SYNOPSIS

Name of Sponsor/Company	Daiichi Sankyo Co., Ltd.
Name of Finished Product	NARURAPID® TABLETS
Name of Active Ingredient	hydromorphone hydrochloride (INN)
Title of Study	DS-7113b phase III study A randomized double-blind comparison study with immediate release (IR) oxycodone in opioid-naive patients with cancer pain
Investigators	-
Study Centre(s)	50 sites
Publication (reference)	
Studied Period	December 2013 – October 2014
Phase of Development	Phase 3
Objectives	To evaluate the efficacy and safety of DS-7113b IR tablet additionally dosed in a randomized double-blind comparison study with IR oxycodone in opioid-naive patients under cancer pain management refractory to non-opioid analgesics.
Methodology	A multicenter, active controlled, randomized, double-blind, parallel-group study
Number of Patients (planned and analyzed)	Planned:180 subjects Analyzed: 172 subjects
Diagnosis and Main Criteria for Inclusion	Inclusion: ・ Patients receiving non-opioid analgesics for cancer pain, who have not been receiving opioid analgesics ・ Patients whose VAS is ≥ 35 mm and judged necessary to be treated with strong opioid analgesics ・ Patients with an ECOG Performance Status (PS) is ≤ 3, etc. Exclusion: ・ Patients with serious hepatic, renal, or respiratory disorder. ・ Patients with symptom(s)/finding(s) falling under the contraindications or relative contraindications stated in the package insert for oxycodone hydrochloride powder and morphine hydrochloride preparations, etc.
Test Product, Dose and Mode of Administration, Batch Number	Test product (batch number): DS-7113b tablet 1 mg (D7113T1H12T05) DS-7113b tablet 2 mg (D7113T1H12T06) DS-7113b tablet 4 mg (D7113T1H12T07)

<table>
<tr><td></td><td>Dosage and Administration:
As in the table below, subjects received a hydromorphone tablet or a placebo tablet orally four times daily for 5 days. The initial doses of hydromorphone hydrochloride was 4 mg/day. When it was judged that a dose increase or reduce was necessary during the period of study drug administration, it was possible to increase or reduce the dose step by step.
<table><tr><th></th><th>Daily dose</th></tr><tr><td>1</td><td>4 mg</td></tr><tr><td>2</td><td>8 mg</td></tr><tr><td>3</td><td>12 mg</td></tr><tr><td>4</td><td>16 mg</td></tr></table></td></tr>
<tr><td>Duration of Treatment</td><td>Treatment period: 5 days
Post-treatment obsevation period: 1 day</td></tr>
<tr><td>Reference Therapy, Dose and Mode of Administration, Batch Number</td><td>Reference Therapy (batch number):
Oxycodone hydrochloride powder 2.5 mg (W3078)
Oxycodone hydrochloride powder 5 mg (W3107)
Dosage and Administration:
As in the table below, subjects received oxycodone hydrochloride powder or placebo powder orally four times daily for 5 days. The initial doses of oxycodone hydrochloride was 10 mg/day. When it was judged that a dose increase or reduce was necessary during the period of study drug administration, it was possible to increase or reduce the dose step by step.
<table><tr><th></th><th>Daily dose</th></tr><tr><td>1</td><td>10 mg</td></tr><tr><td>2</td><td>20 mg</td></tr><tr><td>3</td><td>40 mg</td></tr><tr><td>4</td><td>60 mg</td></tr></table></td></tr>
<tr><td>Criteria for Evaluation</td><td>Efficacy: Change of VAS between pre-treatment and end of treatment (Primary endpoint)
Safety: Adverse event, Clinical laboratory evaluation</td></tr>
<tr><td>Statistical Method</td><td>Primary endpoint:
Summary statistics were calculated for VAS scores at baseline, at treatment completion/discontinuation and for the change in VAS scores. Analysis of covariance (ANCOVA) was conducted using the baseline VAS scores as a covariate to calculate the 95% CI</td></tr>
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	(two-sided) for a difference in the least squares mean in the magnitude of change in VAS scores between the hydromorphone and oxycodone groups. *P*-values and least squares means for each group were calculated.
Summary - Conclusion	・ The intergroup difference (95% CI) in the least squares mean for the change in VAS scores at completion/discontinuation of treatment was −3.4 mm (−9.8 to 3.1 mm). Given that the upper limit of the 95% CI was <10 mm, the non-inferiority limit determined at the time of planning. Therefore, the non-inferiority of hydromorphone relative to oxycodone was suggested. ・ The incidence of adverse events was 83.0% in the hydromorphone group and 77.4% in the oxycodone group. No significant intergroup differences of the incidence of adverse event and serious adverse event were observed. Therefore, the efficacy and safety of hydromorphone tablets are comparable to those of oxycodone immediate-release formulation.
Date of Report	March 26, 2018