Appendix 4: List of protocol amendments in zanamivir prophylaxis trials* [posted as supplied by author]

Study ID	Prespecified outcomes	Protocol amendments
167-101	**Primary:** • Proportion of subjects who, during prophylaxis (d1 to d28), developed symptomatic, laboratory-confirmed influenza A or B infection **Secondary:** • Proportion of subjects who, during prophylaxis (d 3 to d 28), developed symptomatic, laboratory-confirmed influenza A or B infection • Proportion of subjects who, during prophylaxis (d 1 to d 28), developed laboratory-confirmed influenza infection • Proportion of subjects who, during prophylaxis (d 1 to d 28), developed laboratory-confirmed influenza infection and developed fever of 37.5 °C or more • Proportion of subjects who, during prophylaxis (d 1 to d 28), developed fever of 37.5 °C or more irrespective of the laboratory test results • Number of days, out of 28, the subject recorded use of relief medications (acetaminophen and cough suppressant) • Maximum recorded score on diary card • Development of secondary complications of influenza • Other outcomes to explore unique aspects of zanamivir based on the results	1st. Nov.8. 1999 2nd.Dec.15.1999 3rd.Jan.25.2000
NAI30010	**Primary:** • Proportion of randomized families in which at least one randomized contact develops symptomatic, laboratory-confirmed influenza A or B infection **Secondary:** • Proportion of randomized families for which at least one randomized contact develops laboratory-confirmed influenza infection • Proportion of randomized families for which at least one contact case (including non-randomized family contacts <5 years of age) develops symptomatic, laboratory-confirmed influenza • Time to alleviation of clinically significant symptoms for randomized index cases • Time to alleviation of clinically significant symptoms and no use of relief medication for randomized index cases • The number of days out of 28 at least one member of the family (including the index case) was unable to perform all their normal activities	22/09/1998 Administrative errors, expand efficacy evaluations and viral sensitivity testing to include additional subjects, and further define/clarify secondary end-points, efficacy measurements and influenza diagnosis.

	• The number of days out of 28 at least one member of the family (including the index case) recorded the use of relief medication • The proportion of randomized families for whom at least one randomized member develops a secondary complication of influenza • Temperature of randomized index case as measured at the clinic visit on Study Day 5	
NAI30031	**Primary:** • Proportion of randomized families in which at least one randomized contact develops symptomatic, laboratory-confirmed influenza A or B infection **Secondary:** • Proportion of randomized families for which at least one randomized contact develops laboratory-confirmed influenza infection • The proportion of randomized households for which at least one randomized contact case develops symptomatic influenza-like illness (irrespective of laboratory confirmation) • The proportion of randomized households in which at least one randomized contact case develops symptomatic, laboratory-confirmed influenza, excluding any failures that occurred within 1 day of the start of prophylaxis • The proportion of randomized households in which at least one randomized contact case develops laboratory confirmed influenza and a febrile illness (defined as a temperature ≥37.8°C) during Days 1 to 11 • The number of days out of 28 at least one randomized contact case was unable to perform all their normal activities • The number of days out of 28 at least one randomized contact case recorded the use of relief medication • The proportion of randomized households for whom at least one randomized contact case develops any secondary complication of influenza	**Amendment 01** was dated 20 Jul 2000 and applied to all study centres. The purpose was to incorporate comments from the Food and Drugs Administration (FDA), exclude subjects with severe asthma, correct administrative errors in the original protocol, reflect a change in procedures for Canada and remove the requirement for involvement of household contact cases under five years of age. **Amendment 02** was dated 08 Nov 2000 and applied to centres in Sweden only. The purpose was to allow extra blood (approx. 5mL extra) to be taken from all subjects at Day 1 and Day 28 and from contact cases who developed influenza-like illness during the study. This blood was used to investigate the development of influenza cell-mediated immune response. Participation in this sub-study was optional for the investigators and subjects. The data from this sub-study are not included in this CSR.
NAI30034	**Primary:** • Proportion of randomised subjects who, during prophylaxis, develop symptomatic, laboratory-confirmed influenza A or B infection **Secondary:** • The proportion of randomised subjects who, during prophylaxis, develop influenza-like illness • The proportion of randomised subjects who develop laboratory-confirmed influenza • The proportion of randomised subjects who, during prophylaxis, develop symptomatic, laboratory confirmed influenza and where symptoms begin on Day 2 or later • The proportion of randomised subjects who, during prophylaxis,	The protocol (10 August 2000) was amended five times, but only once during the study. Amendments No. 03 and No. 05 were implemented worldwide while the other three amendments were limited to study sites in specific countries. The amendments are summarized below: **Amendment No. 01 (16 August 2000) —** was initiated prior to subject enrollment and applied to all German study sites and to some Canadian study sites. It allowed their sites to only enroll Community-Dwelling High-risk Subjects aged 18 years. **Amendment No. 02 (22 August 2000) —** was initiated prior to subject enrollment and applied to all study sites in

	develop symptomatic, laboratory confirmed influenza and where symptoms begin on Day 3 or later • The proportion of randomised subjects who, during prophylaxis, develop a febrile illness with laboratory confirmation of influenza infection. A febrile illness is defined as a temperature of >37.8°C • The proportion of randomised subjects who, during prophylaxis, develop a febrile illness irrespective of laboratory confirmation of influenza • The proportion of randomised subjects, who, during prophylaxis, develop a secondary complication of influenza and have subsequent associated laboratory confirmation of influenza infection • The proportion of randomised subjects who, during prophylaxis, develop a complication of influenza • The proportion of randomised subjects who, during prophylaxis, require antibiotics to treat complications of influenza • The total number of days incapacitated/confined to bed • The proportion of randomised subjects who require an OTC medication • The total number of OTC medications used • The proportion of randomised subjects who require a prescription medication • The total number of prescription medications used • The proportion of randomised subjects who have an unscheduled healthcare contact • The total number of unscheduled healthcare contacts	Norway and France. It allowed their sites to only enroll Community-Dwelling High-risk Subjects aged >18 years. **Amendment No. 03 (29 September 2000) —** was initiated prior to subject enrollment and applied to all sites worldwide. It was written in response to correspondence regarding protocol NAI30034 received on 11 September 2000, from the US Food and Drug Administration (FDA), US Department of Health and Human Services, Division of Antiviral Drug Products. The amendment: • clarified the primary efficacy endpoint such that feverishness and/or temperature >37.8°C were counted as one symptom • revised the inclusion criteria for females of child-bearing potential • added provision for assessment of the number of normal activities that subjects are able to perform • revised some of the statistical analysis methods • clarifications added to the Concurrent Medication Section for subjects who might receive influenza anti-viral treatment • instructed the Investigator to categorize any additional medical condition as: neurological disease, renal disease, hepatic disease, endocrine disease, or other **Amendment No. 04 (25 October 2000) —** was initiated prior to subject enrollment and only applied to study sites in Denmark and the UK. It allowed their sites to only enroll Community-Dwelling High-risk Subjects aged >18 years. **Amendment No. 05 (08 December 2000) —** applied to all study sites worldwide. It was written in response to correspondence regarding protocol NAI30034 received on 04 December, 2000, from the FDA, U.S Department of Health and Human Services, Division of Antiviral Drug Products. Although 91 subjects started treatment prior to 08 December 2000, the amendment did not complicate the study as the amendment primarily addressed end of study procedures. The amendment addressed (A) the addition of a 1-week post-prophylaxis period and (B) changes to the definition of confirmed influenza:

		A. Required an additional 1-week post-prophylaxis follow-up on Days 30-35: • required **all** subjects to complete Diary Card 3 (Day 30-35) • required a follow-up clinic visit on Day 36 to assess adverse events, changes in concurrent medications, and to review and collect Diary Card 3 • instructed subjects who experienced symptoms of ILI up to Day 35 to return to the clinic for an ILI visit. Therefore the ILI Visit could occur anytime from Day 2 to 35 (however, the ILI Convalescent Visit had to take place no later than Day 49) B. Amended the definition of confirmed influenza. A positive PCR result was not • included as part of the primary endpoint. Additionally, serology results were not included in the primary endpoint if the subject had been vaccinated within 21 days prior to randomization or during the study
NAIA/B2009	**Primary:** • The proportion of patients with symptomatic influenza during the treatment period **Secondary:** • The proportion of patients with symptomatic influenza in the five days immediately following treatment period • The proportion of patients with a fever • Number of days over the study period (Day 1 to 5) that the patient recorded any symptom on the diary card as 'none' or 'mild' • Number of days over the study period (Day 1 to 5) that the patient recorded the overall symptom assessment on the diary card as 'none' or 'mild'	**01.** 18/8/1995 To correct typographical errors and inconsistencies, alter Section 3.3 'Use in females' and add in a paragraph to the statistics section, all centres **02.** 8/11/1995 To clarify exclusion criteria following FDA comments, all centres **03.** 8/11/1995 To bring consent requirements in line with Norwegian Ethics Committee recommendations, All Norwegian centres **04.** 8/11/1995 To specify minimum age for inclusion of 18 years as requested by Ethics/Regulatory authorities in Norway, Denmark and Italy, centres in Norway, Denmark and Italy **05.** 16/11/1995 Standard Danish administrative amendment, All centres in Denmark **06.** 23/1/1996 To document the primary outcome measures and statistical methods following discussions with FDA, all centres
NAIA2006	**Primary:** • Proportion of patients with laboratory confirmed influenza during treatment plus at least two clinically significant symptoms of influenza of 'moderate' or 'severe' severity during the study treatment period **Secondary:** • The proportion of patients with influenza • The proportion of patients with a fever (temperature 37.8°C) during the treatment period (Days 1 to 5) • Number of days over the study period (Day 1 to 5) that the patient recorded any symptom on the diary card as 'moderate' or 'severe' • Mean severity of each influenza related symptoms over time • Frequency of supportive drug usage, e.g., acetaminophen, cough mixtures, and decongestants	**01**. 3 Oct 1994, prior to recruitment, all centres: 35 minor amendments, plus new statistical analysis plan. **02**. 9 Feb 1995, after recruitment commenced, all centres: Changed the exclusion of patients with influenza vaccines administered since August 1993 to patients with influenza vaccines administered since October 1, 1994.
NAIA3003	**Primary:** • Proportion of randomized residents who, during prophylaxis, develop a	**1.** **Amendment 01** was dated July 1998. To extend the study for 1 year and to clarify the procedure regarding the collection of AE and concomitant medication information. Adverse event and concomitant medication

	new sign or symptom onset and have subsequent associated laboratory confirmation of influenza infection **Secondary:** • The proportion of randomized residents who, during prophylaxis, develop febrile illnesses and have subsequent associated laboratory confirmation of influenza infection • The proportion of randomized residents who, during prophylaxis, develop complications of influenza and have subsequent associated laboratory confirmation of influenza infection • The proportion of randomized residents who, during days 3-15 of prophylaxis, develop a new sign or symptom onset with subsequent associated laboratory confirmation of influenza infection • The proportion of randomized residents, during prophylaxis, who have laboratory confirmed influenza infection	information was collected during the study period (Day 1-28). **2.** **Amendment 02** was dated Mar1999. The purpose of this amendment was to allow an interim safety analysis to be conducted. **3.** **Amendment 03** was dated Sep1999. The purpose of this amendment was to allow a second interim safety analysis to be conducted. **4.** **Amendment 04** was dated Sep1999. The purpose of this amendment was to increase the number of nursing homes participating in the study and to extend the study for 1 year. It also added new information regarding the FDA approval of zanamivir.
NAIA3004	**Primary:** • Proportion of randomized residents who, during prophylaxis, develop a new sign or symptom onset and have subsequent associated laboratory confirmation of influenza infection **Secondary:** • The proportion of randomized residents who, during days 3-15 of prophylaxis, develop new sign or symptom onset with subsequent associated laboratory confirmation of influenza • The proportion of randomized residents who, during prophylaxis, develop a febrile illness and have subsequent associated laboratory confirmation of influenza infection. A febrile illness is defined as a temperature of > 99.0°F or > 37.2°C • The proportion of randomized residents who, during prophylaxis, develop a complication of influenza and have subsequent associated laboratory confirmation of influenza infection • The proportion of randomized residents with laboratory confirmation of influenza infection during prophylaxis	**Amendment 01** was dated July 1998. The purpose of this amendment was to extend the study for 1 year and to clarify the procedure regarding the collection of AE and concomitant medication information. AE and concomitant medication information was collected during the study period (Day 1-28). **Amendment 02** was dated March 1999. The purpose of this amendment was to allow an interim safety analysis to be conducted **Amendment 03** was dated Aug 1999. The purpose of this amendment was to extend the recruitment period until the required number of subjects was recruited, with addition of centers in The Netherlands and Israel. The procedure for reporting serious adverse events (SAEs) was changed such that SAEs were reported to International Product Surveillance and Phannacovigilance (IPSP) at Glaxo Wellcome Research and Development, UK. **Amendment 04** was dated Sept 1999. The purpose of this amendment was to allow an interim safety analysis to be conducted.
NAIA3005	**Primary:** • Proportion of randomised subjects who, during prophylaxis, develop symptomatic, laboratory-confirmed influenza A or B infection **Secondary:** • Proportions of randomized subjects who develop laboratory confirmed influenza infection, symptomatic laboratory confirmed influenza infection during days 3-28 of prophylaxis, febrile illness, and a secondary complication of influenza during prophylaxis • The maximum recorded score for each of the symptoms recorded on the	**Protocol amendment 01** (dated 20 October 1997) made 12 modifications to the protocol. Some of the major modifications are as follows: • subjects who had received or who should receive influenza vaccine were not excluded from the study • subjects were stratified according to their vaccination status • CPK was added to the list of chemical laboratory tests performed • subjects were asked to complete a questionnaire at the Screening Visit to determine occupational status and

	diary card • Maximum score for global assessment of symptoms • Number of days the patient recorded relief medication use and was able to perform all normal activities • Proportion of randomized subjects requiring antibiotics • Proportion of randomized subjects who missed time from work/school because of influenza and the duration missed from work/school	tobacco use • statistical methods section was revised to allow for stratification of vaccinated subjects **Protocol amendment 02** (dated 06 January 1998) made seven modifications to the protocol. Some of the major modifications are as follows: • in the efficacy evaluations, nasal symptoms (nasal congestion, rhinorrhea) were changed to nasal congestion (blocked, runny nose) • blood for hemagglutination inhibition would only be collected at the Screening Visit and at Day 35 • randomization of subjects would begin within three working days of the influenza outbreak and must have been completed within 5 working days of the outbreak
NAIB2006	**Primary:** Proportion of patients with laboratory confirmed influenza plus at least two clinically significant symptoms of influenza of "moderate" or "severe" severity during the study treatment period **Secondary:** • Proportion of days over the study treatment period that individual influenza symptoms, for those patients with laboratory confirmed influenza during treatment, are rated as 'moderate' or 'severe' • Additional derived variables may be considered if the above measures are not found to be sensitive to treatment differences	**Protocol Amendment 1** applied to centres in France only and was dated 1st August 1994. This amendment was made in order to make the protocol consistent with the requirements of French law. **Protocol Amendment 2** (dated 21 September 1994) applied to all study centres and was made in order to correct and clarify inconsistencies in the Protocol Summary, Study Plan, and Study Procedures i.e. to clarify that only symptomatic patients completed an additional Diary Card from Day 6 to Day 21; and to make clarifications to the consent for contact case patients.
PE-01	**Primary:** • Proportion of subjects who, during prophylaxis (day 1 to day 5), developed symptomatic influenza **Secondary:** • The proportion of subjects who, during prophylaxis (day 6 to day 10), developed symptomatic influenza • The proportion of subjects who, during prophylaxis (day 1 to day 10), developed symptomatic influenza • The number and proportion of subjects who, during prophylaxis (day 1 to day 5 or day 6 to day 10), developed symptomatic influenza	

*The prespecified outcomes are as reported in the study protocols