SYNOPSIS

Name of Sponsor/Company	Daiichi Sankyo Co., Ltd.
Name of Finished Product	CRAVIT ® INTRAVENOUS DRIP INFUSION
Name of Active Ingredient	Levofloxacin
Title of Study	Phase III clinical study of DR-3355 injection in patients with surgical infection
Investigators	
Study Centre(s)	8 sites
Publication (reference)	None
Studied Period	Date of obtaining first consent: August, 2012 Date of last observation: December, 2013
Phase of Development	Phase 3
Objectives	The aim of this open-labeled study is to evaluate efficacy and safety of DR-3355 injection at a dose of 500 mg once-daily in patients with surgical infection. Additionally, the efficacy and the safety are evaluated after switching from DR-3355 injection to levofloxacin oral agent.
Methodology	Open-label, multicentre study
Number of Patients (planned and analyzed)	Planned: 30 patients Registered: 22 patients Analyzed: Valid for analysis of clinical efficacy 18 patients Valid for analysis of bacteriological efficacy 16 patients Valid for analysis of PK 6 patients Valid for analysis of safety 22 patients
Diagnosis and Main Criteria for Inclusion	Diagnosis: 1) Secondary infection after injury, burn, or operation 2) Acute cholecystitis, acute cholangitis Inclusion: a) Patients with age of 20 or older at the time of obtaining informed consents b) Inpatients c) Patients who need the treatment using injection d) Patients who satisfied the below criteria at the start of therapy, and provided proper specimen for cultivation of pathogenic bacteria before the start of therapy or within 24 hours from the start of therapy 1) Secondary infection after injury, burn, or operation Patients who have at least one item in systemic inflammation and 2 or more items in local findings, and receive initial treatment this time <Systemic inflammation> Fever, increased WBC count, marked left shift, increased CRP level, increased pulse rate, or increased respiration rate <Local findings> Redness, spontaneous pain/tenderness, pulsation, local warmth, swelling/induration, or discharge of pus/effusion 2) Biliary infection Patients who satisfied No.1 or 2, and 3, and below criteria of acute cholecystitis or cholangitis, and receive initial treatment this time 1. Patients scheduled for surgery, percutaneous drainage, or biliary drainage, or done.

	2. Patients confirmed bile or purulent fluid from indwelling drain 3. Malfunctioning gastrointestinal tract (ex. nausea/vomiting, hypoactive bowel sound, obstruction to the discharge of intestinal tract gas, symptoms of ileus) <Acute cholecystitis> At least one item in A, one or more item in B, and C A) Fever, increased WBC count, increased CRP level B) RUQ mass/pain/tenderness or Murphy's sign C) Imaging findings characteristic of acute cholecystitis <Acute cholangitis> All items in A, or at least one item in A and all items in B A) Fever, abdominal pain (RUQ or upper abdominal), jaundice B) Increased serum ALP, or γ-GT levels; increased WBC count, or increased CRP level; biliary dilatation, or evidence of an etiology (stricture, stone, etc) on imaging findings
Test Product, Dose and Mode of Administration, Batch Number	Test product (batch number): DR-3355inj (D3355I0H11T01A) Oral levofloxacin (D3355F0S11T01A) Dosage and administration: Intravenous administration of DR-3355inj at 500 mg, once daily Oral administration of levofloxacin at 500 mg, once daily
Duration of Treatment	Three to fourteen days DR-3355inj at 500 mg as a single daily dose by the intravenous route for at least three days. Intravenous therapy could be followed by levofloxacin by the oral route at a single, daily dose of 500 mg to complete a 14-day course of therapy. The timing of the switch to oral therapy should be done at the discretion of the physician and in accordance with clinical response.
Reference Therapy, Dose and Mode of Administration, Batch Number	None
Criteria for Evaluation	Primary endpoint: Clinical efficacy at the test of cure Secondary endpoint: Bacteriological efficacy at the test of cure
Statistical Method	The point estimate of the efficacy rate and the two-sided 95% confidence interval were calculated by diagnosis.
Summary - Conclusion	Efficacy summary: The primary endpoint was the clinical efficacy rate at the test of cure in PPS. The efficacy rate was 90.0 % (9/10) in patients with secondary infection after injury, burn, or operation. All five patients with acute cholecystitis and three patients with acute cholangitis were judged as cure. The bacteriological efficacy rate at the test of cure in PPS(bacterial) was 90.0% (9/10) in patients with secondary infection after injury, burn, or operation. The bacteriological efficacy in three patients with acute cholecystitis and three patients with acute cholangitis was all judged as eradication. All causative organisms disappeared in seventeen strains of secondary infection after injury, burn, or operation, four strains of acute cholecystitis, and four strains of acute cholangitis at the test of

	cure. The mean drug concentration two hours after a single treatment of DR-3355 injection at 500 mg in 2 patients with acute cholecystitis was 19.2 μg/mL in bile, 9.6 μg/mL in plasma, and the bile/plasma ratio was 1.97. The mean drug concentration two hours after a single treatment of DR-3355 injection at 500 mg in 4 patients with acute cholangitis was 12.0 μg/mL in bile, 6.8 μg/mL in plasma, and the bile/plasma ratio was 1.82. Safety summary: The incidence of adverse events was 63.6% (14/22) up to the test of cure. The events which occurred in two patients were vomiting, dermatitis contact, injection site erythema, or injection site pain. The incidence of adverse events was 54.5% (12/22) up to the end of intravenous treatment. The severity of schizophrenia in a patient was moderate, and the other adverse events were mild. There was not adverse event that led to withdrawal. Incidence of adverse drug reactions was 13.6% (3/22) up to the test of cure, and 9.1% (2/22) up to the end of intravenous treatment. Conclusion: From these results, DR-3355inj (including switch therapy to levofloxacin oral agent) is useful for treatment of secondary infection after injury, burn, or operation, acute cholecystitis, and acute cholangitis, and there is no important problem in the safety.
Date of Report	July 3, 2014