.054	18.5	15.0	.057
9	36.8	36.7	.092	13.7	11.0	.166	16.9	13.7	.092
10	36.8	36.7	.380	13.5	9.8	.059	15.9	11.8	.024
11	36.8	36.7	.480	12.6	9.1	.05	14.7	10.8	.035
12	36.7	36.7	.828	11.7	8.1	.029	13.5	9.4	.018
13	36.7	36.7	.648	10.2	6.9	.035	12.0	8.2	.020

BEST POSSIBLE COPY

APPEARS THIS WAY ON ORIGINAL

Table XII-D6. Temperature and symptom scores by day and treatment; NAIA3002, influenza positive (differences were smaller or absent for ITT population)

Day (NAIA 3002, flu +)	Mean T (P)	Mean T (Z)	p value	Mean 5-Sx score (P)	Mean 5-Sx score (Z)	p value	Mean 8-Sx score (P)	Mean 8-Sx score (Z)	p value
0	38.8	38.8	.699	61.8	62.5	.330	65.2	65.3	.414
1	38.4	38.1	<.001	54.6	51.4	.012	58.0	55.1	.033
2	37.8	37.6	.005	41.8	38.6	.030	46.0	43.3	.072
3	37.5	37.4	.167	32.9	27.9	<.001	36.7	32.5	.004
4	37.3	37.2	.178	26.0	21.6	<.001	29.2	25.5	.007
5	37.1	37.1	.877	20.4	17.8	.026	23.3	21.0	.072
6	37.1	37.0	.580	16.9	15.2	.110	19.5	17.9	.190
7	37.0	37.0	.718	14.5	13.2	.182	16.6	15.4	.306
8	37.0	37.0	.813	12.0	11.2	.344	14.0	13.1	.407
9	37.0	37.0	.995	10.6	10.2	.561	12.4	11.6	.401
10	37.0	36.9	.805	9.6	8.4	.188	11.2	10.1	.288
11	36.9	36.9	.867	8.5	7.4	.209	10.0	8.9	.269
12	36.9	36.9	.913	7.5	6.2	.106	8.9	7.4	.090
13	36.9	36.9	.831	6.5	5.6	.299	7.7	6.6	.215

Table XII-D7. Temperature and symptom scores by day and treatment; NAIB3002, influenza positive

Day (NAIB 3002, flu +)	Mean T (P)	Mean T (Z)	p value	Mean 5-Sx score (P)	Mean 5-Sx score (Z)	p value	Mean 8-Sx score (P)	Mean 8-Sx score (Z)	p value
0	39.0	39.0	.430	62.5	62.5	.443	65.1	65.8	.420
1	38.6	38.4	.106	55.7	51.3	.011	60.4	56.7	.008
2	38.0	37.7	.001	46.8	37.4	<.001	51.4	43.2	<.001
3	37.8	37.4	<.001	37.3	28.0	<.001	42.2	33.2	<.001
4	37.5	37.3	.003	29.5	21.4	<.001	34.1	25.0	<.001
5	37.3	37.1	.002	24.3	17.1	<.001	28.8	20.2	<.001
6	37.2	37.0	.025	21.4	13.6	<.001	24.4	17.2	<.001
7	37.2	37.1	.042	19.0	11.4	<.001	21.6	14.5	<.001
8	37.2	37.1	.096	16.5	10.3	<.001	19.2	12.8	<.001
9	37.2	37.1	.339	15.6	9.3	<.001	17.7	11.4	<.001
10	37.1	37.0	.186	13.0	8.2	.002	15.0	9.7	<.001
11	37.1	37.0	.050	12.1	7.3	.003	13.9	8.4	<.001
12	37.1	37.0	.198	11.1	6.1	<.001	12.7	7.1	<.001
13	37.1	37.0	.311	9.3	5.6	.007	11.1	6.4	.001

This submission also contains a table provided in response to a request for information on patients who developed pneumonia or other lower respiratory tract infection during treatment and prophylaxis studies. The table, which lists specified items of diagnostic information from phase 2 and 3 treatment studies and NAIA3005 (completed phase 3 prophylaxis study), was incomplete in the submission and a replacement was faxed on May 14, 1999. The applicant proposes that if all subjects diagnosed with pneumonia or bronchitis are considered as "lower respiratory infection", this diagnosis was made in 109/2074 placebo subjects (5.2%) and 103/2842 zanamivir subjects (3.6%). Looking

BEST POSSIBLE COPY

further at the table, of the 8 placebo and 11 zanamivir subjects reported as having Xray confirmed pneumonia (0.4% for each), the following diagnostic information is provided.

- NAIA2005, NAIB2005, NAIB2007, NAIA2008: no documented cases.
- NAIB2008: no placebo cases, 5 zanamivir cases (1 influenza A, 4 influenza negative).
- NAIB3001: 1 case in placebo and 1 in zanamivir group, both with influenza A.
- NAIA3002: 2 cases in placebo group (1 influenza A, 1 influenza negative); 3 cases in zanamivir group (all influenza A).
- NAIB3002: 4 cases in placebo group (2 influenza A of whom one was reported with *S. pneumoniae* and one with *H. influenzae*, 2 influenza negative); 2 cases in zanamivir group (one influenza A, one influenza negative).
- NAIA3005: one case in placebo group (influenza A), none in zanamivir group.

Comment: overall this suggests that 5 placebo subjects and 6 zanamivir subjects with confirmed influenza virus infection also had radiographically confirmed pneumonia in these studies. The analyses of all lower respiratory infections and of confirmed pneumonia do not suggest that zanamivir particularly predisposes patients to this complication but also do not demonstrate a reduced risk as might have been hoped with effective influenza treatment.

**APPEARS THIS WAY
ON ORIGINAL**

XII-E. Amendment dated May 6, 1999

The principal new information in this amendment is the construction of an "amantadine-like" analysis of outcomes in the three principal phase 3 studies. This submission also contains the applicant's summary of selected components of amantadine and rimantadine review information obtained from the FDA through FOIA. Based on the rapid/medium/slow resolver analyses used in the original amantadine studies as already summarized above, the applicant defined these categories as follows using selected elements of the data available from the phase 3 zanamivir studies.

Rapid resolver was defined as "Temperature drop to <100°F (37.8°C) at 24 hours of treatment (on both measurements) **and** 50% or greater reduction from pretreatment value in composite symptom score for the major symptoms (cough, headache, myalgia, sore throat, and feverishness) at 24 hours or 36 hours **and** no subsequent increase in composite symptom score to ≥ 50% of baseline value on any occasion from 48 hours to day 14."

Medium resolver was defined as "Temperature drop to <100°F (37.8°C) at 36 hours of treatment (on both measurements), with or without a ≥ 50% reduction in composite symptom score at 36 hours **and** not a rapid resolver."

Slow resolver was defined as "Not a rapid or medium resolver (i.e., temperature did not decline to <100°F (37.8°C) at 36 hours."

Missing was defined as "no composite symptom score (at 24 or 36 hours) or no temperature recorded (at 24 or 36 hours)." Scores were calculated as the numerical sum of scores recorded for the five symptoms noted; other symptoms recorded in the phase 3 zanamivir studies were apparently not included in the analysis included in this submission. Results of the analysis so defined are summarized in the table below. The p values using a Wilcoxon test are given as .019 for NAIB3001, .002 for NAIB3002, and .013 for NAIA3002.

Table XII-E1. "Amantadine-like" analysis of phase 3 studies (using 5 symptoms)

"Amantadine-like analysis"	NAIB3001 placebo (n=160)	NAIB3001 zanamivir (n=161)	NAIB3002 placebo (n=141)	NAIB3002 zanamivir (n=136)	NAIA3002 placebo (n=257)	NAIA3002 zanamivir (n=312)
Rapid	14 (9%)	23 (16%)	10 (7%)	18 (13%)	25 (10%)	45 (15%)
Medium	95 (64%)	96 (67%)	47 (33%)	61 (46%)	117 (48%)	152 (52%)
Slow	40 (27%)	25 (17%)	84 (60 %)	55 (41%)	104 (42%)	97 (33%)
Missing	11	17	0	2	11	18

Comment: This construction of an "amantadine-like" analysis must be interpreted with great caution, firstly because it is modeled on studies from more than 20 years ago which could not be taken as appropriate models for contemporary clinical trials and secondly because it is one of many *post hoc* analyses in this NDA. Therefore, its results neither document comparability to amantadine (a comparison for which no direct information is available) nor provide an independent demonstration of efficacy. However, it is useful to have available because it provides additional perspective on the zanamivir studies in the context of other available information about studies of influenza, and illustrates the possibility that the three principal zanamivir treatment studies may appear more similar in certain specialized analyses than in their primary analyses. It is also noteworthy that an analysis using all symptoms measured to assess the symptom reduction in the definition of rapid/medium/slow resolvers would appear more similar to the categories defined in the amantadine review than the analysis presented which uses only five symptoms to form the aggregate score; if an analysis using all recorded symptoms was performed, it has not been submitted.

XII-F. Amendment dated May 10, 1999

This amendment is devoted principally to safety information. Additional information on influenza negative subjects is provided in response to the concern that in NAIA3002, the influenza negative subgroup showed a longer median time to the primary endpoint on zanamivir than on placebo (point estimates differing by one day). This submission for the first time provides p values for treatment differences in the influenza negative subgroups of the principal phase 3 studies (NAIB3001 p=.486, NAIA3002 p=.712, NAIB3002 p=.551). The applicant provides temperature, activity, and adverse event summaries concluding that there is no difference between treatment groups in influenza negative subjects. The time to return to normal activities (Table 440) is reported as 7.25 days for placebo and 7.0 days for zanamivir subjects in NAIA3002 (while the influenza positive

BEST POSSIBLE COPY

subgroup showed no treatment difference for this outcome). Individual symptom breakdowns are not provided. The summary of maximum daily temperature (Table 441) shows mean temperature to be 0.1 degree higher in the zanamivir group at baseline (though the median is 0.1 degree lower); the mean is 0.1 degree higher on days 1, 2, and 5, 0.1 degree lower on day 10, identical on days 7, 8, 9, 11, 12, and 13, and 0.2 degrees higher on days 3, 4, and 6. Investigator global assessment post-treatment is very similar between treatment groups. The adverse event listings that are provided for NAIA3002 do not show striking treatment differences, nor do those presented for the other treatment studies. Thus, overall results do not clearly show either harm or benefit in subjects without a positive diagnostic test for influenza.

Preliminary safety information is provided for NAIA3003, an ongoing nursing home prophylaxis study in which control subjects receive rimantadine during influenza A outbreaks and placebo only during influenza B outbreaks. The tabulations provided indicate that 126 rimantadine subjects, 127 zanamivir subjects, and no placebo-only subjects are included in the update (treatment once daily for 14 days). Of these, 12 (10%) of rimantadine and 10 (8%) of zanamivir subjects discontinued study drug early, 10 (8%) and 9 (7%) due to adverse events. Selected adverse events (>5% in either group, or special interest) are listed in the following table.

Table XII-F1. Preliminary adverse event reports from NAIA3003

Event (during treatment)	Rimantadine (n=126)	Zanamivir (n=127)
Any AE	77 (61%)	79 (62%)
Any cardiovascular event	5 (4%)	4 (3%)
Heart failure	1	1
Any ENT event	31 (25%)	31 (24%)
Nasal signs & symptoms	18 (14%)	14 (11%)
Throat/tonsil discomfort & pain	14 (11%)	14 (11%)
Vocal cord disorders	5 (4%)	11 (9%)
Nasal inflammation	6 (5%)	8 (6%)
Any eye event	5 (4%)	5 (4%)
Blindness & low vision	0	2 (2%)
Any GI event	27 (21%)	33 (26%)
Constipation	7 (6%)	12 (9%)
GI signs & symptoms	8 (6%)	9 (7%)
Diarrhea	6 (5%)	8 (6%)
Abnormal LFTs	2 (2%)	0
Any lower resp event	27 (21%)	28 (22%)
Cough	25 (20%)	27 (21%)
Any musculoskeletal event	14 (11%)	21 (17%)
Musculoskeletal pain	7 (6%)	14 (11%)
Any neurologic event	17 (13%)	27 (21%)
Headaches	10 (8%)	16 (13%)
Dizziness	2 (2%)	7 (6%)
Malaise & fatigue	13 (10%)	16 (13%)
Temp. regulation disturbances	8 (6%)	6 (5%)
Any psychiatric event	2 (2%)	2 (2%)

(table continued on next page)

BEST POSSIBLE COPY

Table XII-F1. Preliminary adverse event reports from NAIA3003 (continued from previous page)

Event (post treatment)	Rimantadine (n=126)	Zanamivir (n=127)
Any AE	45 (36%)	56 (44%)
Any ENT event	7 (6%)	5 (4%)
Any GI event	12 (10%)	19 (15%)
Constipation	4 (3%)	7 (6%)
Any musculoskeletal event	11 (9%)	8 (6%)
Musculoskeletal pain	7 (6%)	5 (4%)
Any neurologic event	11 (9%)	17 (13%)
Headaches	6 (5%)	9 (7%)
Any psychiatric event	2 (2%)	2 (2%)
Any drug-related AE during treatment	51 (40%)	58 (46%)
Any drug-related AE post treatment	6 (5%)	10 (8%)

A request was conveyed to the applicant on May 17, 1999, for more information on the two reports of "Blindness & low vision" in the zanamivir arm, which were classed as possibly drug related. (A communication of June 24, 1999, in response indicated that these referred to transient episodes of blurred vision.) Because this study was designed to use inhaled lactose as a placebo, it cannot be determined whether some of the ENT events occurring in the rimantadine arm could be associated with lactose inhalation. Overall, little difference was seen in adverse event profiles between the zanamivir group and the rimantadine (plus lactose vehicle) group. Laboratory data reports were also similar.

Preliminary safety data are also provided for NAIA3004, a placebo-controlled nursing home prophylaxis study being carried out in Lithuania, with a reported enrollment at the time of the safety update of 84 placebo and 83 zanamivir subjects, of whom 2 zanamivir and no placebo subjects discontinued study medication due to adverse events. Treatment regimen was once daily for 14 days. Selected adverse events are summarized below.

Table XII-F2. Preliminary adverse event reports from NAIA3004

Event	Placebo	Zanamivir
During treatment		
Any AE	27 (32%)	32 (39%)
Any blood & lymphatic	6 (7%)	6 (7%)
Any ENT	4 (5%)	6 (7%)
Any GI event	2 (2%)	5 (6%)
Abnormal LFTs	2 (2%) (1 drug-related)	6 (7%) (1 drug-related)
Abnormal bilirubin levels	3 (4%) (1 drug-related)	0
Cirrhosis	0	1 (1%)
Cholestasis	0	1 (1%)
Any lower respiratory	1 (1%)	6 (7%)
Any neurology	5 (6%)	6 (7%)
Headaches	1 (1%)	2 (2%)
Any psychiatric event	2 (2%)	4 (5%)

(table continued on next page)

BEST POSSIBLE COPY

Table XII-F2. Preliminary adverse event reports from NAI3004 (continued from previous page)

Event	Placebo	Zanamivir
Post treatment		
Post treatment, any AE	19 (23%)	18 (22%)
Increased WBC	2 (2%)	5 (6%)
Abnormal bilirubin levels	5 (6%) (1 drug-related)	6 (7%) (5 drug-related)
Abnormal LFTs	3 (4%) (1 drug-related)	2 (2%) (1 drug-related)

The laboratory tables suggest that differences between treatment groups in hepatic tests may have been present at baseline; however, results of similar tests were also examined in other studies without finding comparable patterns, and additional information was requested from the applicant (see Amendment Dated June 24, 1999, below). Overall the most striking finding in this study was the lower frequency of reporting of many individual adverse events compared with other studies.

Safety and pulmonary function test information were provided for NAI30008, a treatment study being conducted in subjects who have a diagnosis of asthma or COPD. Summaries of pulmonary function tests included baseline, day 6, and day 28 (no pre- and immediately post-dose comparisons as in the phase 1 trial in asthma patients). This interim analysis included 85 placebo and 78 zanamivir subjects, of whom 3 zanamivir subjects discontinued trial medication early (1 AE, 1 consent withdrawn, 1 protocol violation) and 2 had unknown completion status (all placebo subjects completed medication). Selected adverse events are summarized below.

Table XII-F3. Preliminary adverse event reports from NAI30008

Event	Placebo (n=85)	Zanamivir (n=78)
During treatment: any AE	41 (48%)	35 (45%)
Any ENT	14 (16%)	9 (12%)
Sinusitis	4 (5%)	4 (5%)
Any GI event	10 (12%)	7 (9%)
Diarrhea	4 (5%)	5 (6%)
Any neurology	2 (2%)	6 (8%)
Any lower respiratory event	23 (27%)	17 (22%)
Asthma	12 (14%)	11 (14%)
Bronchitis	7 (8%)	4 (5%)
Cough	4 (5%)	2 (3%)
Lower respiratory infection	1 (1%)	2 (3%)
Chest sounds	0	1 (1%)
Lower respiratory failure	0	1 (1%)
Bacterial respiratory infections	1 (1%)	0
Tracheitis	1 (1%)	0
Lower respiratory hemorrhage	1	0
Chronic obstructive airways disease	1	0
Breathing disorders	1	0

(table continued on next page)

BEST POSSIBLE COPY

Table XII-F3. Preliminary adverse event reports from NAI30008 (continued from previous page)

Event	Placebo (n=85)	Zanamivir (n=78)
Post treatment: any AE	22 (26%)	33 (42%)
Any ENT	5 (6%)	9 (12%)
Sinusitis	1 (1%)	4 (5%)
Throat/tonsil discomfort & pain	1 (1%)	3 (4%)
Any GI event	3 (4%)	11 (14%)
Any neurologic event	4 (5%)	6 (8%)
Any lower respiratory event	10 (12%)	12 (15%)
Asthma	6 (7%)	7 (9%)
Bronchitis	3 (4%)	3 (4%)
Cough	1 (1%)	2 (3%)
Viral respiratory infections	1	1
Lower respiratory infections	0	1
Pleuritis	0	1
Lower respiratory hemorrhage	0	1
Breathing disorders	0	1
Lower respiratory failure	1	0

Adverse events leading to drug discontinuation were listed as tachyarrhythmias, sleep disorders, panic, and psychomotor disorders, apparently all in the same patient. Events suggested as occurring post-treatment include a number of reported for organ systems not likely to be affected by the underlying asthma or COPD and not confirmed to be frequent or of concern in other studies. Overall, these preliminary results do not suggest that zanamivir is associated with an excess of respiratory complications in this group of subjects with underlying respiratory disease – but also do not suggest any marked decrease in respiratory complications of influenza attributable to zanamivir treatment.

PFT results suggested little difference between treatment groups in mean and median FEV1 and PEFr under the conditions of measurement. Comparisons between baseline and post-treatment values suggested that a subgroup of these high-risk subjects may have had PFT changes associated with zanamivir, as summarized below. The applicant emphasized that these changes did not have clear clinical correlates or associations with discontinuation from the study (discussion at meeting on July 1, 1999).

Table XII-F4. Preliminary PFT results from NAI30008 (from tables 478 and 479 of May 10 submission)

% decrease from baseline (number of subjects, %)	FEV1, placebo	FEV1, zanamivir	PEFR, placebo	PEFR, zanamivir
Day 6	n=76	n=72	n=82	n=71
No decrease	45 (59%)	48 (67%)	57 (70%)	55 (77%)
Decrease >0-10%	19 (25%)	8 (11%)	14 (17%)	9 (13%)
Decrease >10-20%	7 (9%)	5 (7%)	8 (10%)	2 (3%)
Decrease >20-30%	3 (4%)	5 (7%)	2 (2%)	3 (4%)
Decrease >30-40%	1	4 (6%)	1	0
Decrease >40-50%	1	1	0	2 (3%)
Decrease >50-60%	0	1		

(table continued on next page)

BEST POSSIBLE COPY