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 DS-7113b immediate release (IR) tablet long-term study in patients with cancer pain
Investigators	-
Study Centre(s)	14 sites
Publication (reference)	
Studied Period	October 2013 – February 2015
Phase of Development	Phase 3
Objectives	To evaluate the safety, efficacy and pharmacokinetics following long-term (maximum of 84 days) treatment of DS-7113b IR tablets in patients with cancer pain on opioid analgesics, patients with cancer pain without opioid analgesics, or patients who had completed DS7113-A-J301 study (DS-7113b phase III study, a randomized double-blind comparison study with IR oxycodone in opioid-naive patients with cancer pain) and hoped to continue administration of DS-7113b tablet
Methodology	A multicenter, open-label, uncontrolled study
Number of Patients (planned and analyzed)	Planned: 50 subjects Analyzed: 48 subjects
Diagnosis and Main Criteria for Inclusion	Inclusion: ・ Patients on opioid analgesics less than 240 mg in morphine equivalent and judged effective to be treated with strong opioid analgesics (Opioid-use group) ・ Patients who have not been on opioid analgesics, whose VAS is 35 mm and over and judged necessary to be treated with strong opioid analgesics (Opioid-naïve group) ・ Patients who prefer to take DS-7113b IR tablets after completion of the study treatment of DS7113-A-J301 trial (J301 group) ・ Patients with an ECOG Performance Status (PS) is ≤ 3, etc. Exclusion: ・ Patients with symptom(s)/finding(s) falling under the contraindications or relative contraindications stated in the

<table>
<tr><td></td><td>package insert for oxycodone hydrochloride powder and morphine hydrochloride preparations, etc.
・ Patients with serious hepatic, renal, or respiratory disorder.</td></tr>
<tr><td>Test Product, Dose and Mode of Administration, Batch Number</td><td>Test product (batch number):
DS-7113b tablet 1 mg（D7113T1H12T05*、D7113T2H13M03）
DS-7113b tablet 2 mg（D7113T1H12T06*、D7113T2H13M06）
DS-7113b tablet 4 mg（D7113T1H12T07*、D7113T2H13M07）
*They are also used as rescue medication.
Dosage and Administration:
As in the table below, subjects received a hydromorphone tablet orally four or six times daily for up to 84 days. The initial dose of Opioid-use group depended on their pre-opioid daily dose. 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 colspan="4">Daily dose</th></tr>
<tr><th></th><th colspan="2">Opioid-use group</th><th>Opioid naïve group</th><th>J301 group</th></tr>
<tr><td>Number of daily dose</td><td colspan="2">6 times</td><td></td><td>4 times</td></tr>
<tr><td>Initial dose</td><td colspan="2">Converted according to the daily dose of pre-treatment opioid</td><td>4 mg</td><td>The dose when J301 trial is completed</td></tr>
<tr><td>1</td><td colspan="2">4 mg</td><td></td><td>4 mg</td></tr>
<tr><td>2</td><td colspan="2">6 mg</td><td></td><td>8 mg</td></tr>
<tr><td>3</td><td colspan="2">12 mg</td><td></td><td>12 mg</td></tr>
<tr><td>4</td><td colspan="2">18 mg</td><td></td><td>16 mg</td></tr>
<tr><td>5</td><td colspan="2">24 mg</td><td></td><td>24 mg</td></tr>
<tr><td>6</td><td colspan="2">36 mg</td><td></td><td>36 mg</td></tr>
<tr><td>7</td><td colspan="2">48 mg</td><td></td><td>48 mg</td></tr>
</table>
Dosage as rescue medication:
In opioid-based patient group and non-opioid patient group, the dose per rescue medication is administered according to the daily dose as shown in the table below.
<table>
<tr><th></th><th>Dose per one rescue medication</th></tr>
<tr><td>1</td><td>1 mg</td></tr>
</table></td></tr>
</table>

<table>
<tr><td></td><td>
<table>
<tr><td>2</td><td>1 mg</td></tr>
<tr><td>3</td><td>2 mg</td></tr>
<tr><td>4</td><td>3 mg</td></tr>
<tr><td>5</td><td>4 mg</td></tr>
<tr><td>6</td><td>6 mg</td></tr>
<tr><td>7</td><td>8 mg</td></tr>
</table>
</td></tr>
<tr><td>Duration of Treatment</td><td>Treatment period: up to 84 days
Post-treatment observation period: 2 day</td></tr>
<tr><td>Reference Therapy, Dose and Mode of Administration, Batch Number</td><td>None</td></tr>
<tr><td>Criteria for Evaluation</td><td>Efficacy: Efficacy rate (post-switch improvement and analgesia improvement) at each visit and early termination visit (Primary endpoint) , use of rescue medication
Safety: Adverse event, Clinical laboratory evaluation</td></tr>
<tr><td>Statistical Method</td><td>Primary endpoint: Efficacy rate and its 95% CI were calculated at each evaluate point</td></tr>
<tr><td>Summary - Conclusion</td><td>・ The efficacy rate at FAS was as high as 80.9% at Visit 2 at the time of evaluation just after initiation of administration, and that at each evaluation time was almost 80% or more. Eleven of 47 subjects continued to be administered to Visit 8 at the longest 85th day, and high efficacy rates were maintained even for subjects who were continuously administered for a long period of time.
・ Regarding safety, most adverse events observed were events commonly associated with the original disease or events commonly observed when opioid analgesics were used, except for safety issues to be noted when using strong opioid analgesics noteworthy things were not recognized.
・ Even when DS-7113b tablet was administered as a rescue medicine, no noteworthy safety problem was noticed. A significant pain improvement was confirmed for its effectiveness as a rescue medicine.
As described above, DS-711b tablet was confirmed to be safe and effective when used as a regular treatment with a strong opioid analgesic in patients with various cancer pain and as a rescue medicine.</td></tr>
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Date of Report	March 26, 2018