Appendix 3: List of prespecified outcomes and protocol amendments in zanamivir treatment trials [posted as supplied by author]

Study ID	Prespecified outcomes*	Protocol amendments
JNAI-01	**Primary:** • Time to alleviation influenza symptoms **Secondary:** • Time to alleviation of individual symptoms	116 cases were recruited by 21st April 1995. Termination of this study was determined by principal investigator on 15th May 1995 and approved on 9th June 1995.
JNAI-04	Not defined	Draft was decided on June 25 to 28 1996 and accepted on July 10 1996 Stopped recruiting participants and terminated prematurely on June 25 because the sponsor decided to change formulation
JNAI-07	**Primary:** • Time to alleviation 3 major influenza symptoms **Secondary:** • Time to alleviation of individual symptoms • Change in antibody titre	Unclear (protocol not available)
NAI30008	**Primary:** • Time until alleviation of clinically significant symptoms of influenza **Secondary:** • Time to alleviation of clinically significant symptoms of influenza and no use of relief medication. As well as showing alleviation of clinically significant symptom • Time until the patient returns to normal activities • Sleep disturbance • Maximum daily temperature • Total number of tablets of supplied paracetamol taken over the treatment period • Total number of spoonfuls of supplied cough mixture taken over the treatment period • Incidence of complications of influenza • Mean PEFR as recorded on the Diary Card over the treatment	**Amendment 1**, dated 8 June 1998 (applied to all sites): • clarified some administrative errors in the original protocol • clarified when to perform screening physical examination • for inclusion criterion 2, clarified that for sites using rapid diagnostic tests to pre-screen subjects only subjects who met all entry criteria and were diagnosed as influenza positive were eligible • for exclusion criterion 3, added a clarification that subjects should be excluded with other respiratory conditions that could affect the safety or efficacy data (e.g., cystic fibrosis, lung abscesses or active tuberculosis) • amended the definition of serious adverse event to meet the updated GW standard operating procedure (SOP) • defined exacerbations of asthma/COPD as any worsening of COPD/asthma requiring a change in therapy for that condition (either increase in current medication or addition of new agents • clarified when respiratory function tests were to have been performed as follows. At each clinical visit (Days 1, 6 and 28) an FEVi measurement was performed. The best of three peak flow readings were also recorded. In addition, subjects recorded the best of three peak flow readings each morning and evening on Days 1-28 in their Diary Card • removed sodium, potassium, chloride, bicarbonate, urea, creatinine, total protein, albumin, phosphorus, uric acid, calcium and blood glucose from the list of clinical chemistry parameters tested • removed the nasal swab option as a sample for the diagnosis of influenza and the requirement to store an aliquot of the virus culture.

	period • FEV1 and PEFR as recorded in the Clinic on Days 6 and 28 • Productivity and healthcare resource utilization • Day 2 and 3 viral titers from throat swabs	• for secondary efficacy endpoints, added mean PEFR and clarified the definition of sleep disturbance • modified the definition of complications of influenza as follows: added pneumonia and respiratory failure under "respiratory infections", added cardiac complications (e.g., congestive heart failure, angina, myocardial infarction, arrhythmias), added ear nose and throat (ENT) complications (e.g., sinusitis, otitis media and pharyngitis) **Amendment 2**, dated 6 July 1998 (applied to all sites, except where specified): • further amended inclusion criterion 2 to change the temperature definition of fever (>_37.2°C) for subjects aged AS years to that for other subjects (>_37.8°C) • amended inclusion criterion 3 to reduce the time frame from onset of first influenza-like symptoms to the first dose of study medication from "within two calendar days" to "within 36 hours (1.5 days)" • added the following to secondary efficacy endpoints: FEVi and PEFR at clinic visits on Days 6 and 28, Day 2 and 3 viral titres from throat swabs (for subjects completing this assessment). Minor clarifications to secondary efficacy endpoints were also made • defined how the additional secondary endpoints were analysed statistically • included viral sensitivity testing on Days 1 and 6, and (where feasible) on Days 2 and 3 (Northern American and European centres only) • deleted quick test methods (e.g., immunofluorescence) for laboratory confirmation of influenza • provided information regarding the regulatory requirements for study centres in the US and in Canada **Amendment 3**, dated 8 September 1998 (applied to all sites, except where specified): • clarified some administrative errors in the protocol • changed the lower age limit for inclusion criterion 1, from "males or females A2 years" to "males or females A8 years" (applicable only to sites in Denmark, France, Germany and Italy) **Amendment 4**, dated 27 November 1998 (applied to Norwegian sites only): • changed the lower age limit for inclusion criterion 1, from "males or females A2 years" to "males or females A8 years" (Norway) **Amendment 5**, dated 15 December 1998 (applied to selected US sites only). The purpose of this amendment was to recruit approximately 40 subjects in order to obtain 24-hour urine cortisol levels on at least 20 subjects taking daily inhaled steroids: • included 24-hour urine collections on Days 1 and 5 on subjects taking daily inhaled steroids • detailed the procedures involved in assessing the cortisol levels. Subjects had to make an additional visit to the clinic on Day 2 to return the Day 1 collection and were provided with supplies and instructions for the Day 5 collection

		• identified the subject population to be recruited for the 24-hour urine collection • identified the additional laboratory parameters that will be assessed (cortisol level, serum creatinine and urine creatinine for creatinine clearance **Amendment 6**, dated 24 March 1999 (applied to all sites): • added an interim safety analysis of key safety data (AEs, study drug discontinuations and pulmonary function tests) to the statistical section for regulatory review. No statistical analysis was performed on any of the efficacy data and the study blind was maintained. The final efficacy analysis was not affected **Amendment 7**, dated 7 April 1999 (applied to all sites): • revised inclusion criterion 5. The section previously was: patients will have a documented history of asthma or COPD The definition of COPD for this study is 'cough productive of sputum for most days of 3 consecutive months for 2 successive years'. The definition of asthma for this study is a 'documented history of asthma requiring medication in the last 12 months'. This section was amended to: • subjects must meet the protocol definitions of asthma or COPD. The definition of COPD for this study will include the following: `Physician diagnosis of chronic airflow limitation as evidenced by either a documented history or a study Day 1 presentation of a decrease in the FEVi percent predicted of 80°/c.' (includes chronic bronchitis and/or emphysema; excludes bronchiectasis, cystic fibrosis and bronchiolitis obliterans). The definition of asthma for this study is: `A documented history of asthma requiring medication in the last 12 months or a history of reversible airflow obstruction as evidenced by a 12% response to bronchodilator therapy. • revised inclusion criterion 8. This section previously was: Patients who, in the opinion of the investigator, are able to be managed on an outpatient basis and will not be medically compromised by their participation in the study. This section was amended to: Subjects managed on an in-patient or outpatient basis may be enrolled in the study. If managed on an in-patient basis, the subject must be willing and able to follow the required dosing regimen and to complete the Diary Card and questionnaires • obtained baseline information about subjects' sleep disturbance related to asthma or COPD • included study Days 2 and/or 3 throat swabs for viral sensitivity in the Southern Hemisphere and clarified that the Study Day 1 physical examination was to be done at all study sites • included a physician global assessment of symptoms at Days 1 and 6 • added determination of severity of asthma and COPD to Day 1 assessments and provided severity classifications of asthma and COPD and related calculations

		• provided clarification about obtaining clinic FEV1. (Record best of three efforts). • included a statement regarding the continuation of the study in the Southern Hemisphere's 1999 influenza season and the possibility of the study continuing in the Northern Hemisphere in the fall and winter of 1999 and 2000 • added the Diskhaler Ease of Use Questionnaire to the Diary Card. (The questionnaire was to be completed by the subject on Day 2) • revised secondary efficacy endpoints to add Investigator Global Assessment of Symptoms. Also, changed the endpoint from "Day 2 and 3 viral titres (for subjects completing this assessment) to "Day 2 and 3 viral titres" • revised statistical information related to the additional assessments Amendment 8, dated 26 July 1999 (applied to all sites): • revised inclusion criterion 2 to clarify that the use of rapid diagnostic tests at entry was not mandatory • provided minor clarification to the severity definition
NAI30009	**Primary:** • The time to alleviation of clinically significant symptoms of influenza **Secondary:** • Time to alleviation of clinically significant symptoms of influenza and no use of relief medication • Time until the subject returns to normal activities • Incidence of complications of influenza • Mean overall assessment Diary Card symptom score over post-treatment assessments • Number of days out of Study Days 2 to 5 where cough was recorded as moderate or severe • Maximum daily temperature • Number of days of recorded use of relief medication • Total number of 12 hour periods during which supplied relief medication taken • Global assessment of symptoms at the post-treatment visit • Study Day 3 viral titer from throat swab (optional for all subjects)	The protocol for this study was amended four times, in each ease before enrollment of any subjects. The purpose of this amendment was to increase the number of study visits and clinical assessments, to obtain swabs for viral sensitivity testing from subjects, to broaden the scope of safety laboratory monitoring and to increase the number of Patient Questionnaires to be completed by subject's parent. In addition, a site specific amendment was issued as part of **Amendment 01**. This amendment applied to all study sites in Sweden and this section of the amendment specified that study sites in Sweden could not dispense 'cough mixture' as relief medication, as it is not routinely prescribed by doctors in Sweden. **Amendments 2** (dated 110ct1998) **and 3** (dated Oct1998) applied to all sites in Germany and Norway, respectively. Norway subsequently did not participate in the study as regulatory approval was not obtained. These amendments were issued in response to Ethics/Regulatory requirements in those countries. The amendments specified that enrollment of females should be restricted to pre-menarchal females only. As a result only females who were of non-child bearing potential (i.e., physiologically incapable of becoming pregnant, including any female who was pre-menarchal) was eligible to enter and participate in the study. **Amendment 04** (date which applied to 2 sites in Canada specified these two study sites would not dispense 'cough mixture' as relief medication. The use of cough medicine as relief medication in a clinical study did not reflect normal medical practice in Canada.

NAI30011	**Primary:** • Time to Alleviation of Influenza Symptoms **Secondary:** • Time Absent from Work Due to Influenza Symptoms	Dec 1998 **Amendment No. 01**: This amendment provides guidelines in determining whether influenza is circulating in communities which have participating study sites. The surveillance of influenza is essential to comply with the third inclusion criterion. Aug 1999 **Amendment No. 02:** This amendment revises the primary endpoint to time to alleviation of influenza symptoms. The laboratory test for influenza antibody detection by hemagglutination inhibition has been removed and will not be performed on subjects enrolled in the study. Prior use of zanamivir is in the list of excluded medications. Clarification on the timing of relief medication is provided. The setting has been expanded to allow use of clinics that serve the primary care needs of employed subjects.
NAI30012	**Primary:** • Time to alleviation of clinically significant symptoms of influenza **Secondary:** • Time to alleviation of clinically significant symptoms and no use of relief medications • Incidence of complications of influenza • Incidence of antibiotic use, associated with influenza complications • Time to alleviation of individual symptoms • Time to afebrile status • Supportive use of relief medications • Global Assessment of Symptoms by the investigator • Subject's overall assessment of influenza • Time to return to normal activities • Assessment of subject's routine functioning • Healthcare resource utilisation • Ease of use of the inhaler device • Subject satisfaction with the inhaler device and the study medication • Virus quantitation and susceptibility	This protocol was amended twelve times. Amendments 01 — 04 were made prior to subject enrollment. Amendments 05 — 12 were made during recruitment phases. **Protocol Amendment 01** (dated 23 Mar 1999) applied to all sites and included 'Diabetes mellitus' as an additional high-risk factor. **Protocol Amendment 02** (dated 13 Apr 1999) applied to all sites and removed reference regarding payment to subjects for participation in the study. **Protocol Amendment 03** (dated 10 May 1999) applied to Australian sites and removed **ROTADISK** labelling requirements listed in the protocol which are not required in Australia. **Protocol Amendment 04** (dated 07 June 1999) applied to all sites and required documentation of whether subject diagnosed with the complication `pneumonia' had x-ray confirmation of their disease amended the descriptions in the 4-point scale for 'Subject's Overall Assessment of Influenza' **Protocol Amendment 05** (dated 29 July 1999) applied to all sites and addition of 'Overall assessment of influenza' as a secondary endpoint stratified the statistical analysis for vaccination status • included a section on 'Payment of Subjects' for North American centres • included a subsection entitled 'Safety' as required by the Document Standard **Protocol Amendment 06** (dated 30 July 1999) applied to all sites and • removed the Day 3 Visit • addition of Day 56 Subject Contact • addition of text to clarify that adverse event and concurrent medication information was to be collected up to Day 29 (Follow-up Visit) only

		Protocol Amendment 07 (dated 15 Oct 1999) applied to all sites and • clarified inclusion criteria and further defined/clarified the collection and analysis of data based on comments received from the U.S. Food and Drug Administration • addition of MOS-6A General Health Survey • provided clarification to enhance study conduct **Protocol Amendment 08** (dated 07 Dec 1999) applied only to the Czech Republic and included a Day 3 or Day 4 telephone contact. **Protocol Amendment 09** (dated 08 Feb 2000) applied to all sites and • confirmed that Protocol Amendment 07 applied to all Southern Hemisphere sites clarified that the MOS-6A General Health Survey would be used only in those countries where it was validated **Protocol Amendment 10** (dated 30 Oct 2000) applied to all sites and confirmed that subjects who were randomised into this study during any previous influenza season were not to be recruited into the study again. **Protocol Amendment 11** (dated 24 Nov 2000) applied to all sites and clarified exclusion criteria to ensure subjects with severe persistent asthma were no longer recruited into the study. Subsequent to Protocol Amendment 11 (Section 5.2), subjects with underlying airways disease (e.g., asthma, chronic obstructive pulmonary disease) were informed of the potential risk of bronchospasm when using zanamivir. The subject was instructed that should they experience any such reaction, they should discontinue treatment and contact the investigator or clinic immediately. **Protocol Amendment 12** (dated 04 Dec 2000) applied to Canadian sites only and confirmed that Canada would use clinical trial supplies which were packed in Europe.
NAI30015	**Primary:** • Time to alleviation of clinically significant symptoms of influenza **Secondary:** • Incidence of Adverse Events • Time to alleviation of clinically significant symptoms and no use of relief medication • Time to afebrile status	This protocol was amended once on 05 October 1999 Add an extra 'Fitness for Duty Classification' and amend classification 'K', and to ensure consistency between 'fitness for duty' questions stated in the protocol with those stated in the diary. Clarify where the 'time of sampling' was to be documented for swabs taken at specific timepoints Clarify that compliance checks that are carried out during the study were documented in the Drug Accountability/Dispensing log and summarised in the compliance section on Day 6. Remove reference to 'Record of Death' from the protocol

	• Time to return to normal activities • Incidence of complications of influenza • Incidence of use of antibiotics to treat complications of influenza • Mean of each individual Diary symptom score over post-treatment assessments • Maximum daily temperature • Total number of 12 hour periods during which supplied paracetamol was taken over the treatment period • Viral titre from throat swab on Study Days 2 and 3 (mandatory for all subjects) • MEP abnormalities (in a sub-set of subjects)	
NAI30020	**Primary:** • Time to normal temperature within patients **Secondary:** • Time until the easing of remaining clinical main symptoms of influenza	Not reported (only synopsis available)
NAI30028	**Primary:** • Time up until all of the clinically significant primary symptoms of influenza have regressed **Secondary:** • Time up until return to normal activity • Incidence of complications • Productivity	No amendments
NAIA/B2008	**Primary:** • Time to alleviation of major influenza symptoms **Secondary:** • Time to eradication of major	**Amendment 01:** 18 August 1995 To correct typographical errors and inconsistencies, alter Section 3.3 'Use in females' and add in a paragraph to the statistics section **Amendment 02:** 21 August 1995 Standard French administrative amendment

	influenza symptoms • Time to eradication of each of the symptoms on the Diary Card • Time until the patient returns to normal activities • Number of days that the overall symptom assessment is recorded as "none" or "mild" • Number of days that at least one symptom is recorded as "none" or "mild" • Number of days that sleep disturbance is recorded as "not at all" or "slightly" • Mean daily temperature over the treatment period • Mean daily number of administrations of supplied relief medication • Mean daily number of administrations of supplied cough mixture over the treatment period • Investigator rated Global Assessment of Symptoms at the Post-treatment Visit • Hospitalisation • Secondary infection • Use of anti-infective medication	**Amendment 03:** 8 November 1995 To specify minimum age for inclusion of 18 years as requested by Regulatory/ Ethics Authorities **Amendment 04:** 8 November 1995 To clarify exclusion criteria, following FDA comments **Amendment 05:** 16 November 1995: Standard Danish administrative amendment **Amendment 06:** 14 December 1995 To document extra daily nasal wash sampling to be performed at this study center for analysis (including quantitative analysis) of influenza virus **Amendment 07:** 23 January 1996 To clarify the primary outcome measures and the statistical methods following further regulatory and statistical advice from FDA
NAIA2005	**Primary:** • Time to alleviation of major influenza symptoms **Secondary:** • Time to eradication of major influenza symptoms • Mean daily temperature over the study treatment period • Mean daily viral shedding over the study treatment period • Number of days over the study period that sleep disturbance is recorded as "moderate" or "severe" • Investigator Global Assessment of	**Protocol amendment 1** (dated 3 October 1994) made 35 modifications to the protocol. Some of the major modifications are outlined below: • amended protocol to include both Investigational New Drug Application (IND) numbers: 43,776 and 46,050 • modified the inclusion criteria to specify fever as a temperature 37.8°C or 100.1°F • changed 'rescue medications' to 'relief medications' • changed patient populations from S=subset of patients at centers with experience in virology and X=all patients to C=core center patients (centers with experience in virology), T=target patients (patients with whom symptom assessments and diary cards were reviewed by study site personnel) and X=all patients • defined target patient population as one out of every 6 patients (except core center patients) who was targeted for additional face-to-face diary card review and clinical symptom assessment by site study staff on Days 2, 4 and 8. A separate randomization schedule to identify the target patients was also provided by Glaxo Wellcome Inc

	Symptoms • Number of days over the entire study period that a patients' Overall Symptom Score is reported as moderate or severe • Mean severity of each influenza related symptoms over time • Time to return of normal daily activities • Time to eradication of fever, maintained over the next 24 hours • Time to eradication of headache • Time to eradication of myalgia • Frequency of use of relief medication	• added urine pregnancy test on Day I to the blood pregnancy tests to be performed on Days 1 and 21 • modified adverse events to include those that were temporally related to study drug administration even though the investigator considered it to be part of the natural progression of influenza • clarified the clinical symptom assessment and the diary card review for the core center and target patients • added section on unscheduled visits and clarified the withdrawal information • revised statistical methods section **Protocol amendment 2** (dated 9 February 1995) made the following modification to the protocol: • changed one exclusion criteria from patients with influenza vaccines administered since August 1993 to patients with influenza vaccines administered since 1 October 1994 Both of these protocol amendments applied to all centers involved in the study. Protocol **Amendment 1** was implemented prior to the commencement of recruitment. **Amendment 2** was implemented during the course of recruitment.
NAIA3002	**Primary:** • Time until alleviation of clinically significant symptoms **Secondary:** • Time to alleviation of clinically significant symptoms and no use of relief medication • Time until the patient returns to normal activities • Mean overall assessment diary card symptom score over post-treatment assessments • Mean symptom score over post-treatment assessments on Days I to 5 for individual symptoms • Maximum daily temperature • Total number of tablets of supplied acetaminophen taken over the treatment period • Total number of spoonfuls (5mL) of supplied cough mixture taken over the treatment period • Global assessment of symptoms	**Protocol amendment 01** (dated 21 August 1997) was applicable to all of the investigators and made eight modifications to the protocol. The major modifications are as follows: • reference to 5ml, spoonfuls of dextromethorphan was deleted • study personnel recorded in the CRF, instead of the Diary Card, whether the first dose of study medication was given before or after 14:00 hours • secondary complications would be recorded in the CRF according to the categories provided in Appendix 4 • the second Diary Card, which included symptom assessments and relief medication use, was to be completed twice a day. The questions on subject productivity and ability to perform normal activities would be completed once a day • appendix 4 defined the categories of influenza complications **Protocol amendment 02 (dated 30 October 1997)** only applied to specific sites. Appendix 5 was added to the protocol that allowed the effects of naturally occurring viral infection on the middle ear to be investigated **Protocol amendment 03** (dated 22 December 1997) only applied to two Canadian sites. Appendix 6 was added to the protocol that allowed for provision of throat swab samples for subsequent processing

	at the post-treatment visit • Incidence of complications of influenza • Day 3 viral titer from throat swab (for centers completing this assessment) • Productivity and healthcare resource	
NAIB2005	**Primary:** • Time to alleviation of major influenza symptoms **Secondary:** • Time to eradication of major influenza symptoms • Mean daily temperature over the study treatment period • Mean daily viral shedding over the study treatment period • Proportion of days over the study period that sleep disturbance is recorded as 'moderate' or 'severe'. • Investigator rated Global Assessment of Symptoms • Proportion of days over the study period that patient Overall Symptom Assessment (OSA) is recorded as 'moderate' or 'severe' • Proportion of days over the study period that at least one symptom is rated as 'moderate' or 'severe' • Time until the patient returns to normal activities • Time until feverishness is rated as 'none' • Time until headache is rated as 'none' • Time until myalgia is rated as 'none' • Mean daily use of relief mediation over study treatment period • Proportion of days over the study period that individual symptoms are rated as 'moderate' or 'severe'	Protocol **amendment 1** (dated 1 August 1994) applied to centers in France only and was an administrative amendment which was made in order to make the protocol consistent with the requirements of French law (n° 88-1138 10 December 1988). Protocol **amendment 2** (dated 31 August 1994) referred to centers in Ireland only. This amendment excluded patients who had received any other investigational drug in the previous 16 weeks before the study as this is a requirement of Irish law. Both of these amendments were implemented prior to the commencement of recruitment

NAIB2007	Primary: Time to alleviation of major influenza symptoms Secondary: • Time to eradication of major influenza symptoms • Mean daily temperature over the study treatment period • Mean daily viral shedding over the study treatment period • Proportion of days over the study period that sleep disturbance is recorded as 'moderate' or 'severe'. • Investigator rated Global Assessment of Symptoms • Proportion of days over the study period that patient Overall Symptom Assessment (OSA) is recorded as 'moderate' or 'severe' • Proportion of days over the study period that at least one symptom is rated as 'moderate' or 'severe' • Time until the patient returns to normal activities • Time until feverishness is rated as 'none' • Time until headache is rated as 'none' • Time until myalgia is rated as 'none' • Mean daily use of relief mediation over study treatment period • Proportion of days over the study period that individual symptoms are rated as 'moderate' or 'severe' • Number of hospitalisations • Incidence of secondary infections	Protocol **amendment 1** (dated 11 May 1995) applied to all centers that to date were conducting the study. This amendment excluded patients with asthma due to delay in availability of a bronchial reactivity study. Protocol **amendment 2** (dated 24 January 1996) referred to all centers that to date were conducting the study. As experience had been gained with zanamivir during an additional year of clinical studies and results for a bronchial reactivity study became available, amendments included the inclusion of patients with asthma and reduction in the lower age limit to 13 years. Amendment 2 was incorporated in a revised working protocol including amendment 2. Protocol **amendment 3** (dated 13 June 1996) was implemented for all centers. Glaxo Wellcome had reviewed procedures which necessitated revising the definition of serious adverse events and time line changes for reporting adverse events. Amendments were also made to definitions for primary and secondary efficacy parameters, and statistical analyses were modified. Protocol **amendments 4 to 7** (dated 13 June 1996) referred to particular study centers; amendment was made to the age range included (13 to 65 years, 16 to 65 years and 18 to 65 years, respectively) and inclusion or exclusion of patients with asthma, to meet local regulatory and ethics committee requirements.
NAIB3001	**Primary:** • Time until alleviation of clinically significant symptoms of influenza **Secondary:**	Protocol **amendment 1** (dated June 1997) applied to three Australian centers only. This amendment was to add an additional study protocol designed to collect pharmacoeconomic data which involved a face-to-face interview with Influenza Positive patients after their Day 28 visit. The NAIB3001 patient population was chosen to enable a pod of Influenza Positive patients to be interviewed. This study was conducted independently from NAIB3001 and

	• Time to eradication of clinically significant influenza symptoms • Time to eradication of influenza symptoms • Time to alleviation of each of the diary card symptoms calculated separately • Time until the patient returns to normal activities • Mean symptom score over post-treatment assessments • Maximum daily temperature • Mean number of days when sleep was disturbed not at all' or 'slightly' • Mean daily number of tablets or spoonfuls of relief medication over the treatment period • Incidence of complications of influenza	therefore, the results have not been presented in this report.
NAIB3002	**Primary:** • Time until the alleviation of clinically significant symptoms of influenza **Secondary:** • Time to alleviation of clinically significant symptoms of influenza and no use of relief medication • Time until the patient returns to normal activities • Mean overall assessment diary card symptom score over post-treatment assessments • Mean symptom score over post-treatment assessments on Days 1 to 5 for each of the individual symptoms • Maximum daily temperature • Number of tablets or spoonful of relief medication taken over	Protocol **amendment 01** was applicable to all of the investigators. It corrected typographical errors and inconsistencies and included further categories to be used to assess secondary complications of influenza. The major modifications were as follows: • Reference to '5111; spoonfuls of dextromethorphan was deleted • Study personnel recorded, in the (instead of the Diary Card), whether the first dose of study medication was given before or after 14:00 hours • Secondary complications would be recorded in the CRF according to the categories provided in Appendix 9 • The second Diary Card, which included symptom assessments and relief medication use, was to be completed twice a day. The questions on subject productivity and ability to perform normal activities would be completed once a day • The Written Subject Consent Form was amended to include a statement that the subject's doctor/nurse would also need to take a throat swab on Day 6 • Appendix 9 defined the categories to be used to document influenza complications Protocol **amendment 02** applied to all centers in Denmark, France, Holland, Italy and Norway, and specified that the minimum age for inclusion was to be 18 years. This was in response to Ethics/Regulatory issues in those countries. Protocol **amendment 03** was a standard administrative amendment to meet the requirements of French law no. 88-1138, of 20 December 1988,

	treatment period • Global assessment of symptoms at the post-treatment visit • Incidence of complications of influenza • Day 3 viral titer from throat swab (for centers completing this assessment) • Productivity and healthcare resource utilization	and modified by French Law No. 94-630, of 25 July 1994.

*The prespecified outcomes are as reported in the study protocols