25 April 2014
EMA/594074/2014
Committee for Medicinal Products for Human Use (CHMP)

Doribax

(Doripenem)

Procedure No. EMEA/H/000891/P46/030

CHMP assessment report for paediatric use studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Assessment Report as adopted by the CHMP with all information of a commercially confidential nature delete

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ADMINISTRATIVE INFORMATION

Invented name of the medicinal product:	Doribax
INN (or common name) of the active substance(s):	doripenem monohydrate
MAH:	Janssen-Cilag International NV
Currently approved Indication(s)	Doribax is indicated for the treatment of the following infections in adults: Nosocomial pneumonia (including ventilator–associated pneumonia) Complicated intra-abdominal infections Complicated urinary tract infections
Pharmaco-therapeutic group (ATC Code):	J01DH04
Pharmaceutical form(s) and strength(s):	powder for solution for infusion, 250 mg and 500 mg

1. INTRODUCTION

On 7 February 2014 the MAH submitted a paediatric study for Doripenem in accordance with Article 46 of Regulation (EC) No1901/2006, as amended, on medicinal products for paediatric use which was, however, terminated before completion for business reasons and not for any safety concerns

A short critical expert overview has also been provided.

The MAH stated that the submitted paediatric study does not influence the benefit risk for Doribax and that there is no consequential regulatory action.

The study was early terminated for business reasons which limited the enrollment and precludes a meaningful conclusion about the efficacy and safety of doripenem compared with cefepime. Thus no specific benefits or special precautions can be derived from this data.

2. SCIENTIFIC DISCUSSION

Study DORI-PED-3002, was a Phase 3 prospective, randomized, double-blind, double-dummy, active comparator-controlled, multicenter, multinational study to establish the safety and tolerability of doripenem compared with cefepime in the treatment of hospitalized children (3 months to <18 years of age) with cUTI. Secondary objectives were to determine clinical cure rates at the test-of-cure (TOC) visit, to determine clinical improvement rates at the end-of-treatment for EIV visit, to determine clinical relapse rates at the LFU visit, and to characterize PK of doripenem based on a sparse PK sampling scheme.

The DORI-PED-3002 Study was terminated early (05 August 2013) for business reasons and not for any safety concerns. At the time of study termination, only 41 of the planned 120 subjects were enrolled. Given the limited enrollment, meaningful conclusions about the efficacy and safety of doripenem compared with cefepime could not be drawn.

A copy of the abbreviated clinical study report (CSR) is being submitted in accordance with Article 46 of Regulation (EC) No 1901/2006, as amended. This clinical overview summarizes the findings from study DORI-PED-3002 and provides clarity on the context of the data. Study DORI-PED-3002 is included in the current DORIBAX paediatric investigational plan (PIP) decision (P/0071/2012).

The PIP for doripenem was transferred to Shionogi Limited in August 2013; therefore, Janssen-Cilag International NV is no longer the PIP applicant.

Information on the pharmaceutical formulation used in the study(ies)

Doripenem for injection (JNJ-38174942, S-4661) is a sterile, synthetic, parenteral antibiotic of the carbapenem class of β-lactam antibiotics with broad-spectrum, potent, antibacterial activity against aerobic and anaerobic gram-positive and gram-negative bacteria. On 25 July 2008, the European Commission (EC) granted authorisation of DORIBAX (doripenem) 500 mg powder for solution for infusion (EU/1/08/467/001). DORIBAX (doripenem) 500 mg 1-hour and 4-hour infusions are approved for the treatment of adults with nosocomial pneumonia (including ventilator-associated pneumonia [VAP]), and 500 mg 1-hour infusions are approved for the treatment of adults with complicated intra-abdominal infections and complicated urinary tract infections (cUTI). An optional dose of doripenem 1 g 4-hour infusions was approved by the EC for the treatment of adults with VAP on 23 August 2012.

A 250-mg vial strength has also been approved in the European Union (EU/1/08/467/002; date of approval: 15 March 2010). This strength was developed to address the recommendation of the European Medicines Agency's Paediatric Committee (EMEA-000015- PIP01-07) to develop pediatric dose vials with smaller content of drug (eg, 250 mg) to adjust for the lower total dose needed in young patients and to avoid wasting drug product.

Clinical aspects

2.1. Introduction

The MAH submitted a final report for a clinical study according to the PIP.

2.2. Clinical study

Protocol No.: DORI-PED-3002

Title of Study: A Prospective, Randomized, Double-Blind, Multicenter Study to Establish the Safety and Tolerability of Doripenem Compared With Cefepime in Hospitalized Children With Complicated Urinary Tract Infections

Description

Methods

Objectives

The primary objective of this study was to establish the safety and tolerability of doripenem compared with that of cefepime in hospitalized children 3 months < 18 years of age with complicated urinary tract infections (cUTI).

Secondary objectives were to determine clinical cure rates and microbiological response rates at the test of cure (TOC) visit; to determine clinical improvement rates and microbiological response rates of doripenem at the end of treatment with intravenous (IV) study drug therapy (EIV) visit; to determine sustained clinical cure rates and microbiological response rates at the late follow-up (LFU) visit, and to characterize the pharmacokinetics (PK) of doripenem based on a sparse PK sampling scheme.

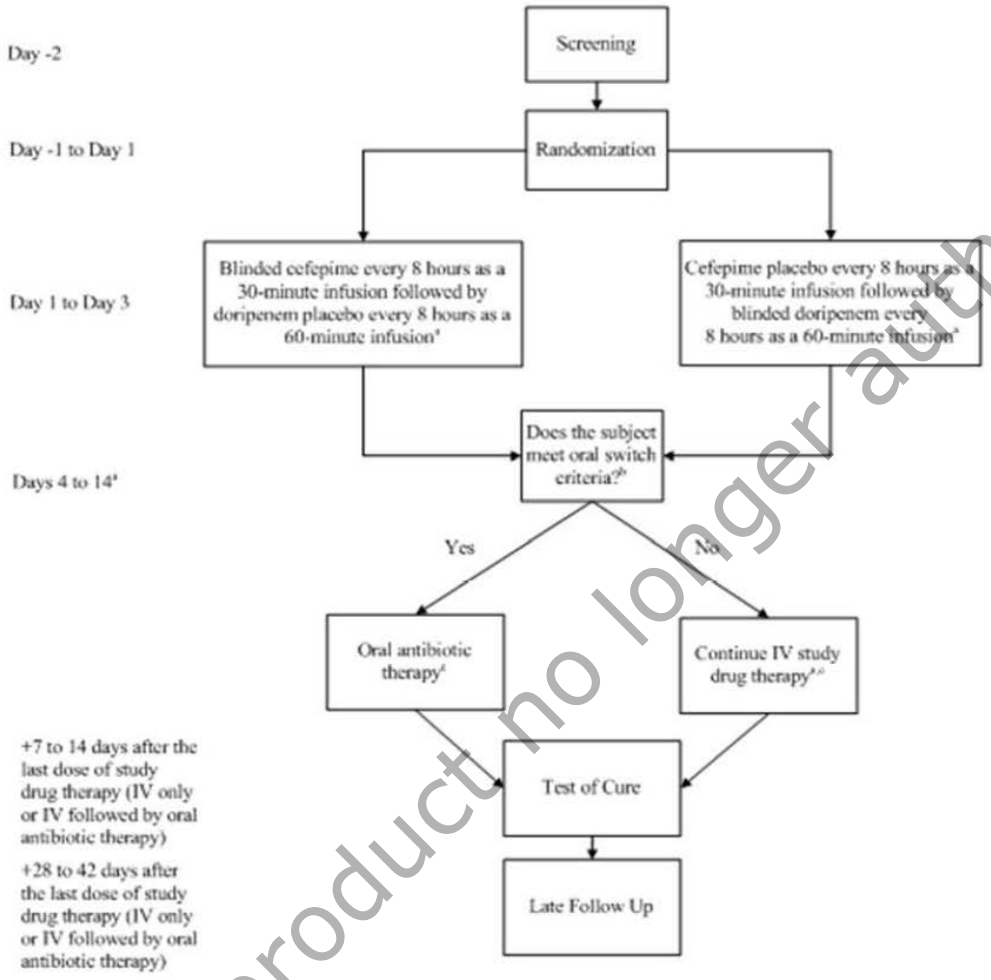
The exploratory objective was to determine the fraction of simulated subjects that met the pharmacodynamic (PD) goal of 35% T>MIC (plasma drug concentrations were greater than minimum inhibitory concentration [MIC] for at least 35% of the dosing interval) for selected MICs over a single dosing interval utilizing the PK model developed from sparsely sampled PK data.

Study design

Methodology: This was a prospective, randomized, double-blind, double-dummy, active comparator-controlled, multicenter, multinational study to establish the safety and tolerability of doripenem compared with cefepime in the treatment of hospitalized children with cUTI or pyelonephritis.To be

eligible for enrollment, a subject must have been 3 months to <18 years of age with demonstrated clinical signs or symptoms of cUTI, must have provided a urine specimen with evidence of pyuria, and required treatment with IV antibiotics. Throughout this document, "cUTI" refers to both complicated lower urinary tract infections (cLUTI) and pyelonephritis.

Figure 1: Study Design



[a] End-of-treatment for IV study therapy assessments were performed as soon as possible but within 24 hours after the completion of last dose of IV study drug therapy.

[b] After receiving a minimum of 3 days (9 paired doses) of IV study therapy, subjects in both treatment groups who met protocol-specified criteria demonstrating improvement were switched to oral antibiotic therapy (see Section 6, Dosage and Administration for details on the protocol-specified criteria and oral antibiotic therapy options, in protocol [Appendix 1]).

[c] Early withdrawal assessments were performed for any subject who discontinued the study early at any time.

The study included 3 phases:

- pretreatment phase consisting of an up to 48-hour screening period;
- a 10- to 14-day treatment phase consisting of treatment with IV study drug therapy (doripenem or cefepime) only, or IV study drug therapy plus a switch to oral antibiotic therapy (amoxicillin/
- clavulanate potassium or ciprofloxacin); and

- a posttreatment phase consisting of a TOC visit 7 to 14 days after the last dose of study drug (IV only or IV followed by oral antibiotic therapy) and a LFU visit 28 to 42 days after the last dose of study drug (IV only or IV followed by oral antibiotic therapy).

The IV study drug therapy was administered while the subject was hospitalized for a minimum of 3 days (9 paired doses of IV study drug therapy) and up to a maximum of 14 days. The total duration of the study was approximately 7 to 8 weeks for each subject. All IV antibiotic therapies were administered while the subject was in the hospital.

Baseline urine and blood specimens for culture were collected from all subjects at screening (within

48 hours before the start of the administration of the first dose of IV study drug therapy). If not meeting the definition of study qualifying baseline requirements the subject was to discontinue study drug therapy, but remain in the study, and be followed for safety.

After all screening assessments were completed subjects were randomly assigned in an approximate 3:1 ratio to treatment with doripenem or cefepime, respectively. Randomization within this study was stratified by age (ie, 3 months to <2 years, 2 to <6 years, 6 to <12 years, 12 to <18 years).

Systemic adjunctive therapy was not permitted for cUTI.

Study population /Sample size

Number of Subjects (planned and analyzed): The DORIPED3002 study was 1 of 3 pediatric Phase 3 studies that made up Janssen's overall pediatric clinical development plan. Approximately 420 subjects were to be enrolled in total across the 3 studies (cIAI, cUTI, pneumonia), with each study enrolling a minimum of 90 subjects in the doripenem treatment group and a minimum of 25 subjects in the comparator group. At least half of the total number of doripenem-treated subjects in all 3 studies combined must have been <6 years of age with at least 50 doripenem-treated subjects <2 years of age and at least 100 doripenem-treated subjects 2 to <6 years of age in all 3 studies combined.

Inclusion Criteria

Subjects must have satisfied the following criteria to be enrolled in the study :

- boy or girl 3 months to <18 years of age, inclusive
- had evidence of pyuria as demonstrated by either of the following:
  - a urine specimen that was positive for leukocyte esterase via urine dipstick or urinalysis
  - a urine specimen with ≥10 white blood cells (WBCs) per microliter from an unspun sample or ≥5 WBCs per high power field from a centrifuged specimen.
- had a current documented or suspected cUTI or pyelonephritis as indicated by the following
- clinical signs or symptoms:

Complicated Urinary Tract Infection

- Symptomatic cUTI

Children 3 months to <2 years of age

Must have had at least **one** of the following signs or symptoms:

- Vomiting
- Recent weight loss or failure to thrive
- Abdominal pain
- Irritability
- Poor feeding
- Decrease in normal level of activity

and

- had at least **one** complicating factor (see below)

Children 2 to <18 years of age

Must have had at least **one** of the following signs or symptoms:

- Dysuria
- Increased urinary frequency
- Urgency
- Suprapubic or abdominal pain
- Secondary urinary incontinence

Planned: A minimum of 120 subjects were to be randomly assigned to IV doripenem or IV cefepime in DORIPED3002 study in approximate 3:1 ratio.

Analyzed: 41 subjects were enrolled and 40 subjects were treated in this study.

Treatments

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

Doripenem was supplied as fine white to slightly yellowish off-white powder for IV administration in vials containing 500 mg of sterile powder.

Batch Number/Lot Number			
Test Product/Dose	Route of Administration	[redacted]	Expiration Date
Doripenem 500 mg	Intravenous		31 March 2013
Doripenem 500 mg	Intravenous		31 July 2014
Doripenem 500 mg	Intravenous		31 October 2012
Doripenem 500 mg	Intravenous		31 July 2014

Reference Therapy, Dose and Mode of Administration, Batch No.:

Cefepime, the comparator agent,was supplied as white to pale yellow powder for IV administration

(Note: Cefepime supplied for this study includes both branded and generic forms of the drug available in the market)

Batch Number/Lot Number			
Test Product/Dose	Route of Administration	[redacted]	Expiration Date
Cefepime 2 g	Intravenous		31 December 2010
Cefepime 2 g	Intravenous		31 July 2012
Cefepime 2 g	Intravenous		30 November 2013
Cefepime 2 g	Intravenous		31 July 2012
Cefepime 2 g	Intravenous		31 May 2014

Duration of Treatment: Subjects received a 10- to 14-day course of study drug therapy, which may have consisted of IV study drug only or at least 3 days of IV study drug followed by protocol-specified oral antibiotic therapy. If at any time after receiving at least 9 paired doses (approximately 72 hours)

of IV study drug therapy, the subject did not demonstrate improvement in signs or symptoms of cUTI, or continued to have a fever that was not resolving without an alternative explanation, or continued to have positive urine cultures (≥104 CFU/mL), and required alternative non study antibiotic therapy, the subject was considered a treatment failure and should have discontinued study drug therapy and followed for safety.

Outcomes/endpoints

Criteria for Evaluation:

Efficacy:

Clinical and microbiological outcome assessments were performed at the EIV, TOC, and LFU visits.

Clinical outcomes were based on an assessment of the signs and symptoms of cUTI performed daily while the subject was in the hospital through EIV, and also at the TOC and LFU visits.

The clinical outcomes at EIV were rated as clinical improvement, clinical failure, or indeterminate. The clinical outcomes at the TOC visit were rated as clinical cure, clinical failure, or indeterminate.

Microbiological assessments were based on the urine culture results. If postbaseline cultures were not required per protocol and were not available, the microbiological outcome was inferred from the clinical response.

An overall per-subject microbiological response was determined at EIV, TOC, and LFU.

New pathogens that emerged during and after study drug therapy were assessed.

Pharmacokinetics:

Four blood samples (0.4 mL each) for determination of doripenem and doripenem-M-1 or cefepime plasma concentrations were collected from all subjects. Pharmacokinetic sample collection occurred relative to the start of the infusion of the scheduled fourth, fifth, sixth, or seventh 60-minute dose of doripenem/doripenem placebo. PK blood samples of cefepime plasma concentration were not analyzed for drug concentration.

The 1-hour sample was collected within 5 minutes before the end of the 60-minute doripenem/doripenem placebo infusion. The 2, 4-, and 6-hour samples were collected within ±15 minutes from the scheduled collection times relative to the start of the doripenem/doripenem placebo infusion. Plasma samples were analyzed to determine concentrations of doripenem and doripenem-M-1 using a validated, specific and sensitive liquid-chromatography/tandem mass spectrometry (LC-MS/MS) method. Plasma PK parameters were determined for doripenem and doripenem-M-1 based on the individual plasma concentration time data, using actual sampling times via non-compartmental analysis

Safety

Safety evaluations included the measurement of vital signs, monitoring of reported adverse events (AEs), including serious adverse events (SAEs), concomitant therapy, serum chemistry, hematology assessments, and urinalysis with microscopy. A urine pregnancy test was performed for menarchal

girls unless a serum pregnancy test was preferred at the discretion of the investigator or if required by local regulations. AEs of special interest (ie, hemolytic anemia, hepatocellular injury, renal failure/impairment, seizures, thrombocytopenia, and local intolerability and phlebitis) were assessed.

Statistical Methods:

The cumulative sample size for all 3 pediatric studies (cUTI, cIAI, and pneumonia) was based on obtaining sufficient safety data in children. The primary focus of this study was safety. No pre-specified statistical hypothesis for efficacy was tested in this study. Safety data were summarized for the intent-to-treat (ITT) population. For efficacy, a 95% confidence interval (CI) of the difference in the event rate (doripenem minus cefepime) was calculated to compare the clinical outcome rate between the two treatment groups in the clinical ITT (CITT).

Results

Study population.

A total of 41 subjects were enrolled and randomized in the study; 30 subjects received doripenem and 10 subjects received cefepime. One subject in the doripenem treatment group was excluded from the study due to protocol violation (received prior antibiotic therapy within 96 hours [4 days] before obtaining the pretreatment baseline urine culture).

All 40 subjects who were treated with at least 1 dose of study drug were included in the ITT and CITT analysis sets.

Thirty-two subjects (24 subjects in the doripenem treatment group and 8 subjects in the cefepime treatment group) were included in the MITT analysis set and 8 subjects (6 subjects in the doripenem treatment group and 2 subjects in the cefepime treatment group) were excluded from the MITT analysis set because no susceptible urine pathogens were isolated from the urine culture at baseline.

Pharmacokinetic results:

Thirty-seven subjects had PK blood samples obtained, of which 28 subjects received doripenem. Nine subjects received cefepime and their respective PK blood samples were not analyzed for drug concentration. The mean (SD) doripenem and doripenem-M-1 PK parameters are presented in the table below.

Table 1 Mean (SD) Doripenem and Doripenem-M-1 Plasma Pharmacokinetic Parameters Following Administration of a 500 mg 1 hour IV infusion of Doripenem

(Study DORIPED3002; Pharmacokinetic Analysis Dataset)

Parameter	Doripenem	Doripenem-M-1
N	24	24
C_{max} (µg/mL)	34.3 (10.2)	2.68 (0.993)
t_{max} (h)[a]	0.95 (0.92-1.12)	0.95 (0.92-1.12)
AUC_{last} (µg.h/mL)	60.6 (20.1)	7.48 (3.12)
AUC_{τ} (µg.h/mL)	62.9 (21.2)[b]	8.43 (3.47)[d]
$t_{1/2}$ (h)	0.952 (0.195)[b]	2.03 (0.571)[d]
CL (L/h)	5.90 (4.10)[b]	
Vd_{ss} (L)	6.88 (5.04)[b]	
Vd_{ss}/BW (L/kg)	0.414 (0.296)[b]	
CL_{CR} (mL/min)	140 (45.5)[c]	

[a] Median (range); [b] n=20; [c] n=22; [d] n=19
NOTE: τ equal to 8 hours

The doripenem t1/2 was similar across ages (median for all ages combined 0.9 hour) and is consistent with the historical half-life (approximately 1 hour) in children and adult subjects. Doripenem clearance and body-weight adjusted volume of distribution were similar to those observed in children 3 months to <18 years of age after single 500 mg equivalent doses. Systemic exposures, in terms of Cmax and AUC, were within the range of those observed in children and healthy adult subjects administered 1000 mg (or equivalent mg/kg) doses.

Baseline data

The majority of subjects were female (83.9% [26/31]) in the doripenem treatment group while an equal number of male and female subjects (50% [5/10] each) were included in the cefepime treatment group.

Most of the subjects in both treatment groups were white (90.2%).

Age distribution within each treatment group was similar with the greater percentage of subjects (39.0% [16/41]) in the 3 months to less than 2 years of age group; 12 subjects received doripenem and 4 subjects received cefepime in this age group.

The median duration of the IV study drug therapy for doripenem- and cefepime-treated subjects was comparable (5 days [range: 2 to 11 days] and 6 days [range: 4 to 12 days], respectively). The median duration of study drug therapy (IV + oral) was 13 days (range: 2 to 15 days) for doripenem treatment group and 13 days (range: 11 to 15 days) for cefepime treatment group. The maximum duration of treatment per protocol was 14 days or fourteen 24-hour treatment periods. However, the number of days of treatment is by calendar days. No subject received treatment for more than fourteen 24-hour treatment periods.

Efficacy results

Efficacy was evaluated by comparing the clinical cure rates, clinical improvement rates, favorable per-subject microbiological response, and per-pathogen microbiological eradication rates between the 2 treatment groups.

Clinical endpoints

The primary and secondary objectives of the study included the calculations of the clinical cure rates to compare the 2 treatment groups for the following:

- the clinical improvement rate at the end of treatment with IV study drug therapy (EIV) visit,
- the clinical cure rate at the test-of-cure (TOC) visit and
- the sustained clinical cure rate at the late follow-up (LFU) visit

A total of 40 subjects were treated in the study and were included in the CITT analysis set; 30 in the doripenem treatment group and 10 in the cefepime treatment group. Of the 40 subjects in CITT population, were 32 subjects (24 subjects in doripenem treatment group and 8 subjects (6 subjects in doripenem treatment group and 2 subjects in cefepime treatment group) The remaining 8 subjects (6 subjects in doripenem treatment group and 2 subjects in cefepime treatment group) were excluded from the MITT analysis set because no susceptible baseline urine pathogens were isolated from the urine culture.

The efficacy analyses were performed in the CITT and MITT analysis sets. The results for the primary and key secondary efficacy endpoints are presented in Table 8.

Table 8: Clinical Cure Rate at TOC and LFU and Clinical Improvement at the EIV Visit
(Study JNJ38174942-DORI-PED3002: Clinical Intent-to-Treat Analysis Set)

	---- Doripenem ---			---- Cefepime ----				
	N	n	%	N	n	%	Diff[a](%)	95% CI[b]
Clinical Cure at TOC	30	20	66.7	10	5	50.0	16.7	(-25.3; 58.6)
Clinical Improvement at EIV	30	28	93.3	10	10	100.0	-6.7	(-22.3; 8.9)
Clinical Cure at LFU	30	18	60.0	10	5	50.0	10.0	(-32.3; 52.3)

Primary Efficacy

Clinical Cure Rate at the TOC Visit

The primary efficacy endpoint was the clinical cure rate at the TOC visit. A higher percentage of subjects in the doripenem treatment group were considered clinically cured at the TOC visit as compared to the cefepime treatment group (66.7% [20/30] vs. 50% [5/10]). Clinical cure rates were similar in the doripenem treatment group and in the cefepime group among the two indications, cUTI and pyelonephritis. For doripenem-treated subjects the cure rate was 69.2% (9/13) and for cLUTI and 64.7% (11/17) for pyelonephritis. For cefepime-treated subjects the cure rate was 50% (2/4) for cLUTI and 50% (3/6) for pyelonephritis.

Secondary Efficacy

Clinical Improvement at the EIV Visit

A high percentage of subjects in the doripenem and cefepime treatment groups had clinical improvement at the EIV visit (93.3% [28/30] and 100.0% [10/10], respectively) with cefepime being slightly higher.

Clinical Cure Rate at the LFU Visit

A higher percentage of subjects in the doripenem treatment group was considered to be clinically cured at the LFU visit as compared to the cefepime treatment group (60% [18/30] vs. 50.0% [5/10]).

Summary of Clinical Outcomes

Clinical cure rates were high for both groups at the EIV visit (doripenem - 93.3% [28/30] vs. cefepime - 100.0% [10/10]). At the TOC visit the cure rates decreased for both treatment groups.

A higher percentage of subjects in the doripenem treatment group were considered clinically cured as compared to the cefepime treatment group (66.7% [20/30] vs. 50% [5/10]). The cure rates decreased slightly in the doripenem treatment group at the LFU visit, but remained similar to the TOC visit rates (60% [18/30] vs. 50.0% [5/10]).

Microbiological Outcomes

Of the 40 subjects who were included in the ITT and CITT analysis sets, 32 subjects (24 subjects in the doripenem treatment group and 8 subjects in the cefepime treatment group) were included in the MITT analysis set.

There were 6 secondary microbiological endpoints in this study.

Agreement between Per-Subject Clinical Response and Microbiological Outcome at TOC Visit

The clinical response rates and microbiological outcomes at the TOC visit are presented in Table 10.

Table 10: Agreement Between Per-Subject Clinical Response and Microbiological Outcome at Test of Cure Visit

(Study JNJ38174942-DORI-PED3002: Microbiological Intent-to-Treat Analysis Set)

Treatment Group and Clinical Outcome	Doripenem			Cefepime		
	CURE	FAILURE	Total	CURE	FAILURE	Total
Per-subject Microbiological Outcome						
Microbiological Outcomes						
Favorable	17(89.5)	2(10.5)	19	4(100)	0	4
Non-favorable	0	5(100)	5	0	4(100)	4
Total	17(70.8)	7(29.2)	24	4(50.0)	4(50.0)	8

Favorable per-subject microbiological outcome=Cure or Presumed Cure.
Non-favorable per-subject microbiological outcome=Failure or Presumed Failure.

There was 1 new infection identified in a doripenem-treated subject at the TOC visit and 2 new pathogens identified in doripenem-treated subjects at the LFU visit. No new infections were identified in the cefepime treatment group.

Safety results

Data Sets Analyzed

Safety analyses were performed on the ITT analyses set. This set consisted of all randomized subjects who received at least a partial dose of study drug therapy whether or not they met all of the inclusion

criteria and none of the exclusion criteria. Summaries of TEAEs and other safety data are based on 40 subjects (30 subjects in doripenem treatment group and 10 subjects cefepime treatment group.

Adverse Events

Summary of All Adverse Events

A summary of the TEAEs reported for the 40 subjects (30 doripenem-treated subjects and 10 cefepime-treated subjects) included in the ITT analysis set is provided in Table 11.

Table 11: Treatment-Emergent Adverse Events Summary

(Study JNJ38174942-DORI-PED3002: Intent-to-Treat Analysis Set)

Safety Outcome	Doripenem (N=30) n (%)	Cefepime (N=10) n (%)	Total (N=40) n (%)
Any TEAE	16 (53.3)	7 (70.0)	23 (57.5)
Any Study Drug Related TEAE [a]	7 (23.3)	4 (40.0)	11 (27.5)
Any Serious TEAE	1 (3.3)	3 (30.0)	4 (10.0)
Any Study Drug Related Serious TEAE [a]	0	1 (10.0)	1 (2.5)
Any TEAE of Special Interest [b]	0	2 (20.0)	2 (5.0)
Any Study Drug Related TEAE of Special Interest [a,b]	0	1 (10.0)	1 (2.5)
Discontinuation from Study Due to TEAE	0	0	0
Discontinuation from Study Due to Study Drug Related TEAE[a]	0	0	0
Discontinuation from Study Due to Serious TEAE	0	0	0
Discontinuation from Study Due to Study Drug Related Serious TEAE[a]	0	0	0
TEAE leading to death	0	0	0

Note: Percentages calculated with the number of subjects in each group as denominator.

Treatment-emergent adverse events (TEAEs) are defined as AEs with onset dates on or after the start of first dose of study drug therapy and within 30 days after administration of the last dose of study drug therapy.

[a] Study drug-related treatment-emergent adverse events (TEAEs) included possibly, probably and very likely related adverse events or events with missing relationship.

[b] TEAEs of special interest are hemolytic anemia, hepatocellular injury, renal failure/impairment, seizure, thrombocytopenia and local intolerability and phlebitis.

In the doripenem treatment group, the majority of TEAEs were either mild or moderate in severity. There were 3 subjects with 1 severe TEAE each: leukopenia, neutropenia, and pyuria. Leukopenia and neutropenia were reported in 1 subject. In the cefepime treatment group, there were no TEAEs that were considered severe in severity.

There were no deaths or TEAEs leading to discontinuation of the study drug in this study. Two cefepime-treated subjects reported TEAEs of special interest (infusion site pain and phlebitis)

Table 12: TEAEs Reported by System Organ Class and Preferred Term

(Study JNJ38174942-DORI-PED3002: Intent-To-Treat Analysis Set)

Body System Or Organ Class Dictionary-Derived Term	Doripenem (N=30) n (%)	Cefepime (N=10) n (%)	Total (N=40) n (%)
Total no. subjects with TEAE	16 (53.3)	7 (70.0)	23 (57.5)
Blood and Lymphatic System Disorders	3 (10.0)	1 (10.0)	4 (10.0)
Anaemia	1 (3.3)	0	1 (2.5)
Eosinophilia	1 (3.3)	1 (10.0)	2 (5.0)
Hypochromic Anaemia	0	1 (10.0)	1 (2.5)
Leukopenia	1 (3.3)	0	1 (2.5)
Neutropenia	1 (3.3)	0	1 (2.5)
Neutrophilia	0	1 (10.0)	1 (2.5)
Congenital, Familial and Genetic Disorders	0	1 (10.0)	1 (2.5)
Congenital Thrombocyte Disorder	0	1 (10.0)	1 (2.5)
Eye Disorders	1 (3.3)	0	1 (2.5)
Eye Pain	1 (3.3)	0	1 (2.5)
Gastrointestinal Disorders	7 (23.3)	0	7 (17.5)
Abdominal Pain Upper	1 (3.3)	0	1 (2.5)
Diarrhoea	2 (6.7)	0	2 (5.0)
Nausea	1 (3.3)	0	1 (2.5)
Oral Disorder	1 (3.3)	0	1 (2.5)
Vomiting	3 (10.0)	0	3 (7.5)
General Disorders and Administration Site Conditions	5 (16.7)	3 (30.0)	8 (20.0)
Hyperthermia	1 (3.3)	0	1 (2.5)
Infusion Site Pain	0	1 (10.0)	1 (2.5)
Irritability	1 (3.3)	0	1 (2.5)
Pyrexia	3 (10.0)	1 (10.0)	4 (10.0)
Vessel Puncture Site Pain	0	1 (10.0)	1 (2.5)
Hepatobiliary Disorders	2 (6.7)	0	2 (5.0)
Hyperbilirubinaemia	1 (3.3)	0	1 (2.5)
Jaundice	1 (3.3)	0	1 (2.5)
Infections and Infestations	6 (20.0)	3 (30.0)	9 (22.5)
Anal Candidiasis	1 (3.3)	0	1 (2.5)
Bacteriuria	0	1 (10.0)	1 (2.5)
Candidiasis	0	1 (10.0)	1 (2.5)
Cystitis	1 (3.3)	0	1 (2.5)
Fungal Infection	1 (3.3)	0	1 (2.5)
Nasopharyngitis	3 (10.0)	0	3 (7.5)
Oral Candidiasis	1 (3.3)	0	1 (2.5)
Pharyngitis	0	1 (10.0)	1 (2.5)
Pseudomembranous Colitis	0	1 (10.0)	1 (2.5)
Pyelonephritis Acute	0	1 (10.0)	1 (2.5)
Urinary Tract Infection	1 (3.3)	2 (20.0)	3 (7.5)
Varicella	1 (3.3)	0	1 (2.5)
Injury, Poisoning and Procedural Complications	0	1 (10.0)	1 (2.5)
Overdose	0	1 (10.0)	1 (2.5)
Investigations	1 (3.3)	1 (10.0)	2 (5.0)
Alanine Aminotransferase Increased	1 (3.3)	0	1 (2.5)
Aspartate Aminotransferase Increased	1 (3.3)	0	1 (2.5)
Basophil Count Increased	0	1 (10.0)	1 (2.5)
Platelet Count Decreased	1 (3.3)	0	1 (2.5)
Urine Leukocyte Esterase	0	1 (10.0)	1 (2.5)
Metabolism and Nutrition Disorders	1 (3.3)	1 (10.0)	2 (5.0)
Hypoalbuminaemia	0	1 (10.0)	1 (2.5)
Hypoproteinaemia	1 (3.3)	0	1 (2.5)

Table 12: TEAEs Reported by System Organ Class and Preferred Term

(Study JNJ38174942-DORI-PED3002: Intent-To-Treat Analysis Set)

Body System Or Organ Class Dictionary-Derived Term	Doripenem (N=30) n (%)	Cefepime (N=10) n (%)	Total (N=40) n (%)
Musculoskeletal and Connective Tissue Disorders	0	1 (10.0)	1 (2.5)
Myalgia	0	1 (10.0)	1 (2.5)
Nervous System Disorders	2 (6.7)	0	2 (5.0)
Headache	1 (3.3)	0	1 (2.5)
Myoclonus	1 (3.3)	0	1 (2.5)
Renal and Urinary Disorders	1 (3.3)	1 (10.0)	2 (5.0)
Crystalluria	0	1 (10.0)	1 (2.5)
Haematuria	0	1 (10.0)	1 (2.5)
Leukocyturia	0	1 (10.0)	1 (2.5)
Proteinuria	0	1 (10.0)	1 (2.5)
Pyuria	1 (3.3)	0	1 (2.5)
Respiratory, Thoracic and Mediastinal Disorders	2 (6.7)	1 (10.0)	3 (7.5)
Productive Cough	0	1 (10.0)	1 (2.5)
Rhinorrhoea	2 (6.7)	0	2 (5.0)
Skin and Subcutaneous Tissue Disorders	1 (3.3)	2 (20.0)	3 (7.5)
Hyperhidrosis	1 (3.3)	0	1 (2.5)
Macule	1 (3.3)	0	1 (2.5)
Papule	1 (3.3)	1 (10.0)	2 (5.0)
Rash	0	1 (10.0)	1 (2.5)
Skin Haemorrhage	0	1 (10.0)	1 (2.5)
Vascular Disorders	0	1 (10.0)	1 (2.5)
Phlebitis	0	1 (10.0)	1 (2.5)

Note: Percentages calculated with the number of subjects in each group as denominator.

The majority of the TEAEs were reported in infections and infestations (9/40; 22.5%), general disorders and administration site conditions (8/40; 20%) and gastrointestinal disorders (7/40; 17.5%) SOC.

Most commonly reported TEAEs in the doripenem-treated subjects were vomiting, pyrexia, and nasopharyngitis (n=3 each), and diarrhea and rhinorrhea (n=2 each). The most common TEAE reported in the cefepime treated group was UTI (n=2). These 2 events of relapses of UTI were reported 7 days and 28 days after the last dose of the study drug. For all other TEAEs there was only 1 incident of each AE reported in both doripenem-treated subjects and cefepime-treated subjects.

Table 13: Study Drug Related Treatment-Emergent Adverse Events by Preferred Term
(Study JNJ38174942-DORI-PED3002: Intent-to-Treat Analysis Set)

Dictionary-Derived Term	Doripenem (N=30) n (%)	Cefepime (N=10) n (%)	Total (N=40) n (%)
Total no. subjects with study drug related TEAE	7 (23.3)	4 (40.0)	11 (27.5)
Eosinophilia	1 (3.3)	1 (10.0)	2 (5.0)
Leukopenia	1 (3.3)	0	1 (2.5)
Neutropenia	1 (3.3)	0	1 (2.5)
Diarrhoea	1 (3.3)	0	1 (2.5)
Nausea	1 (3.3)	0	1 (2.5)
Vomiting	1 (3.3)	0	1 (2.5)
Vessel Puncture Site Pain	0	1 (10.0)	1 (2.5)
Jaundice	1 (3.3)	0	1 (2.5)
Anal Candidiasis	1 (3.3)	0	1 (2.5)
Oral Candidiasis	1 (3.3)	0	1 (2.5)
Pharyngitis	0	1 (10.0)	1 (2.5)
Pseudomembranous Colitis	0	1 (10.0)	1 (2.5)
Overdose	0	1 (10.0)	1 (2.5)
Alanine Aminotransferase Increased	1 (3.3)	0	1 (2.5)
Aspartate Aminotransferase Increased	1 (3.3)	0	1 (2.5)
Platelet Count Decreased	1 (3.3)	0	1 (2.5)
Hypoalbuminaemia	0	1 (10.0)	1 (2.5)
Hypoproteinaemia	1 (3.3)	0	1 (2.5)
Myoclonus	1 (3.3)	0	1 (2.5)
Hyperhidrosis	1 (3.3)	0	1 (2.5)
Macule	1 (3.3)	0	1 (2.5)
Papule	1 (3.3)	0	1 (2.5)
Rash	0	1 (10.0)	1 (2.5)
Phlebitis	0	1 (10.0)	1 (2.5)

Eleven subjects reported study-drug related TEAEs (7 subjects in doripenem treatment group and 4 subjects in cefepime treatment group).

Serious Adverse Events

The incidence of treatment-emergent SAEs by SOC and PT is summarized in Table 14.

Table 14: Treatment-Emergent Serious Adverse Events by Preferred Term
(Study JNJ38174942-DORI-PED3002: Intent-to-Treat Analysis Set)

Dictionary-Derived Term	Doripenem (N=30) n (%)	Cefepime (N=10) n (%)	Total (N=40) n (%)
Total no. subjects with SAE	1 (3.3)	3 (30.0)	4 (10.0)
Pseudomembranous Colitis	0	1 (10.0)	1 (2.5)
Pyelonephritis Acute	0	1 (10.0)	1 (2.5)
Urinary Tract Infection	0	2 (20.0)	2 (5.0)
Pyuria	1 (3.3)	0	1 (2.5)

Five treatment-emergent SAEs were reported in 4 subjects. One treatment-emergent SAE of pyuria was reported in a doripenem-treated subject. Four SAEs (pseudomembranous colitis, pyelonephritis acute, and 2 events of relapse of UTI) were reported in 3 cefepime-treated subjects.

Safety Summary

The safety analyses was based on 40 subjects (30 subjects in the doripenem treatment group and 10 subjects in the cefepime treatment group) who were randomized, received at least a partial dose of double-blind study drug, and contributed any safety data after the start of study treatment.

Safety was assessed by comparing frequencies of TEAEs, summaries of protocol specified laboratory evaluations (chemistry, hematology, and urinalysis) and vital signs measurements between the 2 treatment groups.

There was no prespecified statistical hypothesis for this study. Efficacy analyses were considered exploratory. Furthermore, the CI for clinical cure rates were wide due to the small sample size.

Therefore no meaningful conclusions can be made.

Safety

For the doripenem treatment group, of 40 TEAEs reported, most were reported in the system organ class (system organ class) of infections and infestations (9/40), gastrointestinal (8/40), and general disorders and administration site conditions (5/40). Most commonly reported TEAEs in doripenem-treated subjects were vomiting, pyrexia, and nasopharyngitis (3 each), and diarrhea and rhinorrhea (2 each). The most common TEAE reported in the cefepime-treated subjects was UTI (2 each). These 2 new events of relapses of UTI were reported 7 days and 28 days after the last dose of the study drug.

3. RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION

Doripenem administered as 20 mg/kg per dose (up to a maximum of 500-mg dose) as a 1-hour infusion in subjects 3 months to <18 years of age was generally safe and well tolerated in this study. There were no new safety findings identified in subjects treated with doripenem in this study.

The doripenem and doripenem-M-1 concentrations observed in this study fall within the range of those previously measured in adults and children administered 500 mg (or equivalent mg/kg) doses.

The percentage of subjects who were clinically cured at the TOC visits was higher for doripenem-treated subjects as compared to cefepime-treated subjects (66.7% [20/30] vs. 50.0% [5/10]). However, there was no prespecified statistical hypothesis for this study.

Efficacy analyses were considered exploratory and meaningful conclusions cannot be made given the limited subjects enrolled in the trial.

There were no new or unexpected safety findings identified in this study. The safety findings from this study are consistent with the safety profile for doripenem seen in adults.

The major limitation of the study was limited enrollment which precludes a meaningful conclusion about the efficacy and safety of doripenem compared with cefepime. Thus no specific benefits or special precautions can be derived from this data..

As the PIP for doripenem was transferred to Shionogi Limited in August 2013; therefore, Janssen-Cilag International NV is no longer the PIP applicant and no more data regarding pediatric use is presently requested.

Overall conclusion

Clinical

The clinical DORI-PED-3002 protocol was adequate but was terminated early (05 August 2013) for business reasons and not for any safety concerns. At the time of study termination, only 41 of the planned 120 subjects were enrolled.

There was no prespecified statistical hypothesis for this study. Efficacy analyses were considered exploratory. Furthermore, the CI for clinical cure rates were wide due to the small sample size.

Given the limited enrollment, meaningful conclusions about the efficacy and safety of doripenem compared with cefepime could not be drawn. No new safety signals were identified.

Pharmacokinetics

The pharmacokinetics of doripenem and its metabolite doripenem-M1 was studied in children above 3 months of age to less than 18 years of age. The weight based (20 mg/kg up to 500 mg) dosing regimen provided exposures similar to the adult fixed dosing regimen (500 mg).

Recommendation

At present no further pediatric studies with doripenem are requested. The new MAH has not applied for PIP.

x Fulfilled –

No further action required

4. ADDITIONAL CLARIFICATIONS REQUESTED

Not applicable