SYNOPSIS

Name of Sponsor/Company	Daiichi Sankyo Co., Ltd.
Name of Finished Product	INAVIR® DRY POWDER INHALER 20mg
Name of Active Ingredient	Laninamivir Octanoate Hydrate（JAN）
Title of Study	A randomized double-blind controlled exploratory study comparing CS-8958 to oseltamivir phosphate in patients with influenza virus infection (Phase 2)
Investigators	
Study Centre(s)	
Publication (reference)	Not published.
Studied Period	
Phase of Development	Phase 2
Objectives	A 4-arm, randomized, double-blind comparative study in patients with type A or B influenza virus infection was performed to evaluate the efficacy and safety of a single inhalation of CS-8958 5 mg, 10 mg, or 20 mg, with oseltamivir phosphate as the comparator.
Methodology	4-arm, multicenter, randomized, active control, double-blind, parallel comparative study
Number of Patients (planned and analyzed)	Planned number of patients：280 subjects (70 each in CS-8958 5 mg group, 10 mg group, and 20 mg group, and oseltamivir phosphate group) Full analysis set (FAS): 322 patients (CS-8958 5 mg group: 79 subjects, CS-8958 10 mg group: 83 subjects, CS-8958 20 mg group: 77 subjects, and oseltamivir phosphate group: 83 subjects)
Diagnosis and Main Criteria for Inclusion	1) Patients diagnosed with influenza virus infection who met all of the following inclusion criteria ・ Influenza virus-positive by an influenza rapid diagnostic kit ・ Body temperature (axillary) ≥ 37.5°C at the time of informed consent ・ Study treatment could be started within 36 hours after the onset of any influenza symptoms (eg fever [feeling of fever], headache, myalgia/arthralgia, fatigue, chill/sweating, nasal symptoms, sore throat, cough) 2) Aged 20 to 64 years as of informed consent
Test Product, Dose and Mode	CS-8958

of Administration	CS-8958 placebo Patient received a single inhalation of CS-8958 5, 10, 20 mg or placebo using a inhaler.
Duration of Treatment	Single dose (5 days for the control drug)
Reference Therapy, Dose and Mode of Administration	Oseltamivir phosphate 75 mg capsule Oseltamivir phosphate placebo capsule Patient received 75 mg (as oseltamivir) or placebo orally twice daily for 5 days.
Criteria for Evaluation	Primary Endpoint: Time to Resolution of Fever (36.9°C or Lower) Secondary Endpoints: Time to alleviation of influenza illness
Statistical Method	Efficacy Analysis; Primary analysis: The median differences between the oseltamivir phosphate group and each CS-8958 treatment group (the median of the CS-8958 treatment group − the median of the oseltamivir phosphate group) in the time to resolution of fever and 95% CIs were calculated. When the upper limit of 95% CI was less than 24 hours, CS-8958 was to be considered to be an effective therapeutic drug for influenza virus infection. The generalized Wilcoxon test was performed using the oseltamivir phosphate group as a control group. Secondary analysis: The median differences between the oseltamivir phosphate group and each CS-8958 treatment group in Time to alleviation of influenza illness and 95% CIs were calculated. The generalized Wilcoxon test was performed using the oseltamivir phosphate group as a control group. Safety Analysis; Adverse Events: The number of subjects and the incidence by treatment group were obtained for study drug-related adverse events and all adverse events. Similar analysis was also performed for each event and severity.
Summary - Conclusion	Efficacy (primary endpoint): The median of the primary endpoint “time to resolution of fever” was 60.4 hours in the CS-8958 5 mg group, 54.6 hours in the CS-8958 10 mg group, 54.3 hours in the CS-8958 20 mg group, and 42.3 hours in the oseltamivir phosphate group. The median differences (95% CI) between each CS-8958 treatment group and the oseltamivir phosphate group were 18.1 hours (0.9 to 23.4) in

	the CS-8958 5 mg group, 12.3 hours (−3.0 to 18.5) in the CS-8958 10 mg group, and 12.0 hours (−8.3 to 15.0) in the CS-8958 20 mg group. The upper limit of 95% CI of the difference was less than 24 hours, although it was statistically significant in the CS-8958 5 mg group.The medians of the secondary endpoint “time to alleviation of influenza illness” were 92.8 hours in the CS-8958 5 mg group, 82.6 hours in the CS-8958 10 mg group, 81.8 hours in the CS-8958 20 mg group, and 82.7 hours in the oseltamivir phosphate group. The median differences (95% CIs) between each CS-8958 treatment group and the oseltamivir phosphate group were 10.1 hours (−12.1 to 29.8) in the CS-8958 5 mg group, −0.2 hours (−16.9 to 22.4) in the CS-8958 10 mg group, and −0.9 hours (−22.3 to 17.7) in the CS-8958 20 mg group. Values of both CS-8958 10 mg group and 20 mg group were comparable to that of the oseltamivir phosphate group. Safety: Adverse events occurred in 26.6% (21/79) of subjects in the CS-8958 5 mg group, 33.7% (28/83) in the CS-8958 10 mg group, 41.6% (32/77) in the CS-8958 20 mg group, and 33.7% (28/83) in the oseltamivir phosphate group.
Date of Report	August 30, 2011