CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-036/S-001

STATISTICAL REVIEW(S)

Statistical Review and Evaluation

NDA 21-036s
Drug name: Relenza (zanamivir for inhalation)
Applicant: GlaxoWellcome, Inc.
Drug class: P
Indication: Treatment of influenza in pediatric patients

Volumes received: 1, 4-11 dated 25 October 1999
(Received CDER 26 October 1999)
2 floppy diskettes containing datasets for NAI30009 and 30010
Amendments
Reviewer: Z. Jonathan Ma, Ph.D., HFD-725
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Introduction

Zanamivir (Relenza) was approved by the Agency on July 26, 1999 for an indication of treatment of influenza in adults and adolescents (>12 years old). The approved dosing regimen was 10 mg inhaled twice daily for 5 days.

The current supplemental NDA is intended to gain an approval for the same indication in pediatric patients (5-12 years). This submission contained three clinical studies: NAIA1009, NAI30009 and NAI30010. This statistical review focuses on the efficacy evaluation of NAI30009, which provided the primary support for the efficacy claims in this pediatric submission. A short section on NAI30010 is included to support and confirm the efficacy findings of NAI30009. For safety evaluation, see the Medical Officer's review.

Study Design of NAI30009

Title: A double-blind, randomized, placebo-controlled, parallel-group, multicenter study to investigate the efficacy and safety of zanamivir (GG167) 10 mg administered twice daily for 5 days in the treatment of symptomatic influenza A and B viral infections in children ages 5-12

The study recruited pediatric patients aged 5-12 years (male or female). To be eligible for the study, they were required to have influenza-like symptoms as defined by the presence of fever (temperature ≥37.8°C) and, in the judgment of the Investigator, no other clinical evidence of bacterial infection.

The subjects were centrally randomized to receive 5-day zanamivir or placebo of two inhalations (via ROTADISK/DISKHALER) twice daily at approximately 12-hour intervals. The first dose of zanamivir was to be administered on Study Day 1, within the first 36 hours (1.5 days) of their influenza-like symptoms. Subjects were requested to attend a Post-treatment Visit (Study Day 6) on completion of study treatment and a Follow-up Visit on Study Day 14. The patient Diary Cards were filled out by their parents twice daily (approximately 8.00 a.m. and at bedtime) for 14 days (or up to 28 days if symptoms were not alleviated on Day 14).

The study design of 30009 is summarized in Table 1.

Table 1. Summary of Study NAI30009

Overall Design	Multi-center, placebo-controlled, randomized, double-blind, Parallel-Group
Study Treatment	Zanamivir (10 mg, bid)
Control Treatment	Placebo
Duration of Treatment	5 days
Duration of Follow-up	14 - 28 days
Patient Population	Children ages 5-12 years with flu-like symptoms
Primary Efficacy Endpoint	Time to symptom alleviation
Secondary Efficacy Endpoints	Time to alleviation of clinically significant symptoms of influenza and no use of relief medication; time until the subject returned to normal activities; incidence of complications of influenza, etc.
Sample Size	Intent-to-treat (ITT): 471 (224 on zanamivir, 247 on placebo) Influenza positive (IP): 346 (164 on zanamivir, 182 on placebo)
No. of Centers	67 sites: 36 in the US; 6 in Canada and 25 in Europe/Israel

Study Population of NAI30009

The study was carried out between January 11 and April 19, 1999. Subjects were enrolled in a total of 67 sites, including 36 sites in the US, 6 sites in Canada and 25 sites in Europe/Israel.

Among the 471 randomized subjects, 224 received zanamivir and 247 received placebo. Of them, 346 (73%) were laboratory-confirmed influenza positive, including 226 (65%) influenza A cases and 120 (35%) influenza B cases.

The sponsor performed the primary efficacy analyses based on three different patient populations: intent-to-treat (ITT), influenza positive (IP) and per-protocol. The ITT population was defined as all subjects randomized to treatment. The IP population was defined as all subjects who took at least one dose of study medication and had a positive influenza lab test. The Per-Protocol population was defined as all subjects in the IP population who had no major protocol deviations.

The IP population was considered as the primary population for efficacy evaluation, although results based on ITT and Per-Protocol were sometimes presented for purpose of confirmation and comparisons. The sample sizes of the three populations are shown in Table 2.

Table 2. Summary of Sample Sizes

Population	Placebo	Zanamivir	Total
Intent-to-Treat	247	224	471
Influenza Positive	182	164	346
Influenza A	120	106	226
Influenza B	62	58	120
Per-Protocol and Influenza Positive	172	159	331

Table 3 presents demographics characteristics for the ITT and IP populations. There was no detectable difference between the two treatment groups with respect to these variables.

Table 3. Demographics (Intent-to-Treat and Influenza Positive Populations)

	Intent-to-Treat		Influenza Positive	
	Placebo	Zanamivir	Placebo	Zanamivir
	N=247	N=224	N=182	N=164
Female (n)	116 (47%)	97 (43%)	91 (50%)	68 (41%)
Male (n)	131 (53%)	127 (57%)	91 (50%)	96 (59%)
Mean age (years)	8.9	8.5	9.0	8.6
White (n)	223 (90%)	201 (90%)	162 (89%)	148 (90%)
Mean height (cm)	137.6	134.7	138.1	134.6
Mean weight (kg)	35.5	32.7	35.5	32.7

Primary Efficacy Analysis of NAI30009

The primary efficacy endpoint was the time from treatment initiation to the first entry of the confirmed symptom alleviation. The protocol defined primary efficacy analysis was based on Wilcoxon's rank sum test in the IP population.

Symptom alleviation was defined as no fever (temperature < 37.8°C), cough as "none" or "mild", and muscle/joint aches and pains, sore throat, feverishness/chills and headache recorded as "absent" or "minimal" (i.e., scores <2). Confirmed symptom alleviation required 3 consecutive diary card entries, which cover a period of at least 36 hours. Missing entries were ignored for the purpose of calculating the three consecutive entries.

Subjects who had no qualified alleviation were treated as treatment failures and included in the analysis as alleviating after the end of the study.

The sponsor's analyses are presented in Table 4. The median time to alleviation was 5.25 days for the 182 IP patients on placebo and 4.0 days for the 164 IP patients on zanamivir. The difference in median days between the two treatment groups was 1.25 days, which was statistical significant ($p<0.001$) based on Wilcoxon's rank sum test.

Since the diary cards were recorded in every 12-hour interval, time to symptom alleviation was reported in a unit of 0.5 day, such as 2.5, 3.0, 4.5, 6.5, etc. In Table 4, the 182 IP patients on placebo had a median of 5.25, which was obtained as the average of 5 and 5.5, because exactly 91 patients alleviated before 5 days (inclusive) and exactly 91 patients alleviated after 5.5 days (inclusive).

In fact, it would take only one observation for the median of the placebo group to swing between 5 and 5.5. To be more specifically, the median of the placebo group would have been 5 days if one patient had shifted from ≥5.5 days to ≤5 days. Likewise, the median would have been 5.5 days if one patient had shifted from ≤5 days to ≥5.5 days. Hence, the median difference between zanamivir and placebo would be either 1 or 1.5 days, representing an up to 50% variation. Therefore, one must use caution when using the median difference to describe the efficacy of zanamivir under this situation. More discussion on this issue can be found in the Discussion section.

As shown in Table 4, the sponsor also conducted sensitive analyses on two slightly different endpoints: time to alleviation without rise in future symptom score and time to alleviation without rise in future symptom score lasting >1/2 day. The primary comparisons between the two treatment groups in IP population remained statistically significant ($p < 0.001$ and $p=0.041$, respectively), while the difference in median days varied from 0.5 to 2 days. The variation on the median difference reflected possible different patterns in symptom rebound after reaching alleviation between the placebo and zanamivir group. More investigation on this issue can be found in the Discussion section.

Table 4. Primary Efficacy Analyses: Time to Alleviation (Based on Different Criteria) (Wilcoxon's rank sum test, missing = 99, sponsor's analyses)

Population		N	Median days	Difference in median days	P value
Time to alleviation of clinically significant signs and symptoms of influenza					
Influenza Positive	Plb	182	5.25		
	Zanamivir	164	4.0	1.25 (0.5, 2.0)*	<0.001
ITT	Plb	247	5.0		
	Zanamivir	224	4.5	0.5 (0.0, 1.5)*	0.011
Per Protocol	Plb	172	5.0		
	Zanamivir	159	4.0	1.0 (0.5, 2)*	<0.001
Time to alleviation without rise in future symptom score					
Influenza Positive	Plb	182	7.5		
	Zanamivir	164	5.5	2.0	<0.001
ITT	Plb	247	7.0		
	Zanamivir	224	5.5	1.5	0.012
Per Protocol	Plb	172	7.25		
	Zanamivir	159	5.5	1.75	0.001
Time to alleviation without rise in future symptom score lasting >1/2 day					
Influenza Positive	Plb	182	5.5		
	Zanamivir	164	5.0	0.5	0.041
ITT	Plb	247	5.5		
	Zanamivir	224	5.0	0.5	0.223
Per Protocol	Plb	172	5.5		
	Zanamivir	159	5.0	0.5	0.057

*confidence interval of difference between medians was calculated using the percentile bootstrap method

In the following, I would like to discuss [redacted] and perform alternative analyses.

A closer inspection of the data revealed an imbalance in the number of missing observations between the two treatment groups. A total of 41 ITT patients had missing values for time to alleviation, including 30 (12%) from placebo and 11 (5%) from zanamivir. Among them, 27 patients were influenza positive patients, including 21 (12%) from placebo and 6 (4%) from zanamivir. The difference was statistically significant by a chi-square test ($p=0.006$). In other words, there was a statistically significant difference in the number of missing observations between the placebo and the zanamivir groups.

No analysis on the missing data was found in sponsor's study report. Missing observations could occur in two ways: lost to follow up before reaching alleviation, or failed to reach alleviation by the end of the study. The 21 missing values from the IP placebo group were (days): 1, 1.5, 2, 2.5, 4.5, 5, 6, 7.5, 8.5, 12, 12, 12.5, 13, 13, 13, 13, 13.5, 13.5, 23, 24, and 26.5 with a median of 12 days. The 6 missing from the IP zanamivir group were (days): 0, 0, 0, 11.5, 13 and 23 with a median of 5.75 days. It appears that most of the missing occurred within the first phase of follow up period (14 days).

In sponsor's analyses, however, all missing subjects were considered as reaching alleviation after the end of the study and were assigned 99 days for time to alleviation. This is not necessarily a conservative approach. By doing this, the sponsor's analyses inflated the estimates of the median time to alleviation in both groups because most censored subjects would have reached alleviation within 28 days (longest follow-up period) rather than beyond 28 days.

Unfortunately, with a significantly more missing observations from the placebo group than from the zanamivir group, the inflation on the median time to alleviation of the placebo group was likely to be larger than that of the zanamivir group. Hence, the difference of the medians of the two groups was likely to be artificially inflated as well.

I performed the following analyses treating missing as censored at the time of loss to follow up. There were 3 patients (subject IDs: 18471, 30222 and 30255) who did not have any post-dose observation. They are treated as being censored at time zero. The corresponding non-parametric test used is generalized Wilcoxon's test (also called Gehan's test). The results are presented in Table 5.

Table 5. Primary Efficacy Analyses: Time to Alleviation
(Logrank test and Generalized Wilcoxon test, missing treated as censored)

Time to alleviation of clinically significant signs and symptoms of influenza						
Population		N	Median	P-Z	P value	
					Wilcoxon	Logrank
Influenza Positive	Placebo	182	5.0			
	Zanamivir	164	4.0	1.0 (0.5, 2.0)	<0.001	<0.001
ITT	Placebo	247	5.0			
	Zanamivir	224	4.0	1.0 (0.5, 1.5)	0.010	0.001
Per protocol	Placebo	172	5.0			
	Zanamivir	159	4.0	1.0 (0.5, 2.0)	<0.001	<0.001

Compared to sponsor's analyses, all tests remained statistically significant, but the difference in median days was consistently 1.0 day, instead of sponsor's 1.25 days.

I also performed the following additional comparisons and tests, where missing data were excluded. The results are presented in Table 6. For IP population, again, the p values remained significant and the median difference was 1.0 day. It should be noted that t-test may not be a valid test here because the samples were not normally distributed. However, the 0.95 day difference in the means may be viewed as a confirmation for the 1-day median difference between the two groups in the IP population.

Table 6. Primary Efficacy Analyses: Time to Alleviation
(T-test and Wilcoxon's Rank Sum test excluding missing data)

	Placebo	Zanamivir	P-Z	P-value
Influenza Positive	(N = 161)	(N = 158)		
t-test (mean ± s.e.)	5.4 ± 0.25	4.4 ± 0.25	0.95 ± 0.35	0.007
Wilcoxon test (median)	5.0	4.0	1.0	0.009
ITT	(N = 217)	(N = 213)		
t-test (mean ± s.e.)	5.1 ± 0.23	4.8 ± 0.23	0.35 ± 0.32	0.28
Wilcoxon test (median)	5.0	4.0	1.0	0.18

Subgroup Analyses of NAI30009

Possible interactions between treatment and potential risk factors are investigated in Table 7, where the median time to alleviation is tabulated by subgroups on influenza type, gender, race, age, vaccination status, time from onset of symptoms, high risk group, and country. Unless specified otherwise, the discussion focuses on the IP population, although results on ITT population are also presented in Table 7. Again, I employed the generalized Wilcoxon's test where the missing observations were treated as censored.

I first performed analysis based on Cox proportion hazard model:

Time to alleviation = treatment + subgroup variable + treatment × subgroup variable.

The p values for the interaction terms were not significant (shown in the last column of Table 7), indicating that no significant interaction was detected by the Cox model. Nonetheless, potential interaction issues are discussed in the following.

For patients with influenza A, a 1-day difference in the median time to alleviation between zanamivir and placebo was observed (5 days vs. 4 days). The p value was marginally non-significant (p=0.055). For patients with influenza B, the median difference was 2 days between zanamivir and placebo groups (6 days vs. 4 days) and the p value was statistically significant (p=0.0003).

The difference in median days was 1 day in male patients and 0.5 day in female patients, statistically significant in both sexes. For white patients, the treatment difference in median was 1.0 day and was statistically significant (p=0.0002). No treatment effect was detected in the non-white subjects that represented about 8% of the study population.

Again, as pointed out earlier, the measurement unit was 0.5 day and a particular median difference may not portray an accurate treatment effect of zanamivir in this situation.

Table 7. Subgroup Analyses for Time to Alleviation
(Missing was treated as censored, reviewer's analyses)

	Subgroup	Placebo		Zanamivir		P – Z	Wilcoxon P value	Interaction P –value*
Overall								
	IP (Influenza Positive)	182	5.0	164	4.0	1.0	0.0003	
	ITT (Intent-to-treat)	247	5.0	224	4.0	1.0	0.010	
IP	By Influenza Type							
	Influenza A	120	5.0	106	4.0	1.0	0.055	0.18
	Influenza B	62	6.0	58	4.0	2.0	0.0003	
IP	By Demographic Group							
	Sex: Females	91	5.0	68	4.5	0.5	0.021	0.58
	Males	91	5.0	96	4.0	1.0	0.008	
	Race: White	162	5.5	148	4.0	1.5	0.0002	0.28
	Non-white	20	4.0	16	4.0	0	0.92	
	Age: 5-8	75	5.0	78	4.0	1.0	0.027	0.95
	9-12	107	5.5	86	4.25	1.25	0.008	
ITT	By Demographic Group							
	Sex: Females	116	5.0	97	4.5	0.5	0.034	
	Males	131	5.0	127	4.0	1.0	0.14	
	Race: White	223	5.0	201	4.0	1.0	0.009	
	Non-white	24	4.0	23	4.5	-0.5	0.86	
	Age: 5-8	105	5.0	106	4.0	1.0	0.19	
	9-12	142	5.0	118	4.5	0.5	0.033	
IP	By Vaccination Status							
	Not vaccinated	181	5.0	162	4.0	1.0	0.0007	0.046
	Vaccinated	1	14.0	2	2.0	12.0	0.16	
ITT	By Vaccination Status							
	Not vaccinated	242	5.0	217	4.0	1.0	0.011	
	Vaccinated	5	5.5	6	4.5	1.0	0.78	
IP	By Time from Onset of Symptoms							
	0-24 hours	124	5.5	102	4.0	1.5	0.0007	0.89
	>24-36 hours	58	5.0	62	4.0	1.0	0.17	
ITT	By Time from Onset of Symptoms							
	0-24 hours	174	5.0	149	4.5	0.5	0.07	
	>24-36 hours	73	5.0	74	4.0	1.0	0.059	
IP	High Risk Patient Group							
	High Risk Def by MO	16	6.5	22	3.25	3.25	0.003	
	Resp. & Cardiov.	22	5.0	24	3.0	2.0	0.014	0.42
	Others (excl. R & C)	160	5.0	140	4.0	1.0	0.004	
ITT	High Risk Patient Group							
	High Risk Def by MO	28	5.5	30	3.5	2.0	0.07	
	Resp. & Cardiov.	35	5.0	34	3.75	1.25	0.091	
	Others (excl. R & C)	212	5.0	190	4.5	0.5	0.035	
IP	Country							
	NA (USA and Canada)	105	5.0	96	4.0	1.0	0.04	
	USA only	100	5.0	86	4.0	1.0	0.12	0.19
	USA White only	82	5.5	71	4.0	1.5	0.08	
	Others (excluding USA)	82	5.5	78	4.0	1.5	0.0004	
ITT	Country							
	NA (USA and Canada)	148	5.0	130	4.0	1.0	0.13	
	USA only	141	5.0	121	4.0	1.0	0.27	
	Others (excluding USA)	106	5.5	103	4.5	1.0	0.009	

*From the interaction term in Cox model: time to alleviation = treatment + subgroup variable + treatment × subgroup variable.

The age effect was investigated in greater details. Table 8 shows the comparisons between the two treatment groups stratified on every age group. The treatment effect as a function of age appears to have an inverted 'U' shape. That is, age groups 7, 8, 9, and 10 show a treatment effect consistent with that of overall effect, whereas age groups 5, 6, 11, and 12 show a somewhat below average treatment effect.

Table 8. Time to Alleviation: Median Days by Age Group
(Influenza Positive Population, Wilcoxon test, missing treated as censored, reviewer's analyses)

Age Group	Placebo		Zanamivir		P - Z	Wilcoxon test
	n	Median	N	Median		P value
5*	16	3.5	22	3.0	0.5	0.19
6	19	5.0	14	4.5	0.5	0.51
7	16	5.5	15	4.0	1.5	0.34
8	24	5.0	26	4.0	1.0	0.15
9	21	5.5	20	3.5	2.0	0.07
10	26	5.5	27	3.5	2.0	0.03
11	25	5.5	25	5.0	0.5	0.49
12	35	5.0	14	4.75	0.25	0.80
5-6*	35	4.0	36	4.0	0.0	0.13
7-12	147	5.5	127	4.0	1.5	0.002
5-7*	51	5.0	52	4.0	1.0	0.08
8-12	131	5.5	112	4.0	1.5	0.002
5-8*	75	5.0	78	4.0	1.0	0.03
9-12	107	5.5	86	4.25	1.25	0.008

*including one patient of age 4.

Subgroup analysis was also performed on high-risk patient groups. The first high-risk group was identified by Agency's Medical Officer as subjects with any history of wheezing or asthma included in the listing of medical conditions. The median difference was over 3 days and p value was statistically significant (p=0.003). The second high-risk group was identified as those with medical conditions of "respiratory" or "cardiovascular". The median difference was over 2 days and p value was also statistically significant (p=0.014).

A possible geographic difference in treatment effect was seen between the USA patient population and patients from other countries. The treatment effect was not statistically significant (p=0.12) for the USA population which consisted of 54% (186/346) of the total IP patient population, while the treatment effect remained statistically significant (p=0.0004) for the rest (46%) of the IP population.

To explore possible factors associated to the weakness of treatment effect in the USA patient population, Table 9 presents the baseline characteristics of the USA patient population compared with the rest of the patient population for the influenza positive subjects. The USA patient

population had more non-whites (18% for USA vs. 2% for Others), and more patients taking extra relief medication (35% for USA vs. 16% for Others). The USA patient population also had more influenza B patients (40% for USA vs. 28% for others). However, this should be in favor of a stronger treatment effect in the USA, based on previous subgroup analyses.

Subsequently, more subgroup analyses were performed based on race and whether taking extra relief medicine. The results are presented in Table 10.

Table 9. Baseline Characteristics Stratified on Geographic Regions (US and Others) (Influenza positive population, reviewer's analyses)

	USA only			Others		
	Placebo	Zanamivir	Total	Placebo	Zanamivir	Total
	N=100	N=86	186	N=82	N=78	160
Sex: Female	51 (51%)	34 (40%)	85 (46%)	40 (49%)	34 (44%)	74 (46%)
Male	49 (49%)	52 (60%)	101 (54%)	42 (51%)	44 (56%)	86 (54%)
Age: Mean (years)	9.1	8.8	8.9	8.9	8.4	8.7
Race: White	82 (82%)	71 (83%)	153 (82%)	80 (98%)	77 (99%)	157 (98%)
Flu Type A	60 (60%)	51 (59%)	111 (60%)	60 (73%)	55 (71%)	115 (72%)
B	40 (40%)	35 (41%)	75 (40%)	22 (27%)	23 (29%)	45 (28%)
High Risk (Resp & Card)	12 (12%)	15 (17%)	27 (15%)	10 (12%)	9 (12%)	19 (12%)
Taking Extra Relief Med	35 (35%)	31 (36%)	66 (35%)	11 (13%)	14 (18%)	25 (16%)
Mean height (cm)	138	136	137	138	133	136
Mean weight (kg)	36	35	36	34	30	32

As shown in Table 10, the USA white-only population seemed to have a slightly better treatment effect compared to the USA only. The median difference was 1.5 days with a p value of 0.08. Compared with the efficacy in other countries (1.5 day difference, p=0.0004), the USA white population still showed a somewhat weaker efficacy. It was not clear what might have caused that weakness.

A total of 91 IP patients took extra relief medicine during the study. Among them, 35% (66/186) of the USA patient population took extra relief medicine and 16% (25/160) of those from other countries did. As one may expect, taking extra relief medicine could mask zanamivir's effect. However, this expectation was not supported by the results based on the USA patients. In the USA, patients not taking extra relief medicine during the study yielded a slightly worse treatment effect (0.5 day median difference) than those taking extra relief medicine (1.0 day median difference).

The above results on USA population seemed to contradict one's intuition as well as results based on patients from other countries. This contradiction is even more obvious when means are calculated (shaded area in Table 10). After excluding missing observations from the USA, the difference is 0.2 day for those who did not take relief medicine taken (t-test, p=0.75) and 1.0 day for those who did (t-test, p=0.24). It was not clear what might be the underlying reasons.

Table 10. More Results From Subgroup Analyses (Influenza positive population, reviewer's analyses)						
	Placebo		Zanamivir		P – Z	Wilcoxon*
	n	Median	N	Median		P value
USA White only	82	5.5	71	4.0	1.5	0.08
USA only	100	5.0	86	4.0	1.0	0.12
Other Countries (excluding USA)	82	5.5	78	4.0	1.5	0.0004
Overall IP						
Extra Relief Med	46	5.0	45	4.0	1.0	0.13
No Extra Relief Med	136	5.0	118	4.0	1.0	0.001
USA						
Extra Relief Med	35	5.0	31	4.0	1.0	0.24
No Extra Relief Med	65	5.0	55	4.5	0.5	0.30
Extra Relief Med	34	5.9 (mean**)	31	4.9 (mean**)	1.0	0.24 (t-test**)
No Extra Relief Med	54	4.9 (mean**)	53	4.7 (mean**)	0.2	0.75 (t-test**)
Other Countries						
Extra Relief Med	11	5.5	14	4.0	1.5	0.36
No Extra Relief Med	71	5.5	63	4.0	1.5	0.0006
*The generalized Wilcoxon's test treats missing observations as censored.						
**The missing observations are excluded in these analyses.						

Secondary Efficacy Analyses of NAI30009

The sponsor also conducted analyses on a number of secondary efficacy endpoints,

- Time to alleviation of clinically significant symptoms of influenza and no use of relief medication -
  For the IP population, the median difference was 1.5 days between the zanamivir and placebo groups (5.0 vs. 6.5 days, respectively, $p<0.001$).
- Time until the subject returned to normal activities –
  For the IP population, the median difference was 1.0 day between the zanamivir and placebo groups (5.5 vs. 6.5 days, respectively, $p<0.022$).
- Mean overall assessment Diary Card symptom score over post-baseline assessments on Study Days 2 to 5 –
  Lower mean overall symptom scores with zanamivir on Days 2-5 ($p=0.008$)

Other secondary efficacy endpoints included:

- Incidence of complications of influenza
- Number of days out of Study Days 2 to 5 where cough was recorded as moderate or severe at least once during the day.
- Number of days out of Days 2 to 5 each symptom other than cough was recorded.
- Number of days out of Study Days 2 to 5 the subject's parent recorded use of relief medication.

- Total number of 12 hour periods during which supplied acetaminophen (paracetamol) was taken over the treatment period (Study Days 1 to 5).
- Total number of 12 hour periods during which supplied dextromethorphan cough mixture (pholcodine in Europe) was taken over the treatment period (Study Days 1 to 5).
- Investigator Global Assessment of Symptoms at the Study Day 3 visit and at the post-treatment visit. Study Day 3 viral titer from throat swab (optional for all subjects).
- Temperature as measured at the clinic visit on Study Day 3 for those subjects with this assessment.

The results on these endpoints were mostly in favor of zanamivir compared to placebo.

Study NAI30010

Study NAI30010 was a prophylaxis study intended to investigate the efficacy of zanamivir on the prevention of transmission of influenza infections in families. In the current pediatric submission, however, this study mainly serves as a source of safety information on zanamivir in the pediatric patients. The efficacy information of NAI30010 is primarily for confirmatory and supportive purposes.

Among the 68 (influenza positive) index cases who were pediatric patients ages 5-12, 36 were randomized to the placebo group and 32 to the zanamivir group. Among them, 1 patient originally assigned to the zanamivir group actually crossed the treatment groups and took placebo. Also, there was 1 missing observation from the placebo group and 2 missing from the zanamivir group. The following table shows the results of the "as-treated" analyses based on the 65 complete observations (36 in placebo and 29 in zanamivir).

Table 11. Time to alleviation: primary and secondary analyses Study 30010

	Placebo		Zanamivir		P – Z	Wilcoxon Test
	N	median	N	Median		P value
IP	36	5.75	29	3.5	2.25	0.002
5-7	10	4.25	8	3.75	0.5	0.45
8-12	26	6.0	21	3.5	2.5	0.001
White	30	6.0	23	3.0	3.0	0.001
Non-white	6	5.0	6	5.25	-0.25	0.94
Flu Type A	26	5.5	21	3.5	2.0	0.02
Flu Type B	10	8.5	8	3.75	4.75	0.02
High Risk	4	6.25	4	4.25	2.0	0.56
Others	32	5.5	25	3.5	2.0	0.002
USA	30	6.0	24	3.75	2.25	0.003
Others	6	5.0	5	3.5	1.5	0.23

Although the sample size was quite small, somewhat inferior treatment effect was seen in younger ages (5-7) compared to older ages and non-white patients did not seem to respond to

zanamivir, which were consistent with 30009. A different finding was that the USA patients responded better to zanamivir in 30010 than in 30009.

Discussion

Non-parametric tests vs. parametric tests

Through out the review, both parametric and non-parametric methods have been used in the primary statistical analyses. The sponsor used the Wilcoxon's rank sum test, which is a non-parametric method for complete observations, as the primary test. In this review, two non-parametric methods for incomplete data, the generalized Wilcoxon's test (or Gehan's test) and Logrank test, and a parametric method, t-test, were also used in the primary analyses to confirm the findings.

The t-test is optimal under the assumption of normality for the two underlying distributions under comparison, which is not satisfied in this case. The observations of time to alleviation are skewed to the left for both zanamivir and placebo groups. Therefore, the non-parametric tests, which do not require the distributions under comparison to be in a particular form, are more appropriate here.

Strictly speaking, the Wilcoxon's test, tests for the null hypothesis of the equality of the distributions of the two samples, not just the means or medians. The rejection of null hypothesis implies the inequality of the two distributions. Only when the two distributions have a similar shape, one may conclude the inequality of two means or medians from a Wilcoxon's test.

Figure 1 shows the distributions of time to alleviation for the two treatment groups. Two adjacent categories are collapsed in the figure. For example, the number of patients at 1 day includes patients alleviated on both 0.5 and 1 day; the number of patients at 2 days includes patients alleviated on both 1.5 and 2 days, etc. Missing values are also included at time of missing. The two distributions appear to have a similar shape. Figure 2 shows the Kaplan-Meier survival curves for the two treatment groups.

Figure 1. Distributions of time to alleviation for the two treatment groups

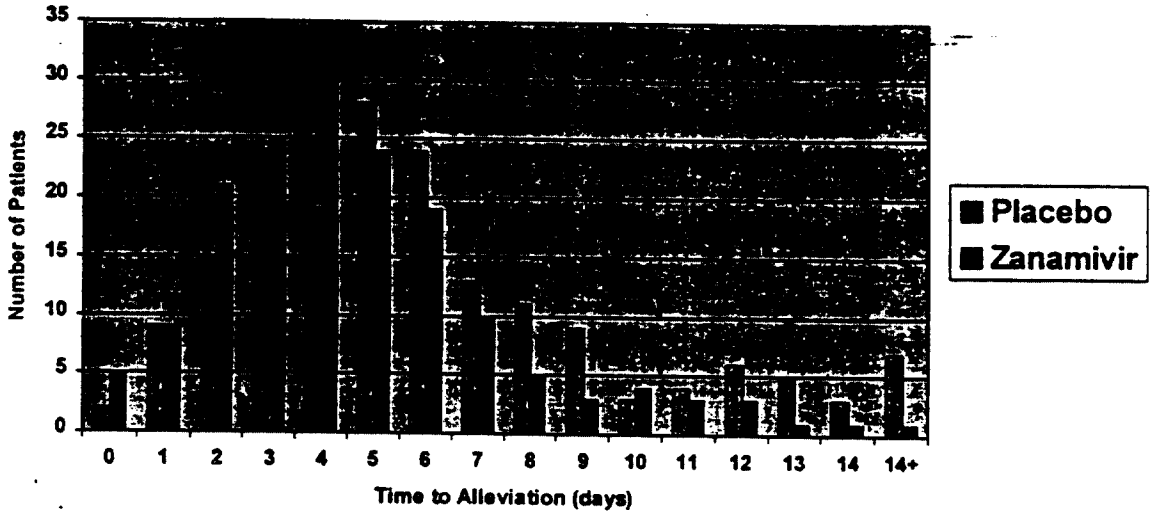
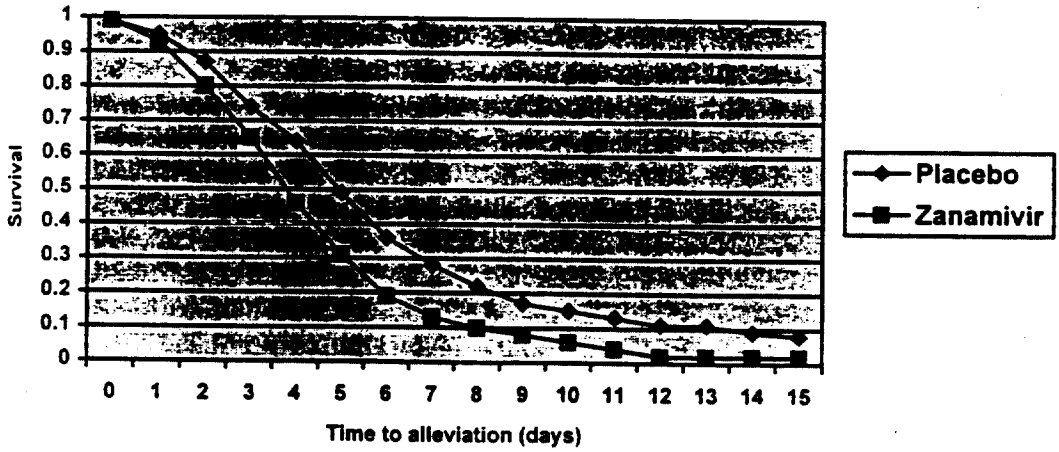


Figure 2. Kaplan-Meier Curves



Medians vs. means

Generally speaking, using medians, instead of means, to describe the efficacy of zanamivir has several advantages. When the samples are not necessarily normally distributed, medians may be a better indicator than the means as to where the most observations may concentrate. Also, medians are usually more robust than means because means are very sensitive to extreme values (outliers). The extreme values do not directly contribute to the medians, only their ranks do. With means, a few extreme values may change the results dramatically.

However, because the data was discrete with a unit of 0.5 day, using median difference to describe efficacy of zanamivir can also be unreliable and even misleading.

The diary card entry was recorded every 12 hours. As a result, the increment of the observed values was 0.5 day. Therefore, the medians and the difference in medians were also likely in an increment of 0.5 day. The only exception would be when the average of two middle values may yield a median with a unit of a quarter (0.25) or three quarters (0.75) of a day.

As demonstrated earlier with sponsor's primary efficacy analyses, a single observation shifting between 5 and 5.5 days would cause the median of the zanamivir group shifting between 5.0 and 5.5 days, and consequently, cause the median difference between zanamivir and placebo shifting between 1.0 and 1.5 days. It represents up to 50% change in efficacy result just because of a single observation.

Also, as seen in the subgroup analyses, for example, males had a median difference of 1 day while females had 0.5 day. But it was not true that zanamivir worked twice as good in males as it did in females (Table 7).

Therefore, one must be cautious to describe the treatment effect of zanamivir using the median difference only. In the following, I intend to offer considerations on how to draw conclusions on the treatment effect based on the collected information available.

The treatment effect

As pointed out earlier, the sponsor's primary efficacy analysis was biased in the direction of exaggerating the treatment effect of zanamivir. The reason was that the sponsor did not handle the missing observations properly in their efficacy analysis. The sponsor's original protocol specified Wilcoxon's test as the test for the primary efficacy analysis. However, the protocol did not specify how to treat the missing data in the Wilcoxon's test. In sponsor's final analysis, they assumed that those subjects who became loss-to-follow-up before reaching alleviation alleviated after the entire study period (28 days). This analysis artificially inflated the difference between the two groups because there were more missing observations from the placebo group than from the zanamivir group.

I performed a generalized Wilcoxon's test (or called Gehan's test) on the primary efficacy endpoint, time to symptom alleviation, treating the missing as censored at the time of censoring. This analysis assumes that the missing is not related to the efficacy outcome. My analysis suggested that there was a statistically significant difference in time to alleviation between the zanamivir and placebo groups (Table 5) for the IP population and a 1-day difference in medians was observed. The sponsor, however, wanted to claim a median difference of 1.25 days.

[redacted] I have also elaborated on why the median difference could be unreliable and misleading when used to describe the treatment effect of zanamivir in this particular trial. Therefore, I think one should be very cautious about making conclusions purely relying on one single analysis. Having said that, I will summarize in the following paragraph why the 1-day difference should better describe the treatment effect of zanamivir in this trial.

[redacted]t. Secondly, my ITT and per-protocol analyses also concurred the 1-day difference in medians (Table 5). Also, after excluding the missing values, the median difference remained to be 1 day and the mean difference was 0.95 day (Table 6). Finally, and maybe most importantly, a 1-day difference in medians was also observed in a majority of the subgroups based on influenza type, gender, race, age, vaccination status, time from onset of symptoms, high risk group, and country, especially in those with relatively large sample sizes (Table 7).

Symptom rebound after reaching alleviation

Table 12 shows that there was a similar portion of subjects who had a rebound in symptom scores after reaching alleviation (for three entries) from placebo and zanamivir groups. In the IP population, 30% (55/182) of the patients on placebo had a rebound and 27% (45/164) of the patients on zanamivir did so. The difference was not statistically significant by a chi-square test ($p=0.56$).

On the other hand, there were more patients on zanamivir experienced symptom rebounds lasting > 1/2 day compared with those on placebo. For the IP population, only 7% (13/182) of the patients on placebo had a rebound lasting more than half a day while 16% (26/164) of the patients on zanamivir did so. The difference was statistically significant by a chi-square test ($p=0.01$).

There was a concern that whether the difference seen here was caused by the difference in total potential exposure time of the two groups. More specifically, the zanamivir group had a shorter average time to alleviation, and hence, was exposed by a longer time for possible symptom rebound after reaching alleviation. In fact, this factor was not likely to influence the results. Firstly, the protocol states that the follow-up was to be extended from 14 days to 28 days for those patients whose symptoms persisted on the Day 13 or 14. Therefore, any

potential longer-than-half-day rebound was not likely to be cut off at the end of 14 days in both groups. Moreover, as shown by Table 12, the placebo group actually had a slightly higher percent of patients with any rebound than the zanamivir group (30% vs. 27%), indicating that the difference in total exposure time after reaching alleviation did not seem to play a role here.

Table 12 also shows that, among the patients who experienced symptom rebound after reaching alleviation, 24% (13/55) had rebounds >1/2 day for the placebo group, whereas 58% (26/45) did for the zanamivir group. The difference was statistically significant (p=0.001).

Table 12. Number of patients who had a rebound in symptom scores after reaching alleviation (Influenza Positive Population, NAI30009)

	Placebo	Zanamivir	Chi-square p value
	N=182	N=164	
#of subjects had a rebound	55 (30%)	45 (27%)	
# of subjects did not	127 (70%)	119 (73%)	0.56
#of subjects had a rebound > ½ day	13 (7%)	26 (16%)	
#of subjects did not	169 (93%)	138 (84%)	0.01
#of subjects had a rebound > ½ day	13 (24%)	26 (58%)	0.001
#of subjects had a rebound = ½ day	42 (76%)	19 (42%)	

Conclusions

- From statistical point of view, I concluded that Study NAI30009 supports the efficacy of inhaled zanamivir 10mg twice daily via Rotadisk/ DISKHALER for 5 days in the treatment of influenza in children 5-12 years of age.
- The sponsor's primary efficacy analyses exaggerated the treatment effect of zanamivir due to the improper handling of missing observations in the statistical analyses. There were statistically significantly more missing observations from the placebo group than from the zanamivir group. In the influenza positive population, 21 (12%) from placebo and 6 (4%) from zanamivir were missing (p=0.006, chi-square test).
- For this particular study design, it may not be reliable to describe the efficacy based on one single median difference. The measurement unit was in 0.5 day and it may bring an undesirable fluctuation to the proposed efficacy size (1-1.5 days of median difference).
- For the Influenza Positive population, based on a spectrum of analyses I performed, I concluded that the difference in median days of time to alleviation was approximately one day, in stead of 1.25 days suggested by the sponsor.
- In the IP population of Study NAI30009, while the proportion of patients who experienced symptom rebound after reaching alleviation (for 3 consecutive entries) was similar between the groups (30% for placebo vs. 27% for zanamivir), a statistically significantly larger proportion of patients on zanamivir (16%, 26/164) experienced a rebound lasting > 1/2 day compared to the patients on placebo (7%, 13/182). The difference was statistically significant by a chi-square test (p=0.01).

- Treatment effect was also observed in patients with type B influenza.
- Neither the youngest age groups (5 and 6) nor the oldest age groups (11 and 12) showed a desirable treatment effect. There was no clear explanation.
- The data from Studies NAI30009 and NAI30010 are not adequate to make firm conclusions on efficacy of zanamivir in non-white patients. However, the limited available information showed no indication of any efficacy in this subgroup.
- A weakness of efficacy in the US population compared to non-US population was seen in Study NAI30009, which is consistent with previous adult studies. There was no clear explanation for this.

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