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 2 Study of Repeated Administration of CS-8958 − A randomized double-blind controlled exploratory study comparing repeated administration of CS-8958 to oseltamivir phosphate in patients with influenza virus infection −
Investigators	
Study Centre(s)	
Publication (reference)	Not published.
Studied Period	
Phase of Development	Phase II
Objectives	A 2-group, 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 double inhalation of CS-8958 20 mg with oseltamivir phosphate as the comparator.
Methodology	2-group, multicenter, randomized, active control, double-blind, parallel comparative study
Number of Patients (planned and analyzed)	Planned number of patients：140 subjects (70 subjects in the CS-8958 group, 70 subjects in the oseltamivir phosphate group) Full analysis set (FAS): 187 subjects (93 subjects in the CS-8958 group, 94 subjects in the oseltamivir phosphate group)
Diagnosis and Main Criteria for Inclusion	Patients with type A or B influenza virus infection who met all of the following inclusion criteria were eligible to participate in the 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 ≥ 20 years as of informed consent
Test Product, Dose and Mode of Administration	CS-8958 CS-8958 placebo Subjects in the CS-8958 groups received CS-8958 20 mg by inhalation once daily for 2 days using an inhaler.
Duration of Treatment	2 days (5 days for the control drug)
Reference Therapy, Dose and Mode of Administration	Oseltamivir phosphate 75 mg capsule Oseltamivir phosphate placebo capsule Subjects in the oseltamivir phosphate group received 75 mg (as oseltamivir) orally twice daily for 5 days.
Criteria for Evaluation	Primary Endpoint: Time to Alleviation of Influenza Illness
Statistical Method	Efficacy Analysis; Primary analysis: The difference in the median time to alleviation of influenza illness between the CS-8958 group and the oseltamivir phosphate group (CS-8958 group − oseltamivir phosphate group) was calculated, and the 95% confidence interval (CI) was then calculated based on the generalized Wilcoxon test statistics. A generalized Wilcoxon test was performed with the oseltamivir phosphate group as the comparator. Safety Analysis; Adverse Events: The number of subjects with adverse events and the incidence of adverse events were presented by causal relationship (all/drug-related) for each treatment group. Serious adverse events, severe adverse events, and adverse events leading to discontinuation were summarized in the same manner. The number of subjects with individual adverse events and the incidence of individual adverse events were also presented by causal relationship (all/drug-related) as well as by severity and causal relationship (all/drug-related) for each treatment group.
Summary - Conclusion	Efficacy (primary endpoint): The Kaplan-Meier plot of the time to alleviation of influenza illness, which was the primary endpoint, showed a tendency toward shorter time to resolution in the CS-8958 group than in the oseltamivir phosphate group. The median time to alleviation of influenza illness was 86.0 hours in the CS-8958 group and 87.4 hours in the oseltamivir phosphate group. The difference in the

	median time to alleviation of influenza illness between the CS-8958 group and the oseltamivir phosphate group (95% CI) was −1.4 (−27.6 to 7.3) hours; the time to alleviation of influenza illness was comparable between the CS-8958 group and the oseltamivir phosphate group. In the comparison of the time to alleviation of influenza illness between the CS-8958 group and the oseltamivir phosphate group using Cox regression, which was performed as the secondary analysis of the primary endpoint, the hazard ratio (95% CI) of the CS-8958 group to the oseltamivir phosphate group was 1.292 (0.939 to 1.779). No statistically significant difference was found between the CS-8958 group and the oseltamivir phosphate group. Safety: The incidence of adverse events was 20.4% (19/93) in the CS-8958 group and 22.3% (21/94) in the oseltamivir phosphate group, and was comparable between the CS-8958 group and the oseltamivir phosphate group.
Date of Report	August 30, 2011