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, placebo-controlled, multi-center phase II study for the evaluation of efficacy and safety of CS-8958 in patients with influenza virus infection
Investigators	
Study Centre(s)	
Publication (reference)	Not published.
Studied Period	
Phase of Development	Phase II
Objectives	The primary objective of this study was to evaluate the efficacy after a single dose of 10 mg or 20 mg of CS-8958 in patients with influenza virus A or B infection using the time to resolution of fever after treatment as the primary endpoint.
Methodology	Randomized double-blind, placebo controlled, parallel group, multi-center study of a single dose of CS-8958 at 10 mg or 20 mg
Number of Patients (planned and analyzed)	Planned number of patients：180 patients CS-8958 10 mg group, 60 patients; CS-8958 20 mg group, 60 patients ; Placebo group, 60 patients Full analysis set (FAS):174 patients CS-8958 10 mg group. 56 patients; CS-8958 20 mg group, 59 patients; Placebo group. 59 patients
Diagnosis and Main Criteria for Inclusion	Patients who met following criteria were enrolled. 1. Male or female patients aged 18 to 64 years. 2. Outpatients. 3. Providing written informed consent. 4. Patients with a positive rapid diagnostic test result for influenza virus A and/or B. 5. Patients with an ear temperature of ≥ 37.8°C. 6. Patients who presented the onset of influenza symptoms (fever, headache, myalgia/arthralgia, fatigue, chill/perspiration, nasal symptom, sore throat, cough, etc.) within 36 hours.
Test Product, Dose and Mode of Administration	CS-8958 CS-8958 placebo Patient received a single inhalation of CS-8958 10 mg, 20 mg or

	placebo using a inhaler.
Duration of Treatment	Single dose
Reference Therapy, Dose and Mode of Administration	None
Criteria for Evaluation	Primary Endpoint: Time to Resolution of Fever (≤ 37.2°C) Secondary Endpoints: Time to alleviation of influenza illness
Statistical Method	Efficacy Analysis; Primary analysis: The time to resolution of fever was analyzed using the generalized Wilcoxon test, and its 95% confidence interval for the difference of median time to resolution of fever between treatment groups were estimated. And median time to resolution of fever, its 95% confidence interval, and other summary statistics were calculated for each treatment group. Secondary analysis:The difference in the median of the CS-8958 treatment groups and its 95% confidence interval was calculated, and the generalized Wilcoxon test was conducted. Safety Analysis; Adverse Events: The number of patients and the incidence in each 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): Primary analysis: The Kaplan-Meier plot was comparable between the treatment groups. The median of the primary endpoint “time to resolution of fever” was 39.7 h in CS-8958 10 mg group, 38.5 h in CS-8958 20 mg group, and 41.0 h in placebo group, and there were no statistically significant differences between each CS-8958 group and the placebo group. The differences (95% confidence interval) of the median time to resolution of fever between each CS-8958 group and placebo group were -1.3 h (-13.5 to 7.5) in CS-8958 10 mg group and -2.5 h (-12.2 to 9.8) in CS-8958 20 mg group. Secondary analysis: The median of the secondary endpoint “time to alleviation of influenza illness” was 62.0 h in CS-8958 10 mg group, 49.9 h in CS-8958 20 mg group, and 84.0 h in placebo group, and there were no statistically significant differences between each CS-8958 group

	and the placebo group. The differences (95% confidence interval) of the median time to alleviation of influenza illness between the CS-8958 groups and placebo group were -22.0 h (-44.7 to 5.6) in CS-8958 10 mg group, and -34.1 h (-43.8 to 4.4) in CS-8958 20 mg group.Although there was no statistically significant difference, all of the doses tested shortened the time to alleviation of influenza illness when compared with placebo. Safety: AEs occurred in 25.9% (15/58) of patients in CS-8958 10 mg group, 21.7% (13/60) in CS-8958 20 mg group, and 22.6% (14/62) in placebo group. No significant safety concerns were raised in all CS-8958 groups.
Date of Report	August 30, 2011