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 2/3 Study of CS-8958 in Pediatric Patients -A randomized double-blind controlled study of CS-8958 comparing with oseltamivir phosphate in patients with influenza virus infection aged 9 years or younger -
Investigators	
Study Centre(s)	
Publication (reference)	Antimicrob Agents Chemother. 2010 Jun;54(6):2575-82.
Studied Period	
Phase of Development	Phase 2, Phase 3
Objectives	A 3-arm, randomized, double-blind comparative study in pediatric patients (aged 9 years and under) with type A or B influenza virus infection was performed to evaluate the efficacy and safety of a single inhalation of CS-8958 20 mg or 40 mg, with oseltamivir phosphate as a control.
Methodology	3-arm, multicenter, randomized, active control, double-blind, parallel comparative study
Number of Patients (planned and analyzed)	Number of Planned Subjects:180 subjects (60 subjects each in CS-8958 20 mg group, 40 mg group, and oseltamivir phosphate group) Full analysis set (FAS):184 subjects (CS-8958 20 mg group: 61 subjects, CS-8958 40 mg group: 61 subjects, and oseltamivir phosphate group: 62 subjects)
Diagnosis and Main Criteria for Inclusion	Patients with type A or B influenza virus infection who met all the following criteria: 1) Influenza virus-positive by an influenza rapid diagnostic kit, and diagnosed with influenza virus infection by the investigators 2) Body temperature (axillary) ≥ 38.0℃ at the time of informed consent 3) Within 36 hours after the onset of any influenza symptoms (eg fever [feeling of fever], nasal symptoms, cough) at the time of informed consent 4) Aged ≤ 9 years as of the last study treatment 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 Patients inhaled a single dose of the following drugs using an inhaler: CS-8958 and CS-8958 placebo in the CS-8958 20 mg group, and CS-8958 in the CS-8958 40 mg group, and CS-8958 placebo in the oseltamivir phosphate group.
Duration of Treatment	Single dose (5 days for the control group)
Reference Therapy, Dose and Mode of Administration	Oseltamivir phosphate dry syrup Oseltamivir phosphate placebo Patients took oral oseltamivir phosphate placebo twice daily for 5 days in the CS-8958 20 and 40 mg groups. In the oseltamivir phosphate group, patients took oral oseltamivir phosphate dry syrup at a dose of 66.7 mg/kg (equivalent to 2 mg/kg of oseltamivir) twice daily for 5 days.
Criteria for Evaluation	Time to alleviation of influenza illness
Statistical Method	Efficacy Analysis; Primary analysis: The median differences between each CS-8958 group and the oseltamivir phosphate group (CS-8958 group − oseltamivir phosphate group) were calculated. The 95% CIs were calculated from generalized Wilcoxon test statistics. In addition, the generalized Wilcoxon test was performed using the oseltamivir phosphate group as a control. Safety Analysis; Adverse Events The number of subjects with adverse events and their incidence were presented by causal relationship (all/related) for each treatment group. Serious adverse events, severe adverse events and discontinuations due to adverse events were also summarized. The number of subjects with each adverse event and the incidence were presented by causal relationship (all/related) and by severity and causal relationship (all/related) for each treatment group.
Summary - Conclusion	Efficacy (primary endpoint): The median time to alleviation of influenza illness was 56.4 hours in the CS-8958 20 mg group, 55.4 hours in the CS-8958 40 mg group, and 87.3 hours in the oseltamivir phosphate group. The median differences (95% CI) between each CS-8958 group and the

	oseltamivir phosphate group were −31.0 (−50.3 to −5.5) hours in the 20 mg group and −31.9 (−43.4 to 0.5) hours in the 40 mg group. The time to alleviation of influenza illness was significantly shorter in the CS-8958 20 mg group than in the oseltamivir phosphate group. Although it was not statistically significant, the time to alleviation of influenza illness in the CS-8958 40 mg group was also shorter than in the oseltamivir phosphate group. Safety: The incidence of adverse events was 34.4% (21/61) in the CS-8958 20 mg group, 24.2% (15/62) in the CS-8958 40 mg group, 29.3% (36/123) in both CS-8958 groups, and 38.7% (24/62) in the oseltamivir phosphate group. There was no major difference in the incidence of adverse events between each CS-8958 group and the oseltamivir phosphate group.
Date of Report	August 30, 2011