SYNOPSIS

Name of Sponsor/Company	Daiichi Sankyo Co., Ltd.
Name of Finished Product	INAVIR® DRY POWDER INHALER 20 mg
Name of Active Ingredient	Laninamivir Octanoate Hydrate（JAN）
Title of Study	A Phase 3 Study of CS-8958 (Postexposure Prophylaxis) －A randomized, double-blind, placebo-controlled study to confirm efficacy in the prevention of influenza virus infection－
Investigators	
Study Centre(s)	
Publication (reference)	Not published.
Studied Period	
Phase of Development	Phase 3
Objectives	A randomized, double-blind, placebo-controlled, comparative study was conducted to investigate the efficacy of 1 inhaled treatment a week (2 inhaled treatments total) of CS-8958 20 mg or 40 mg for the prevention of influenza virus infection in household members of patients with influenza A or B virus infection. The primary efficacy endpoint was the proportion of participants with clinical influenza virus infection, and the objective was to evaluate superiority of CS-8958 to placebo. For safety, the incidence of adverse events was compared between the treatment groups. The optimal clinical dose was investigated on the basis of the results of the efficacy and safety of inhaled treatments of CS-8958 20 mg or 40 mg.
Methodology	A multicenter, randomized, double-blind, , parallel-group, placebo-controlled, comparative study
Number of Patients (planned and analyzed)	Planned: 600 participants (200 in the CS-8958 20 mg group, 200 in the CS-8958 40 mg group, and 200 in the placebo group) Analyzed: Full analysis set (FAS): 610 participants (207 in the CS-8958 20 mg group, 205 in the CS-8958 40 mg group, and 198 in the placebo group)
Diagnosis and Main Criteria for Inclusion	Index patients: 1) Positive result on the influenza rapid diagnostic test 2) No household members with influenza A or B virus infection in

	the 4 weeks prior to informed consent Participants: 1) Household member of a patient with influenza A or B virus infection 2) Negative result on the influenza rapid diagnostic test 3) Body temperature (axillary) at informed consent ≤ 36.9°C 4) No symptoms that cannot be distinguished from influenza(headache, myalgia/arthralgia, fatigue, chills/perspiration, nasal symptoms, sore throat, or cough) at informed consent 5) Investigator has determined that the individual will be able to use the provided inhaler
Test Product, Dose and Mode of Administration, Batch Number	CS-8958-20TC (containing 20 mg as CS-8958) CS-8958-20PTC (placebo, externally indistinguishable from the CS-8958) In the CS-8958 20 mg group: Participants inhaled one CS-8958-20TC and one CS-8958-PTC per week, and a total of two times. In the CS-8958 40 mg group: Participants inhaled two CS-8958-20TC per week, and a total of two times. In the placebo group, Participants inhaled two CS-8958-PTC per week, and a total of two times.
Duration of Treatment	Once a week for 2 weeks, and a total of 2 times
Reference Therapy, Dose and Mode of Administration, Batch Number	-
Criteria for Evaluation	Primary Endpoint: Proportion of participants with clinical influenza virus infection A participant with clinical influenza virus infection was defined as having a clinical influenza virus infection when a positive virus test result was obtained, body temperature was 37.5°C or more, and at least 2 of the 7 influenza symptoms (headache, myalgia/arthralgia, fatigue, chills/perspiration, nasal symptoms, sore throat, and cough) were observed.
Statistical Method	Primary analysis (efficacy): The CS-8958 20 mg group and 40 mg group were compared with the placebo group using the Fisher exact test. A significance level of 5%, 2-sided, was used, and the Holm method was used for

	multiplicity adjustment. In addition, the relative risk compared with the placebo group as well as their 95% confidence intervals (CIs) were calculated. Safety analysis: The numbers and proportions of participants with all-cause and drug-related adverse events were calculated by treatment group.
Summary - Conclusion	The proportion of participants with clinical influenza virus infection was 4.8% (10 of 207) in the CS-8958 20 mg group, 4.9% (10 of 205) in the CS-8958 40 mg group, and 8.6% (17 of 198) in the placebo group. Although the proportion was lower in both the CS-8958 20 mg group and the CS-8958 40 mg group than in the placebo group, the differences were not statistically significant (*P* = 0.1633 [CS-8958 20 mg group], *P* = 0.1643 [CS-8958 40 mg group] by the Fisher exact test). The relative risk reduction (95% CI) compared to placebo was 43.7% (−19.9 to 73.6) in the CS-8958 20 mg group and 43.2% (−21.0 to 73.3) in the CS-8958 40 mg group. The incidence of adverse events was similar among all the treatment groups, and no major safety concerns were noted in either of the CS-8958 group. The aforementioned results suggested that CS-8958 is effective for the prevention of influenza virus infection in household members of patients with influenza virus infection; however, superiority to placebo could not be confirmed, and it was concluded that further study to evaluate appropriate dosage for the prophylaxis of influenza virus infection would be necessary.
Date of Report	Sep, 2014