SUBMISSION

TO

THE NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

FOR

DRUGS FOR THE PROPHYLAXIS OF INFLUENZA – REVIEW OF ZANAMIVIR

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Drugs for Prophylaxis of Influenza – Review of Zanamivir.

Executive Summary

Introduction

Zanamivir obtained a marketing authorisation in 2006 for the post-exposure prophylaxis of influenza A and B in adults and children (≥5 years) following contact with a clinically diagnosed case in a household. In exceptional circumstances, zanamivir may be considered for seasonal prophylaxis of influenza A and B during a community outbreak (e.g. in case of a mismatch between circulating and vaccine strains and a pandemic situation).

The Institute appraised the clinical and cost effectiveness of anti-viral drugs for the prophylaxis of influenza in 2003 but at this time although clinical trial data for prophylactic use were available for zanamivir the marketing authorisation had not yet been obtained. The resulting guidance therefore did not recommend the use of zanamivir.

Clinical Efficacy

During the appraisal conducted in 2003, the health technology assessment (HTA) group included four zanamavir prophylaxis studies in their analyses (studies NAIA2009/NAIB2009, NAIA2010, NAIA3005, and NAI30010). A summary of these results are presented in table 1 below. One Phase II study (NAIB2006) and two Phase III studies (NAIA3003 and NAIA3004) were excluded due to limited published data available at the time. The two Phase III studies have subsequently been published (see Appendix 1 for list of publications) and in addition the clinical reports of all these three studies are included on the CD ROM enclosed with this submission. There are also a further two phase III studies (NAI30031 and NAI30034) that completed in 2002 but had not been published by the deadline of December 2001 set by the assessment group for study inclusion in order for them to proceed with their analyses. One of these studies, NAI30031, was published in 2002 and the clinical reports for both of these studies are also included on the CD ROM with this submission. There are also two Japanese studies, one Phase II study (Study PE-01) and a Phase III study (Study 167-101). However due to low subject recruitment and/or low rate of influenza infection during those seasons, efficacy could not be evaluated. The clinical summaries are included on the CD ROM for completeness. Each of the zanamivir studies that were not part of the original HTA are summarised separately later in this section**.**

Table 1: Summary of Results from Zanamivir Studies included in the 2003 HTA Report

Clinical Efficacy							% Patients with Adverse Events	
Study (setting)	**Duration of prophylaxis**	**Primary Efficacy Parameter**	**Placebo**	**Zanamivir**	**Intervention Difference Odds Ratio (OR) (95% CIs)**	**p-value**	**Placebo**	**Zanamivir**
NAI30010 (post- exposure prophylaxis in the general population) **-ITT group. 15% of subjects were vaccinated.**	10 days	Symptomatic Laboratory confirmed clinical influenza	40/423 (9.5%)	7/414 (1.7%)	0.16 [0.07, 0.37]	<0.001	27/581 (5%)	30/577 (5%)
NAI30010 (post- exposure prophylaxis in the general population) **- influenza positive index cases**	10 days	Symptomatic Laboratory confirmed clinical influenza	33/215 (15.3%)	6/195 (3.1%)	0.18 [0.07, 0.43]	<0.001	-	-
NAIA2009/ NAIB2009 (post- exposure prophylaxis in the general population) **- ITT group. No vaccination of subjects**	5 days	Symptomatic Laboratory confirmed clinical influenza	9/144 (6.3%)	3/144 (2.1%)	0.27 [0.07, 1.05]	0.077	25/144 (17%)	27/144 (19%)
NAIA2010 (Outbreak prophylaxis in the elderly in residential homes) **97% of all residents were vaccinated**	14 days	Laboratory-confirmed influenza A or B	2/40	0/100	0.10 [0.004, 2.17]	0.096	18/40 (45%)	38/98 (39%)

Clinical Efficacy							% Patients with Adverse Events	
Study (setting)	**Duration of prophylaxis**	**Primary Efficacy Parameter**	**Placebo**	**Zanamivir**	**Intervention Difference Odds Ratio (OR) (95% CIs)**	**p-value**	**Placebo**	**Zanamivir**
NAIA3005 (seasonal prophylaxis in a healthy population) **15% of subjects were vaccinated**	28 days	Laboratory confirmed clinical influenza	34/554 (6.1%)	11/553 (2.0%)	0.31 [0.14,0.64]	<0.001	27/554 (5%)	30/553 (5%)

The results across the four studies demonstrate a clear beneficial effect of zanamivir when used as a prophylactic intervention for influenza in the three different study settings. In addition, the results presented in the assessment report by the HTA group based on the studies analysed for both zanamivir and oseltamivir, both selective inhibitors of neuramindase enzymes, suggest comparable levels of protective effect in households and healthy adults.

Study NAI30031

This was a double-blind, placebo-controlled, parallel-group study within households, randomised by family. The objectives of the study were to evaluate the efficacy, safety and tolerability of inhaled zanamivir 10mg once daily for 10 days compared with placebo in the prevention of symptomatic, laboratory confirmed influenza A and B viral infections, and to assess the impact of inhaled zanamivir on subject productivity and healthcare resource utilisation.

Families with two to five members living at home, including at least one adult and one child ≥5 years of age, were recruited. There was no upper age limit and few restrictions on subjects for inclusion (subjects who were pregnant, breast-feeding or immunocompromised were excluded). Once influenza was confirmed as circulating in the community by local surveillance and also surveillance conducted by the investigational site and the first family member (index case) was diagnosed as having ILI, randomisation was initiated (within 1.5 days of symptom onset in the index case) for the other family members ≥ 5 years of age. All the contact cases within one family were randomised to receive the same intervention (either zanamivir or placebo), taken once a day for 10 days. Each index case ≥ 5 years old in each household were provided with relief medication only (paracetamol/acetaminophen and cough mixture (dextromethorphan/pholcodine) for supportive care and not randomised to treatment. Children <5 years of age were enrolled as index cases but did not receive study drug. Subjects were assessed at three visits (start of prophylaxis on Day 1, end of prophylaxis on Day 11 and post prophylaxis follow-up on Day 28) plus a during prophylaxis contact (Day 5) and post prophylaxis contact (Day 14). Index cases (all ages) and contact cases (≥ 5 years of age) completed a diary card for at least 14 days, recording details of symptoms and temperature twice daily, and use of relief medication each day. If any influenza-like symptoms were recorded as present on Day 14, a second diary card was completed until Day 28. The primary endpoint was the proportion of randomised households in which at least one randomised contact case developed symptomatic, laboratory-confirmed influenza. The results for the primary parameter are presented in Table 2 below.

Table 2: Summary of Primary Efficacy Analysis - Relative Risk of Laboratory-Confirmed, Symptomatic Influenza in Households : NAI30031 (ITT Population)

	Placebo N=242	**Zanamivir** N=245
Families/households with symptomatic, laboratory confirmed influenza; symptoms any time from Day 1 to Day 11		
Present in at least one contact case, n (%)	46 (19%)	10 (4%)
Not present, n (%)	196 (81%)	235 (96%)
Treatment comparison:		
Relative odds (95% CI)	0.17 (0.07, 0.37)	
p-value	<0.001	
Approximate relative risk1 (95% CI)	0.19 (0.10, 0.36)	

1. Approximate relative risk = risk on zanamivir/risk on placebo

Seven per cent of index cases and 10% of contact cases were vaccinated prior to randomisation of the households.
In this study, where index cases were provided with relief medication only and were not treated with either zanamivir or placebo, zanamivir demonstrated clinically meaningful and statistically significant protective benefit in the prevention of transmission of influenza in the family/household setting (p<0.001). The relative risk of 0.19 represents a protective efficacy for zanamivir of 81%. The frequency and nature of adverse events reported during prophylaxis were similar between groups with 52% of placebo patients and 42% of zanamivir patients experiencing at least one event. Across those households reporting at least one contact case with symptomatic influenza-like illness, the placebo group required a mean of 15.1 hours off work/school per household compared with

10.9 hours in the zanamivir group (p=0.693). In the placebo group, an average of 2.6 days were spent incapacitated or confined to bed per household with one or more contact cases with symptomatic influenza-like illness, compared with 1.8 days in the zanamivir group (p=0.053). Thirty-two percent (78/242) of households randomised to placebo had at least one contact case with symptomatic ILI who had an additional healthcare contact. This figure was significantly reduced in the zanamivir group (20% of households [50/245]; p=0.004).

Study NAI30034

This was a randomised, double-blind, placebo-controlled, parallel-group study in community-dwelling subjects aged >12 years who were at high risk of developing complications from influenza. High risk was defined as subjects ≥ 65 years of age, subjects with diabetes mellitus and subjects with chronic disorders of the pulmonary or cardiovascular systems. The objectives were to evaluate the efficacy of inhaled zanamivir 10mg once daily for 28 days compared with placebo in the prevention of symptomatic, laboratory-confirmed influenza A and B viral infections, to evaluate the safety and tolerability of inhaled zanamivir compared with placebo, and to assess the impact of inhaled zanamivir on subject productivity and healthcare resource utilisation.

Once an influenza outbreak was declared in the community using local surveillance and also surveillance conducted by the investigational site, eligible subjects were stratified according to their vaccination status and randomised to prophylaxis with either zanamivir or placebo (within 5 days of the onset of the influenza outbreak) for 28 days. Following the first prophylaxis visit on Day 1, subjects attended the clinic on three occasions while receiving prophylaxis (Days 7, 14 and 21), an end of prophylaxis visit (Day 28) and a post-prophylaxis visit. Subjects completed a diary card for at least 28 days, recording details of symptoms and temperature twice daily, and use of relief medication each day. The primary endpoint was the proportion of randomised subjects who developed symptomatic, laboratory-confirmed influenza A or B infection during prophylaxis. The results for the primary parameter are presented in Table 3 below.

Table 3: Summary of Primary Efficacy Analysis - Relative Risk of Laboratory-Confirmed, Symptomatic Influenza in Community-Dwelling Setting: NAI30034 (ITT Population)

	Placebo N=1685	**Zanamivir** N=1678
Symptomatic influenza confirmed by culture/serology (Days 1 to 28)		
Present n (%)	23 (1%)	4 (<1%)
Not present, n (%)	1662 (99%)	1674 (>99%)
Treatment comparison		
Relative odds (95% CI)	0.17 (0.04, 0.50)	
p-value	<0.001	
Approximate relative risk[1] (95% CI)	0.17 (0.07, 0.44)	

[1]Approximate relative risk = risk on zanamivir/risk on placebo

A total of 2257/3363 (67%) subjects, 1141/1685 (68%) in the placebo group and 1116/1678 (67%) in the zanamivir group, had been vaccinated for the current season. The study was conducted during a season with low influenza activity. Large numbers of high-risk subjects were randomised to obtain relatively few subjects who developed symptomatic influenza. Despite this, the study demonstrated statistically significant protective benefit in subjects who received zanamivir, with 1.4% of subjects who received placebo compared with 0.2% of subjects who received zanamivir developing symptomatic, laboratory-confirmed influenza (p<0.001; relative risk of 0.17, protective efficacy of 83%). The frequency and nature of adverse events reported during prophylaxis were similar between the placebo and zanamivir groups with 51% of patients in each group experiencing at least one event . There were no observed differences between the zanamivir and placebo-treated groups in the number of days subjects were incapacitated or confined to bed (mean of 0.4 days in the placebo group and 0.3 days in the zanamivir group) and other humanistic and resource utilisation measures.

Study NAIA3003

This was a randomised (at individual level), double-blind, parallel-group study enrolling subjects who were residents of nursing homes in the US. The objectives were to evaluate the efficacy of inhaled zanamivir 10mg once daily for 14 days compared with standard of care in the prevention of influenza infections in the nursing home setting, to evaluate the safety and tolerability of zanamivir, to assess the emergence and transmission of resistant virus during influenza outbreaks, and to assess the pharmacoeconomic impact of influenza in the nursing home setting. Standard of care was rimantadine for influenza A and placebo for influenza B. There was no upper age limit and subjects who were of childbearing potential or immunocompromised were excluded. Subjects participated in twice weekly surveillance and swabs were taken for culture if a new respiratory illness was reported. Once an influenza outbreak was declared in the nursing care unit or epidemic unit (area for which one nursing station had responsibility) subjects were randomised to intervention. An influenza outbreak was declared when the following occurred within 7 days, an EU must have had: 1) either 10% of subjects or 10 subjects with new respiratory illness, and 2) influenza isolated from a resident of the same building. Following the start of prophylaxis on Day 1, subjects were assessed on a daily basis for the 14-day prophylaxis period. Post-prophylaxis assessments were conducted on Days 14 to 18 and subjects were reviewed at a follow-up visit on Day 28. As the study was conducted over multiple influenza periods, some subjects could be randomised more than once. The

primary analysis used only the first randomisation for each subject. The primary endpoint was the proportion of randomised subjects who, during prophylaxis, developed a new sign or symptom and had laboratory confirmation of influenza. The results for the primary parameter are presented in Table 4 below.

Table 4: Summary of Primary Efficacy Analysis - Relative Risk of Laboratory-Confirmed, Symptomatic Influenza in Nursing Home Setting: NAIA3003 (ITT Population, 1st randomisation)

	Standard of care N=191	**Zanamivir** N=184
Symptomatic laboratory –confirmed influenza (Days 1 to 15)		
Present n (%)	16 (8%)	7 (4%)
Not identified, n (%)	175 (92%)	177 (96%)
Treatment comparison		
Relative odds (95% CI)	0.41 (0.14, 1.11)	
p-value	0.085	
Approximate relative risk[1] (95% CI)	0.44 (0.19, 1.02)	

[1]Approximate relative risk = risk on zanamivir/risk on placebo

Of the subjects with vaccination information available (88%), 323/331 (98%) had received immunoprophylaxis for the current season. The incidence of symptomatic, laboratory-confirmed influenza was reduced from 8% among recipients of standard of care (rimantadine for influenza A, placebo for influenza B) to 4% in zanamivir recipients on the first occasion on which they were randomised. This represents a protective efficacy in favour of zanamivir of 56% (95% CI –2% to 81%, p=0.085). The percentage of patients experiencing at least one adverse event during prophylaxis were 55% in the rimantadine group, 46% in the placebo group and 58% in the zanamivir group. Subjects given zanamivir prophylaxis in this study had slightly fewer additional healthcare professional consultations (6% subjects) compared with standard of care (8% subjects) in the nursing home setting, although this difference was not statistically significant.

Study NAIA3004

This was similar in design to Study NAIA3003, evaluating the efficacy and safety of inhaled zanamivir 10mg once daily for 14 days in the nursing home setting. However, Study NAIA3004 was conducted mainly in Lithuania where rimantadine is not used as the standard of care for influenza A. Therefore, the study was placebo-controlled. The study was conducted over three influenza seasons which meant some patients were randomised more than once. The primary analysis included patients from their first randomisation. The primary endpoint was the proportion of randomised subjects who, during prophylaxis, developed a new sign or symptom and had laboratory confirmation of influenza. The results for the primary parameter are presented in Table 5 below.

Table 5: Summary of Primary Efficacy Analysis - Relative Risk of Laboratory-Confirmed, Symptomatic Influenza by Household: NAIA3004 (ITT Population, 1st randomisation)

	Placebo N=249	**Zanamivir** N=240
Symptomatic laboratory –confirmed influenza (Days 1 to 15)		
Present n (%)	23 (9%)	15 (6%)
Not identified, n (%)	226 (91%)	225 (94%)
Treatment comparison		
Relative odds (95% CI)	0.68 (0.31, 1.44)	
p-value	0.355	
Approximate relative risk[1] (95% CI)	0.71 (0.38, 1.31)	

[1]Approximate relative risk = risk on zanamivir/risk on placebo

Immunoprophylaxis was recorded for 9% (45/489) of subjects for the first randomisation. The incidence of symptomatic influenza was 9% among placebo recipients and 6% in zanamivir recipients. This risk reduction of 29% was not statistically significant (95% CI–31% to 62%, p=0.355). One of the most likely reasons for the discrepant results is that randomisations appeared to have occurred very late in the progression of the influenza outbreak, with 35% of subjects who could potentially be randomised, having already developed symptoms before prophylaxis could be started. The incidence of adverse events during prophylaxis was similar between the two treatment groups with 37% of patients in the placebo group and 32% of patients in the zanamivir group reporting at least one event Ten per cent (25/249) of subjects in the placebo group had additional healthcare consultations compared with 8% (18/240) of subjects in the zanamivir group (p=0.476). All of these consultations resulted in new services being provided to the subjects.

Study NAIB2006

This was a randomised, double-blind, parallel-group Phase II study to evaluate the efficacy and safety and tolerability of zanamivir 10mg twice daily in the prevention of influenza A and B viral infections. The twice daily regimen is outside the current licensed dose for zanamivir. Patients (contact cases) eligible for this study had to have been exposed to an index case with an influenza-like illness within the previous 48 hours. Exposure was defined as living in the same household, sleeping in the same room or confined

to the same room/area as the index case. The index case was a person with symptoms of influenza-like illness which was verified for the influenza virus using antigen detection methods and/or positive culture. Eligible patients were randomised to prophylaxis with inhaled zanamivir (10mg) or matching placebo twice daily for five days. The contact cases were clinically assessed on Day 1, received study medication on Days 1 to 5 and were followed up on days 6 and 21. The primary endpoint was the proportion of patients with laboratory confirmed influenza during prophylaxis with study medication plus at least two clinically significant symptoms of influenza of moderate or severe severity during the study dosing period. The results for the primary parameter are presented in Table 6 below.

Table 6: Summary of Primary Efficacy Analysis - Relative Odds of Laboratory-Confirmed, Influenza NAIB2006 (ITT Population)

			Symptomatic influenza		Presence of influenza	
	Number with influenza infection	Number with symptomatic influenza	Relative odds (95% CI)	p-value* (Zanamivir vs Placebo)	Relative odds (95% CI)	p-value* (Zanamivir vs Placebo)
Placebo	4/32	4/32				
Zanamivir	5/30	3/30	0.82 (0.15, 4.49)	0.816	1.54 (0.34, 7.00)	0.574

*based on Mantel-Haenszel chi-squared test, stratified for centre.

There was no evidence of a protective effect of zanamivir against laboratory confirmed infection with influenza, or against the development of symptomatic influenza in contact cases exposed to index cases (individuals with ILI). However the number of patients recruited into the study was small and differences were therefore difficult to identify. The study was designed to include 111 patients per intervention arm but only 62 patients in total received either of the study medications. Furthermore the influenza rate in the placebo group was 13% which was less than the predicted 32%. The numbers of patients reporting adverse events were the same between groups both during and post treatment (7 patients and 5 patients in both groups for each period respectively.)

Cost-Effectiveness

We have not conducted a formal cost-effectiveness analysis.

Summary

The previous NICE guidance issued in November 2003 recommended oseltamivir for post-exposure prophylaxis of influenza in at-risk patients aged 13 years or more. The guidance included a recommendation for prophylaxis with oseltamivir for at-risk people who had not received a flu vaccination, and in some circumstances, for people who had been vaccinated. The efficacy and safety data seen in the zanamivir studies also support the use of this drug for prophylaxis of influenza A and B in household and community dwelling settings, both for post-exposure and seasonal prophylaxis.

Declaration

This submission contains, or references, all the relevant evidence in the possession of GlaxoSmithKline related to the review of zanamivir for the prophylactic treatment of influenza A and B in adults or children.

References

1. Summary of Product Characteristics – Relenza .
2. National Institute for Clinical Excellence – Technology Appraisal Guidance No.65 September 2003.

APPENDIX 1: RELENZA CLINICAL PUBLICATIONS

Publications of Phase II Prophylaxis Studies

Title : Short-term treatment with zanamivir to prevent influenza: Results of a placebo-controlled study

Author : Kaiser L Henry D Flack NP Keene O Hayden FG

Citation : CLIN. INFECT. DIS. 2000;30(3):587-589.

Studies : NAIA/B2009

Publications of Phase III Prophylaxis Studies

Title : Inhaled zanamivir versus rimantadine for the control of influenza in a highly vaccinated long-term care population

Author : Gravenstein S Drinka P Osterweil D Schilling M Krause P Elliott M Shult P Ambrozaitis A Kandel R Binder E Hammond J McElhaney J Flack N Daly J Keene O

Citation : J. Am. Med. Dir. Assoc. 2005;6(6):359-366.

Study : NAIA3003

Title : Inhaled zanamivir versus placebo for the prevention of influenza outbreaks in an unvaccinated long-term care population

Author : Ambrozaitis A Gravenstein S Van Essen GA Rubinstein E Balciuniene L Stikleryte A Crawford C Elliott M Shult P

Citation : J. Am. Med. Dir. Assoc. 2005;6(6):367-374.

Study : NAIA3004

Title : Zanamivir in the prevention of influenza among healthy adults: A randomized controlled trial

Author : Monto AS Robinson DP Louise M James H Hinson M Elliott MJ Crisp A

Citation : J. AM. MED. ASSOC. 1999;282(1):31-35.

Study : NAIA3005

Title : Inhaled zanamivir for the prevention of influenza in families

Author : Hayden FG Gubareva LV Monto AS Klein TC Elliott MJ Hammond JM Sharp SJ Ossi MJ

Citation : NEW ENGL. J. MED. 2000;343(18):1282-1289.

Study : NAI30010

Title : Zanamivir prophylaxis: An effective strategy for the prevention of influenza types A and B within households

Author : Monto AS Pichichero ME Blanckenberg SJ Ruuskanen O Cooper C Fleming DM Kerr C

Citation : J. Infect. Dis. 2002;186(11):1582-1588.

Study : NAI30031

APPENDIX 2: SUMMARY OF CLINICAL STUDIES IN THE ZANAMAVIR PROPHYLAXIS PROGRAMME

Study		Number of Subjects (ITT Population)			Duration of Prophylaxis
		Placebo	Zanamivir	Rimantadine	
Phase III Studies					
Family/Household					
NAI30010	Double-blind, randomized, placebo-controlled, parallel-group, multicenter study of the efficacy and safety of 10mg of inhaled zanamivir once daily in the prevention of transmission of symptomatic influenza A and B viral infections within families	423	414	n/a	10 days
NAI30031	Double-Blind, Randomised, Placebo-Controlled, Parallel-Group, Multicentre Study of the Efficacy and Safety of 10mg of inhaled zanamivir once daily in the Prevention of Transmission of Symptomatic Influenza A and B Viral Infections within Households	630	661	n/a	10 days
Community					
NAIA3005	Double-blind, randomized, placebo-controlled, parallel-group, multicenter study to investigate the efficacy and safety of 10mg of inhaled zanamivir once daily in the prevention of symptomatic influenza A and B viral infections in community dwelling adults	554	553	n/a	28 days
NAI30034	Double-Blind, Randomized, Placebo-Controlled, Parallel-Group, Multicentre Study of the Efficacy and Safety of 10mg of inhaled zanamivir once daily in the Prevention of Symptomatic Influenza A and B Viral Infections in Community-Dwelling High-risk Subjects aged >12 years. Publication Information: This is currently submitted to a journal and will hopefully be in print later this year.	1685	1678	n/a	28 days
Nursing Home					
NAIA3003	Double-Blind, Randomized, Parallel-Group, Multi-Center Study of the Efficacy and Safety of Inhaled Zanamivir 10mg once daily compared to the Standard of Care in Controlling Nursing Home Influenza Outbreaks	13	238	231	14 days
NAIA3004	Double-blind, randomized, placebo-controlled, parallel-group, multi-center study of the efficacy and safety of inhaled zanamivir 10 mg once a day in controlling nursing home influenza outbreaks	252	242	n/a	14 days
Phase II Studies					
Exposed to suspected influenza					
NAIA2006	Efficacy of 10mg of inhaled zanamivir twice daily, or 6.4mg intransal zanamavir twice daily or a combination of both vs placebo	15	49[1]	n/a	5 days
NAIB2006	Efficacy of 10mg of inhaled zanamivir, twice daily vs placebo	32	30	n/a	5 days
NAIA/B2009	Efficacy of 10mg of inhaled zanamivir twice daily, or 6.4mg intransal zanamavir twice daily or a	144	431[2]	n/a	5 days

	combination of both vs placebo				
Nursing Home					
NAIA2010	Efficacy of 6.4mg intransally vs standard care (usually rimantidine)	17	98	23	At least 14 days
Japanese Studies					
167-101	Efficacy of 10mg of inhaled zanamivir once daily vs placebo	158	161	n/a	28 days
PE-01	Efficacy of 10mg of inhaled zanamivir twice daily, or 6.4mg intransal zanamavir twice daily or a combination of both vs placebo	11	33	n/a	5 days
Epidemiology Studies					
EPI40081	Respiratory Events in Patients Receiving Relenza	-	5450	-	

1. 17 subjects received inhaled zanamivir, 15 subjects received intranasal zanamivir, and 17 subjects received inhaled plus intranasal zanamivir.
2. 144 subjects received inhaled zanamivir, 141 subjects received intranasal zanamivir, and 146 subjects received inhaled plus intranasal zanamivir