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 Phase 3 Study of CS-8958 − A randomized double-blind comparative study of CS-8958 in patients with influenza virus infection aged 10 to 19 years −
Investigators	
Study Centre(s)	
Publication (reference)	Not published.
Studied Period	
Phase of Development	Phase 3
Objectives	A randomized, double-blind comparative study was conducted to assess the efficacy and safety after a single inhalation of CS-8958 20 mg or 40 mg in patients (aged 10 to 19 years) with type A or B influenza virus infection.
Methodology	A 2-arm, multicenter, randomized, uncontrolled, double-blind, parallel comparative study
Number of Patients (planned and analyzed)	Planned number of patients：120 subjects (CS-8958 20 mg group: 60 subjects, CS-8958 40 mg group: 60 subjects) Full analysis set (FAS): 120 subjects (CS-8958 20 mg group: 64 subjects, CS-8958 40 mg group: 56 subjects)
Diagnosis and Main Criteria for Inclusion	Patients with type A or B influenza virus infection who met all of the following inclusion criteria were enrolled in this study. 1) Influenza virus-positive by an influenza rapid diagnostic kit, and diagnosed with influenza virus infection by the investigators 2) Body temperature (axillary) ≥ 37.5°C at the time of informed consent 3) Within 36 hours after the onset of any influenza symptoms (fever [feeling of fever], headache, myalgia/arthralgia, fatigue, chill/sweating, nasal symptoms, sore throat, cough) at the time of informed consent 4) Aged 10 to 19 years as of informed consent 5) Patients the investigators considered able to inhale the study

	drug using the inhaler
Test Product, Dose and Mode of Administration	CS-8958 CS-8958 placebo Subjects received a single inhalation of CS-8958 20 or 40 mg using an inhaler.
Duration of Treatment	Single dose
Reference Therapy, Dose and Mode of Administration	None
Criteria for Evaluation	Primary Endpoint: Time to Alleviation of Influenza Illness
Statistical Method	Efficacy Analysis; Primary analysis: Kaplan-Meier plots were prepared, summary statistics including the median time to alleviation of influenza illness and 95% confidence intervals (CIs) were calculated by group, and a generalized Wilcoxon test was performed between CS-8958 doses. The inter-dose difference in the median (40 mg group − 20 mg group) was calculated and its 95% CI was calculated based on the statistics obtained by the generalized Wilcoxon test. Safety Analysis; 1) Adverse Events The number of subjects with adverse events and their incidence were presented by causal relationship (all/related) by treatment group. Serious adverse events, severe adverse events and discontinuations due to adverse events were also calculated. The number of subjects with each adverse event and the incidence were presented for causal relationship (all/related) and for severity and causal relationship (all/related) by treatment group. 2) Clinically Significant Adverse Events The number of subjects with neuropsychiatric events during influenza infection (all, by category) was calculated by treatment group.
Summary - Conclusion	Efficacy (primary endpoint): The median time to alleviation of influenza illness, which was the primary endpoint, was 87.1 hours in the 20 mg group and 76.0 hours in the 40 mg group. The median difference (95% CI) between the 20 mg group and 40 mg group was −11.1 (−32.9 to 13.0) hours and the time to alleviation of influenza illness was

	shorter in the 40 mg group compared to the 20 mg group, though it was not statistically significant. The hazard ratio (95% CI) of the 40 mg group to 20 mg group was 1.127 (0.782 to 1.624) and no significant difference was noted. Safety: The incidence of adverse events was 28.1% (18/64) in the 20 mg group, 28.6% (16/56) in the 40 mg group and 28.3% (34/120) in the overall population, and comparable between the 20 mg and 40 mg groups. The incidence of neuropsychiatric events was 3.1% (2/64) in the 20 mg group, 7.1% (4/56) in the 40 mg group and 5.0% (6/120) in the overall population.
Date of Report	August 30, 2011