SYNOPSIS

Name of Sponsor/Company	Daiichi Sankyo Co., Ltd.
Name of Finished Product	NARUSUS® TABLETS
Name of Active Ingredient	hydromorphone hydrochloride (INN)
Title of Study	DS-7113b extended-release (ER) tablet phase III study A DS-7113b extended-release tablet long-term study in patients with cancer pain
Investigators	-
Study Centre(s)	16 sites
Publication (reference)	
Studied Period	October 2014 – August 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 ER tablets in patients with cancer pain on opioid analgesics, patients with cancer pain without opioid analgesics, or patients who had completed DS7113-B-J303 study (DS-7113b extended-release ER tablet phase III study, a randomized double-blind comparison study with oxycodone in opioid-naive patients with cancer pain) and hoped to continue administration of DS-7113b ER tablet.
Methodology	A multicenter, open-label, uncontrolled study
Number of Patients (planned and analyzed)	Planned: 50 subjects Analyzed: 50 subjects
Diagnosis and Main Criteria for Inclusion	Inclusion: ・ Patients on opioid analgesics (oral morphine, oral oxycodone, transdermal fentanyl, or tramadol) 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 ER tablets after completion of the study treatment of DS7113-B-J303 trial (J303 group) ・ Patients with an ECOG Performance Status (PS) is ≤ 3, etc. Exclusion: ・ Patients with serious hepatic, renal, or respiratory

<table>
<tr><td></td><td>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.</td></tr>
<tr><td>Test Product, Dose and Mode of Administration, Batch Number</td><td>Test product (batch number):
DS-7113b ER tablet 2 mg（D7113T2H14M01）
DS-7113b ER tablet 6 mg（D7113T2H14M03）
DS-7113b ER tablet 12 mg（D7113T2H14M05）
DS-7113b ER tablet 24 mg（D7113T1H14M07、D7113T1H14M08）
DS-7113b tablet 1 mg（D7113T2H13M03）
DS-7113b tablet 2 mg（D7113T2H13M06）
DS-7113b tablet 4 mg（D7113T2H13M08）
Dosage and Administration:
<Titration period>
Opioid-use group and opioid-naïve group received a hydromorphone tablet orally 4 times or 6 times daily for up to 7 days by the achievement of pain control. The initial dose of Opioid-use patient group depended on their pre-opioid daily dose, and the initial dose of opioid-naïve group was 4 mg daily.

<Treatment period>
As in the table below, subjects received a hydromorphone ER tablet orally once daily for up to 84 days. 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 colspan="2">Daily dose</th><th></th></tr>
<tr><th></th><th>Opioid-use group</th><th>Opioid-naïve group</th><th>J303 group</th></tr>
<tr><td>Initial dose</td><td colspan="2">DS-7113b daily dose after achieving pain control</td><td>The dose when J303 trial is completed</td></tr>
<tr><td>1</td><td colspan="3">4 mg</td></tr>
<tr><td>2</td><td colspan="3">6 mg</td></tr>
<tr><td>3</td><td colspan="3">8 mg</td></tr>
<tr><td>4</td><td colspan="3">12 mg</td></tr>
<tr><td>5</td><td colspan="3">18 mg</td></tr>
</table></td></tr>
</table>

	6 24 mg 7 36 mg 8 48 mg
Duration of Treatment	Titration period: up to 7 days Treatment period: up to 84 days Post-treatment observation period: 1 day
Reference Therapy, Dose and Mode of Administration, Batch Number	None
Criteria for Evaluation	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
Statistical Method	Primary endpoint: Efficacy rate and its 95% CI were calculated at each evaluate point.
Summary - Conclusion	・ The efficacy rate at FAS was as high as 78.0% at Visit 2 at the time of evaluation just after initiation of DS-7113b ER tablet administration, and that at each evaluation time was almost 70% or more. Twenty of 50 subjects continued to be administered to Visit 8, 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. ・ In addition to the scheduled administration of DS-7113b ER tablets, 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 ER tablet was confirmed to be safe and effective for-long-term use as a regular treatment with a strong opioid analgesic in patients with various cancer pain.
Date of Report	March 26, 2018