Janssen Research & Development*

Synoptic Clinical Study Report

An Open-Label Study to Evaluate the Penetration of Doripenem in Cerebrospinal Fluid After Doripenem Administration in Pediatric Subjects Less Than 1 Year Chronological Age

Protocol DORI-PED-1002; Phase 1

JNJ-38174942 (Doripenem)

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Name of Finished Product	Doribax®
Name of Active Ingredient(s)	JNJ-38174942 (Doripenem)

Protocol No.: DORI-PED-1002

Title of Study: An Open-Label Study to Evaluate the Penetration of Doripenem in Cerebrospinal Fluid After Doripenem Administration in Pediatric Subjects Less Than 1 Year Chronological Age

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Principal Investigator(s): Prof Karel Allegaert, MD – UZ Gasthuisberg, Leuven, Belgium

Study Center(s): Belgium (1)

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Study Period: First (only) subject enrolled: 27 May 2012; last observation: 02 June 2012.

Phase of Development: 1

OBJECTIVES

The primary objective of this study was to evaluate the penetration of doripenem in cerebrospinal fluid (CSF) after administration of doripenem to pediatric subjects less than 1 year of age with or without a ventriculoperitoneal (VP) shunt who were scheduled for a lumbar puncture (LP) or VP shunt tap. Safety and tolerability were also to be assessed.

METHODS

This was a single-center, open-label study to characterize the penetration of doripenem in CSF, in pediatric subjects less than 1 year of age who were hospitalized but medically stable, had a documented or suspected infection, and were planning to, or undergoing treatment with IV antibiotics. Subjects were required to have CSF sampling from either a LP or VP shunt tap. Doripenem was not to replace the subjects' prescribed antibiotic(s).

The study included 3 phases: a pretreatment phase consisting of an up to 24-hour screening period; a 2-day open-label period during which 5 doses of doripenem were administered and CSF and blood samples were collected for pharmacokinetic assessments, and a post-treatment phase consisting of an end-of-study (or early withdrawal) assessment within 24 hours of administration of the last dose of doripenem and a follow-up visit approximately 1 week after administration of the last doripenem infusion. The total duration of the study was to be approximately 10 days. All doses of doripenem were to be administered while the subject was in the hospital.

Clinical laboratory tests, vital sign assessments, and physical examination were to be conducted at specified time points as found in the Time and Events schedule of the study protocol, in addition to pharmacokinetic procedures of CSF and blood sampling. Adverse events were to be reported.

Number of Subjects (planned and analyzed):

Planned: Approximately 10 subjects less than 1 year of age were to be enrolled in this study, including at least 4 subjects less than 12 weeks of age. At least 4 subjects were to have CSF

samples collected via scheduled LP. Analyzed: One female subject who received the first dose of doripenem on the third day of life participated in this study. The study was terminated early for business reasons and is not related to any safety issues or concerns.

Diagnosis and Main Criteria for Inclusion:

Male and female pediatric subjects less than 1 year old who had documented or suspected bacterial infection(s), and were planning to or were undergoing treatment with IV antibiotics; and had a need for CSF sampling from a LP or VP shunt tap.

Test Product, Dose and Mode of Administration, Batch No.:

Doripenem infusion solution at a concentration of 10-mg/mL; Subjects <12 weeks of age (birth to 83 days old on the day of first drug administration) were to receive a 10 mg/kg doripenem 1-hour infusion every 8 hours. Subjects 12 weeks to <1 year of age (84 days to 364 days old on the day of first drug administration) were to receive a 30 mg/kg doripenem 1-hour infusion every 8 hours. Each subject was to receive 5 doses of doripenem. Batch numbers: B168274 and B138295.

Duration of Treatment:

The total duration of the study, including the pretreatment phase, open-label treatment phase, and posttreatment phase, was to be approximately 10 days: a pretreatment phase consisting of an up to 24-hour screening period; a 2-day open-label period during which 5 doses of doripenem were administered and CSF and blood samples were collected, and a post-treatment phase consisting of an end-of-study (or early withdrawal) assessment within 24 hours of administration of the last dose of doripenem and a follow-up visit on Day 7, 8 or 9 to assess and record any new adverse events and to follow up on any ongoing adverse events.

Criteria for Evaluation:

The total amount of blood drawn for clinical laboratory tests and pharmacokinetic evaluations was to be:

- approximately 2.6 mL for subjects whose body weight <1000g: 1.6 mL for clinical laboratory safety assessments, 0.4 mL for pharmacokinetics, 0.6 mL due to potential loss by use of indwelling IV cannula;
- approximately 3.3 mL for subjects whose body weight ≥1000 g: 1.6 mL for clinical laboratory safety assessments, 0.8 mL for pharmacokinetics, 0.9 mL due to potential loss by use of indwelling IV cannula.

Pharmacokinetics:

One CSF sample (approximately 0.2 mL) and one time-matched blood sample (0.2 mL collected within 5 minutes before or after the time of CSF sample collection) were to be obtained from all subjects for the measurement of doripenem concentrations in CSF and plasma, respectively. These time-matched samples were to be collected within 3 hours after the completion of any of the 5 doripenem infusions. In subjects who weighed ≥1000 g, a second pharmacokinetic blood sample was to be collected respective to the CSF pharmacokinetic sample collection (within 15 minutes after the time of CSF sample collection). For subjects who had an additional LP or VP shunt tap planned within 3 hours after a subsequent doripenem infusion as part of their standard of care therapy, a second optional set of time-matched CSF and blood sample(s) could have been collected if there was sufficient left-over CSF that could have been used as a pharmacokinetic study sample.

Safety:

Blood samples for serum chemistry and hematology were obtained for evaluation of laboratory safety parameters. The investigator reviewed the laboratory reports and documented this review.

Blood sample collection for clinical laboratory safety assessments was limited to 2 time points over the study period (from screening through follow-up), each requiring approximately 0.8 mL of blood volume.

Vital sign measurements included blood pressure, pulse rate, respiratory rate (and documentation if a subject was on a ventilator or not), and temperature (skin probe, rectal, axillary, or other). Vital signs were measured at the times specified in the Time & Events Schedule,
before the start of study drug infusion and within 15 minutes after the end of each doripenem infusion.

Physical examinations including body weight were conducted at times indicated in the Time & Events Schedule in the protocol.

Adverse events were to be reported from the time the subject's parent or legally authorized representative signed the informed consent form until the subject completed the last study procedure.

Statistical Methods:

Sample Size Determination: The sample size of a total of 10 subjects, with at least 4 subjects less than 12 weeks of age, to complete the study was not based on statistical considerations, but was considered adequate to generate meaningful descriptive measures of the plasma and CSF concentration of doripenem.

Pharmacokinetics: Individual doripenem concentrations in CSF and plasma were to be listed, and doripenem CSF concentration as a percentage of the plasma concentration at each collection time-point was to be estimated. Plasma concentration, CSF concentration, and CSF concentration as a percentage of concurrent plasma concentration data at each time point were to be summarized with mean, standard deviation, coefficient of variation, median, minimum, and maximum.

Safety: Safety from screening to the follow-up assessment was to be evaluated by examining the incidence of, severity of, and relationship to study drug, type of adverse events, changes in clinical laboratory results, physical examination results, vital sign measurements, and concomitant therapy from screening through study completion. Data were to be summarized using descriptive statistics.

RESULTS

STUDY POPULATION

One subject was enrolled into the study.

This 41-week-old gestational age white female with a birth weight of 3.70 kg and communicating congenital hydrocephalus, reported group B *Streptococcus agalactiae* sepsis, meconium aspiration syndrome, and suspected meningitis was enrolled in the study on the third day of life. Her physical examination at baseline was significant for icteric skin. Vital signs at baseline included axillary temperature of 36.8° C, respiratory rate of 38/per minute, pulse of 118 beats/minute, and blood pressure of 52 systolic/38 diastolic mmHg. The subject began empiric antibiotic treatment with amikacin 57 mg IV daily and amoxicillin 193 mg IV TID on the first day of life for the streptococcal sepsis. Amikacin was discontinued on the third day of life and amoxicillin on the seventh day of life. On the third day of life, the subject weighed 3700 g and she received the first dose of doripenem 10 mg/kg from 16:01 to 17:01. At 17:18 (17 minutes after the end of administration of the first dose of doripenem), cerebrospinal fluid was collected by lumbar puncture to rule out meningitis. The investigator reported this sample being obtained by a "traumatic tap". CSF was reported as translucent and of yellow color, glucose was 37 mg/dL, protein 893 mg/L, white blood cell count (WBC) of 4.4/microliter (differential was not done since WBC were < 5). Red blood cell count was not determined. Results of the CSF gram stain and culture

were negative. No additional samples of CSF were reported. The subject received 5 infusions of doripenem administered approximately 8 hours apart and she completed the study. No adverse events or local infusion site reactions were reported for this subject.

No other subjects were enrolled.

PHARMACOKINETIC RESULTS

One subject was enrolled who weighed ≥1000 g. One CSF PK sample and 2 time-matched blood PK samples were collected respective to the first of the 5 doripenem infusions the subject received. The samples were analyzed for doripenem concentrations (and doripenem-M-1 for plasma only) using a validated, specific and sensitive liquid-chromatography/tandem mass spectrometry (LC-MS/MS) method under the supervision of the Sponsor's Bioanalytical Laboratory Department of Bioanalysis. The concentration data is summarized in Table 1.

Table 1: Concentrations of Doripenem and Doripenem-M-1 in Plasma and Doripenem in Cerebrospinal Fluid after a Single Doripenem Dose (Study DORI-PED-1002)

Sample Time (minutes)[a]	Biological Matrix	Concentration (µg/mL)
Doripenem		
17	Cerebrospinal Fluid	0.331[b]
10	Plasma	26.6
29	Plasma	24.4
Doripenem-M-1		
10	Plasma	1.15
29	Plasma	1.26

Note: Samples collected after a single doripenem 10 mg/kg 1-hour infusion
[a] Sample time respective to the end of the doripenem 1-hour infusion
[b] Reported as 331 ng/mL

The CSF to plasma ratio of doripenem concentrations was approximately 0.012 and 0.014 at 7 minutes pre- and 12 minutes post-CSF sample collection, respectively. The plasma concentrations appear consistent, generally double, to those observed in subjects of the same chronological age who received a single 5 mg/kg dose in a separate study (DORI-PED-1003).

SAFETY RESULTS

A safety committee composed of the medical monitor, 1 of the study's investigators, and 1 expert in pediatrics reviewed the safety information from this subject while the study was ongoing.

It was determined that there were no untoward changes in test results of chemistry, hematology, or vital signs. No adverse events were reported.

The committee determined that there were no safety issues identified from this subject.

STUDY LIMITATIONS

The objectives of the study could not be achieved as the study was terminated early for business reasons, and is not related to any safety issues or concerns. Only 1 subject was enrolled into the study.

DISCUSSION AND CONCLUSIONS

Text removed for purposes of posting to ClinicalTrials.gov.

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