EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

25 April 2014

Committee for Medicinal Products for Human Use (CHMP)

Doribax

(Doripenem)

Procedure No. EMEA/H/000891/P46/031

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 4 February, 2014, the MAH submitted a final report for paediatric study for doripenem/Doribax in accordance with Article 46 of Regulation (EC) No1901/2006, as amended, on medicinal products for paediatric use. This study was, however, terminated early due to business reasons and not for any safety concerns.

At the time of study termination, only 7 subjects of the planned 120 subjects were enrolled and treated in this study

A short critical expert overview has also been provided.

Enrollment in this study was too limited to determine the comparable efficacy and safety with cefepime for the pediatric population under study.

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

2. SCIENTIFIC DISCUSSION

Information on the pharmaceutical formulation used in the study

Doripenem for injection 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 authorization 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 (NP), including ventilator-associated pneumonia (VAP), and 500 mg 1-hour infusions are approved for the treatment of adults with complicated intra-abdominal infections (cIAIs) and complicated urinary tract infections (cUTIs). An optional dose of doripenem 1g 4-hour infusion 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 (EMA) Pediatric Committee (PDCO; EMEA-000015-PIP01-07) to develop pediatric dose vials with a smaller content of drug (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:

Protocol DORI-PED-3003; Phase 3

Prospective, randomized, Double-Blind, Multicenter Study to Establish the Safety and Tolerability of Doripenem Compared With Cefepime in Hospitalized Children With Bacterial Pneumonia

Study DORI-PED-3003 was a Phase 3 prospective, randomized, double-blind, active comparator-controlled, multicenter study to establish the safety and tolerability of doripenem compared with that of cefepime in hospitalized children 3 months to <18 years of age with suspected bacterial pneumonia, including nosocomial pneumonia (NP), VAP, and community-acquired pneumonia (CAP), including severe CAP.

Secondary objectives were to determine clinical cure rates at the time of cure (TOC) visit, clinical improvement rates at the end-of-treatment visit for intravenous study drug therapy (EIV), and clinical relapse rates at the last follow-up visit (LFU), and to characterize the pharmacokinetics (PK) of doripenem based on a sparse PK sampling scheme.

This study was terminated early on 5 August 2013 due to business reasons and not for any safety concerns. At the time of study termination, only 7 subjects of the planned 120 subjects were enrolled and treated in this study.

Study DORI-PED-3003 is included in the current DORIBAX pediatric investigational plan (PIP) decision (P/0071/2012). (The PIP for doripenem was transferred to Shionogi Limited on August 2013; therefore Janssen-Cilag International NV is no longer the PIP applicant.)

All 3 pathogens (*Staphylococcus aureus*, *Streptococcus pneumoniae*, and *Klebsiella pneumoniae*) isolated from the lower respiratory tract (LRT) culture in 2 of the doripenem-treated subjects (2 pathogens in 1 subject and 1 pathogen in 1 subject) were susceptible pneumonia pathogens and no pathogens were isolated in cefepime-treated subjects.

2.2. Clinical study

Description

Protocol DORI-PED-3003; Phase 3

Study Period: 01 December 2010 to 21 March 2012

On 13 February 2012, the US Food and Drug Administration (FDA) placed the DORI-PED-3003 study on clinical hold. However, prior to clinical hold being lifted on 05 August 2013, the 3 pediatric studies (DORI-PED-3001, DORI-PED-3002, and DORI-PED-3003) were terminated early for business reasons and were not related to any safety concerns. Hence, the database lock date was on 03 October 2013.

Study Centers: There were 28 study centers across 10 countries (Argentina, Brazil, Colombia, Latvia, Lithuania, Mexico, Panama, Poland, Ukraine, and United States of America [USA]); subjects were screened at 4 sites and enrolled at 3 sites situated in Poland, Ukraine and Colombia when the study was put on hold.

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 to <18 years of age with suspected bacterial pneumonia including nosocomial pneumonia (NP), ventilator-associated pneumonia (VAP), and severe community-acquired pneumonia (CAP).

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 intravenous (IV) study drug therapy (EIV) visit,
- to determine clinical relapse rates at the late follow-up (LFU) visit, and
- to characterize pharmacokinetics (PK) of doripenem based on a sparse PK sampling scheme.

Study design

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 suspected or confirmed bacterial pneumonia who required IV antibiotics.

To be eligible for enrollment a subject had to be

- 3 months to <18 years of age, and have had clinical evidence of pneumonia, requiring hospitalization and treatment with parenteral antibiotics
- severe CAP or NP (defined as pneumonia acquired after 48 hours of hospitalization), including VAP (defined as pneumonia acquired after 48 hours of mechanical ventilation) based on the presence of a new or progressive alveolar/lobar infiltrate on chest radiograph, fever or hypothermia, leukocytosis or leucopenia with neutrophilia or immature band forms,
- clinical signs or symptoms of pneumonia or the requirement for mechanical ventilation for pneumonia.

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 followed by oral antibiotic therapy (amoxicillin/clavulanate potassium);
- 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 maximum duration of study drug therapy was 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.

Study population / Sample size

Number of Subjects (planned and analyzed):

The DORIPED3003 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 pediatric studies (cIAI, cUTI, pneumonia), with each study enrolling a minimum of 90 subjects in the doripenem 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 were to be <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.

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

Analyzed: 7 subjects were enrolled and treated in this study.

Diagnosis and Main Criteria for Inclusion:

- Boy or girl, 3 months to <18 years of age; had new or progressive radiographic infiltrate(s) (alveolar, lobar, or consolidation) consistent with a bacterial pneumonia that was not related to cardiac or other disease processes
- Clinical presentation compatible with bacterial pneumonia
- Diagnosis of NP, VAP, or severe CAP; and based on the judgment of the investigator, required hospitalization initially and antibacterial therapy for 10 to 14 days for the treatment of the current pneumonia.

Main exclusion criteria:

- History of hypersensitivity reaction to any β-lactam antibiotics; concomitant infection including meningitis or other central nervous system infection requiring systemic antibiotic or antifungal therapy;
- more than 24 hours of systemic antibacterial therapy in the 48 hours preceding start of infusion of first dose of the IV study drug therapy;
- presence at baseline of *Stenotrophomonas maltophilia* or *Burkholderia cepacia* pulmonary infection; mono-microbial pneumonia at randomization caused by a single pathogen that was nonsusceptible to doripenem or cefepime, including but not limited to methicillin-resistant *Staphylococcus aureus* (MRSA) or atypical bacteria;
- acute respiratory distress syndrome;

- conditions at baseline that might interfere with the assessment or interpretation of the diagnosis or response to therapy;
- acute pulmonary edema as the sole cause of the infiltrate on chest x-ray;
- severe full thickness burns to >15% of the body; girls who were pregnant, nursing, or menarchal, and if sexually active not practicing, before screening, and did not agree to continue using a highly effective method of birth control for 30 days after last dose of study drug therapy;
- had any rapidly progressing disease or immediately life-threatening illness;
- clinically significant laboratory abnormalities of hematocrit, absolute neutrophil count, platelet count, serum alanine aminotransferase, aspartate immunodeficient
- requiring prophylactic antimicrobial therapy to prevent *Pneumocystis jirovicei* infection, *Toxoplasma gondii*, or herpes viruses,
- and/or required chronic or intermittent inmunoglobin replacement therapy;
- receiving chemotherapy for current malignancy;
- organ or bone marrow transplant and treated with chronic immunosuppressive therapy for prevention of organ transplantation rejection;
- receiving imuran, methotrexate, or chronic corticosteroid therapy;
- cystic fibrosis diagnosis;
- history of uncontrolled epilepsy;
- receiving probenecid or valproic acid.

Treatments

Test Product, Dose and Mode of Administration, Batch No.: Doripenem was supplied as fine and white to slightly yellowish off-white powder for IV administration (20 mg/kg up to a maximum of 500 mg/dose) in vials containing 500 mg powder.

Batch Number/Lot Number		
Test Product/Dose	Route of Administration	Expiration Date
Doripenem 500 mg	Intravenous	31 October 2011
Doripenem 500 mg	Intravenous	31 October 2012
Doripenem 500 mg	Intravenous	31 March 2013
Doripenem 500 mg	Intravenous	31 July 2014

Reference Therapy, Dose and Mode of Administration, Batch No.: Cefepime was supplied as white to pale yellow powder for IV administration (**50** mg/kg per dose up to a maximum of **2** g/dose) containing 2 g of cefepime. (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	Expiration Date
Cefepime 2 g	Intravenous	31 December 2010
Cefepime 2 g	Intravenous	31 July 2012
Cefepime 2 g	Intravenous	31 July 2012

Randomization and Blinding

Doripenem was administered as a 60-minute infusion and cefepime was infused over 30 minutes. Therefore, to maintain the study blind, a double-dummy design was implemented and all subjects received a 30-minute infusion of study drug immediately followed by a 60-minute infusion of study drug every 8 hours. Subjects who were randomly assigned to the doripenem group received a 30-minute IV infusion of placebo (matched to cefepime) immediately followed by a 60-minute infusion of doripenem 20 mg/kg per dose up to a maximum of 500 mg/dose every 8 hours. Subjects who were randomly assigned to the cefepime group received a 30-minute IV infusion of cefepime **50** mg/kg per dose up to a maximum of **2** g/dose immediately followed by a 60-minute infusion of placebo (matched to doripenem) every 8 hours.

Duration of Treatment

Subjects received a 10- to 14-day course of study drug therapy, which could have consisted of IV study drug only or at least 3 days of IV study drug followed by oral amoxicillin/clavulanate potassium. If, at any time, after receiving at least 9 paired doses (approximately 72 hours) of IV study drug therapy, a subject did not demonstrate improvement in signs and symptoms of pneumonia, or continued to have a fever that was not resolving and was without alternative explanation, or had clinical evidence of worsening pneumonia and required alternative non-study antibiotic therapy, the subject was considered a treatment failure and was discontinued from study drug therapy and followed for safety.

Outcomes/endpoints

Efficacy: Clinical outcome assessments based on the signs and symptoms of pneumonia were performed at the EIV, TOC, and LFU visits outcomes.

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

Pharmacokinetics Evaluations: 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-minutes dose of doripenem/doripenem placebo.

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

In addition to the standard safety evaluations, treatment-emergent adverse events (TEAEs) 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 studies 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.

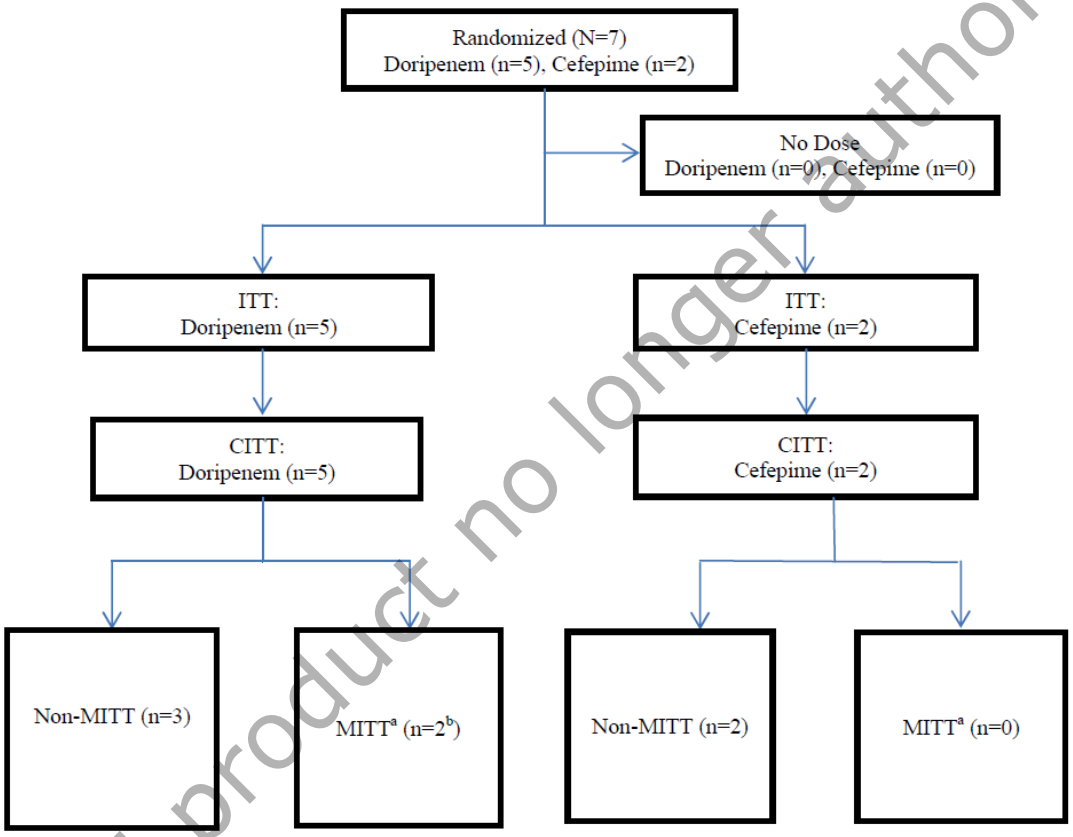
Results

Recruitment / Number analysed

This study was conducted from 01 December 2010 to 21 Mar 2012. Originally, the study was planned to enroll a minimum of 120 subjects but since it was terminated early (05 August 2013), only 7 subjects were enrolled in this study at 1 center each in Poland, Ukraine, and Colombia.

Baseline data

Figure 2: Subject Disposition



All 7 subjects completed the TOC and LFU visits, thereby completing the study.

Table 2: Subject Disposition

(Study JNJ-38174942-DORI-PED3003: All Randomized Subjects Analysis Set)

	Doripenem (N=5) n (%)	Cefepime (N=2) n (%)	Total (N=7) n (%)
Randomized Subjects	5 (100)	2 (100)	7 (100)
Randomized but not Treated	0	0	0
Subjects Who Completed Study [a, b]	5 (100)	2 (100)	7 (100)
Treated with IV Therapy Only	2 (40.0)	0	2 (28.6)
Treated with IV and Oral Therapy	3 (60.0)	2 (100)	5 (71.4)
MITT treated with IV Therapy Only	0	0	0
MITT treated with IV and Oral Therapy	2 (40.0)	0	2 (28.6)
Subjects who did not Complete Study	0	0	0
Follow-up Visits Completed	5 (100)	2 (100)	7 (100)
Had TOC and LFU [c]	5 (100)	2 (100)	7 (100)
Had TOC but not LFU	0	0	0
Not TOC nor LFU	0	0	0
Not TOC but Completed LFU	0	0	0

IV=Intravenous, LFU=Late follow Up, MITT=Microbiological Intent-to-Treat, TOC=test of cure

Note: percentages are based on the number of subjects randomly assigned to each treatment group

However, 1 subject (Subject 3057002) receiving IV doripenem was discontinued from study drug on study Day 9 due to an AE (empyema). The event resolved on study Day 13. The subject was followed for safety and completed the study after the LFU assessment performed 98 days after the TOC visit.

Table 3: Reasons for Discontinuation From Study Drug Therapy and Discontinuation From Study

(Study JNJ-38174942-DORI-PED3003: All Randomized Subjects Analysis Set)

Category Reasons For Discontinuation	Doripenem (N=5) n (%)	Cefepime (N=2) n (%)	Total (N=7) n (%)
Subjects Who Received IV Study Drug Therapy	5 (100)	2 (100)	7 (100)
Subjects Who Did Not Complete IV Therapy	1 (20.0)	0	1 (14.3)
Adverse Event	1 (20.0)	0	1 (14.3)
Subjects Who Received Oral Therapy	3 (60.0)	2 (100)	5 (71.4)
Subjects Who Completed Study Through the LFU Visit[a]	5 (100)	2 (100)	7 (100)

IV=Intravenous, LFU=Late Follow Up

Demographics and Baseline Characteristics

Demographic and baseline characteristics of all randomized subjects (ie, ITT analysis set) were similar between the treatment groups. All 7 randomized subjects in both treatment groups were male except for 1 female subject who was treated with cefepime. All subjects were white; most subjects were in the age group of 2 to <6 years (n=5 [71%]) with a mean age of 5 years. Six subjects had CAP and 1 subject had severe CAP; none of the subjects had NP or VAP. None of the subjects reported bacteremia at baseline.

Antimicrobial susceptibility

A baseline distribution of pathogens based on the susceptibility to the study drug therapy received is provided in Table 5 below.

Table 5: Baseline Pathogen and Susceptibility Characteristics to Study Drug Received

(Study JNJ38174942-DORI-PED3003: Microbiological Intent-to-Treat Analysis Set)

Baseline Pathogen	Doripenem MIC, n (%)				Cefepime MIC, n (%)			
Dictionary Derived Term	S	NS	NA	Total	S	NS	NA	Total
Gram-positive, Aerobic	2 (100)	0	0	2	0	0	0	0
Staphylococcus aureus	1 (100)	0	0	1	0	0	0	0
Streptococcus pneumoniae	1 (100)	0	0	1	0	0	0	0
Gram-negative, Aerobic	1 (100)	0	0	1	0	0	0	0
Klebsiella pneumoniae	1 (100)	0	0	1	0	0	0	0

S=Susceptible, NS=Non-susceptible, NA=Not available, Total=The number of pathogens

Extent of Exposure

The median duration of the IV study drug therapy for doripenem-treated and cefepime-treated subjects was similar (ie, 9 days and 9.5 days [total range: 5 to 15 days]). For subjects who switched to oral therapy, the median duration of oral treatment for doripenem-treated subjects was 7 days (range: 3 to 11 days) and for cefepime-treated subjects, it was 5 days. For subjects who took IV only or IV and oral therapy, the median duration of study drug therapy was 14 days (range: 9 to 15 days) for doripenem-treated subjects and 13.5 days for cefepime-treated subjects.

The maximum duration of treatment required per protocol was 14 days, or fourteen 24-hour treatment periods. No subject received treatment for more than fourteen 24-hour treatment periods.

Pharmacokinetic results

Plasma samples were collected from all 7 subjects randomized into the study. A non-compartmental PK analysis was conducted on all 5 subjects that were randomly assigned to receive doripenem. Two subjects were excluded from descriptive statistics due to insufficient or variable data in the terminal phase of their respective concentration-time profiles. The PK data from this study are therefore limited.

The mean (standard deviation [SD]) doripenem and doripenem-M-1 PK data is 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 DORIPED3003: Pharmacokinetic Data Analysis Set)

Parameter	Doripenem	Doripenem-M-1
N	5	5
C_{max} (µg/mL)	38.8 (4.79)	3.45 (2.06)
t_{max} (h)[a]	0.92 (0.90-1.08)	0.92 (0.90-1.08)
AUC_{last} (µg·h/mL)	59.7 (9.30)	7.42 (2.97)
AUC_{τ} (µg·h/mL)	61.0 (11.5)[b]	8.58 (3.61)[b]
$t_{1/2}$ (h)	0.866 (0.0970)[b]	1.69 (0.370)[b]
CL (L/h)	6.03 (2.14)[b]	46.7 (21.5)[b]
V_{ss} (L)	6.15 (2.15)[b]	113 (76.2)[b]
CR_{CL} (mL/min)	151 (65.0)	

[a] Median (range)
[b] n=3
NOTE: τ equal to 8 hours

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 1 g (or equivalent mg/kg) doses.

Efficacy results

All 7 subjects who were randomized into the study were treated.

The CITT analysis set included 5 doripenem-treated and 2 cefepime-treated subjects. At least 1 pneumonia pathogen was isolated from the LRT cultures in 2 of the 5 doripenem-treated subjects and none of the cefepime-treated subjects .Therefore, the MITT analysis set consisted of only 2 doripenem-treated subjects.

The results for the primary and key secondary efficacy endpoints are presented in Table 8.

Primary Efficacy: Clinical cure rate at the TOC visit was numerically lower for doripenem-treated subjects as compared with cefepime-treated subjects (3 out of 5 vs. 2 out of 2 [60% vs 100%]) in the CITT analysis set.

Table 8: Clinical Cure Rate at TOC and LFU and Clinical Improvement at EIV
(Study JNJ38174942-DORI-PED3003: Clinical Intent-to-Treat Analysis Set)

	---- Doripenem ---			---- Cefepime ----				
	N	n	%	N	n	%	Diff(a)(%)	95% CI(b)
Clinical Cure at TOC	5	3	60.0	2	2	100.0	-40.0	
Clinical Improvement at EIV	5	4	80.0	2	2	100.0	-20.0	
Clinical Cure at LFU	5	3	60.0	2	2	100.0	-40.0	

(a) Doripenem minus Cefepime;
(b) No Two-sided 95% CI is provided if the sample size in any treatment group is fewer than 5 subjects

Secondary Efficacy: For subjects in the CITT analysis set, the clinical improvement rate at the

EIV visit was numerically lower for doripenem-treated subjects as compared to cefepime-treated subjects Similarly, clinical cure rates at the LFU visit were numerically lower for doripenem-treated subjects as compared with cefepime-treated subjects

Subgroup efficacy analyses by demographic and baseline characteristics were limited due to the small numbers of subjects in each treatment group.

For the 2 subjects in the MITT analysis set, both had a favorable microbiological outcome (ie, cured) at TOC, EIV and LFU visits.

Overall, due to a small sample size (n=7), it was not possible to determine the comparable efficacy of doripenem and cefepime in the treated population.

Safety results

Data Sets Analyzed

Safety analyses were performed on the ITT analyses set which 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.

Safety was assessed by comparing frequencies TEAEs, summaries of protocol specified laboratory evaluations and vital sign measurements between the 2 treatment groups.

Summaries of TEAEs and other safety data are based on 7 subjects (5 doripenem-treated subjects and 2 cefepime-treated subjects) 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, ie, safety population.

A summary of the TEAEs reported for 7 subjects (5 doripenem-treated subjects and 2 cefepime-treated subjects) is provided in Table 9.. Three of the 4 subjects were with doripenem and had all study-drug related TEAEs. One subject was treated with cefepime. Two of the 5 doripenem-treated subjects reported SAEs (empyema and pneumonia), both were considered by the investigator to be unrelated to the study drug.

Table 9: Treatment-Emergent Adverse Events Summary

(Study JNJ38174942-DORI-PED3003: Intent-to-Treat Analysis Set)

Safety Outcome	Doripenem (N=5) n (%)	Cefepime (N=2) n (%)	Total (N=7) n (%)
Any TEAE	3 (60.0)	1 (50.0)	4 (57.1)
Any Study Drug Related TEAE (b)	3 (60.0)	0	3 (42.9)
Any Serious TEAE	2 (40.0)	0	2 (28.6)
Any Study Drug Related Serious TEAE (b)	0	0	0
Any TEAE of Special Interest (c)	0	0	0
Any Study Drug Related TEAE of Special Interest (b)(c)	0	0	0
Discontinuation from Study Due to TEAE(a)	0	0	0
Discontinuation from Study Due to Study Drug Related TEAE(a)(b)	0	0	0
Discontinuation from Study Due to Serious TEAE(a)	0	0	0
Discontinuation from Study Due to Study Drug Related Serious TEAE(a)(b)	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) Subject 3057002 discontinued from study drug due to AE but had LFU visit. This subject is regarded as completed the study
(b) Study drug-related treatment-emergent adverse events (TEAEs) included possibly, probably and very likely related adverse events or events with missing relationship
(c) TEAEs of special interest are hemolytic anemia, hepatocellular injury, renal failure/impairment, seizure, thrombocytopenia and local intolerability and phlebitis

A summary of the incidence of TEAEs by SOC and PT for each treatment is provided in Table 10.

Table 10: TEAEs Reported by System Organ Class and Preferred Term

(Study JNJ38174942-DORI-PED3003: Intent-To-Treat Analysis Set)

Body System Or Organ Class Dictionary-Derived Term	Doripenem (N=5) n (%)	Cefepime (N=2) n (%)	Total (N=7) n (%)
Total no. subjects with TEAE	3 (60.0)	1 (50.0)	4 (57.1)
Gastrointestinal Disorders	3 (60.0)	0	3 (42.9)
Abdominal Pain	1 (20.0)	0	1 (14.3)
Abdominal Pain Upper	1 (20.0)	0	1 (14.3)
Diarrhea	1 (20.0)	0	1 (14.3)
General Disorders and Administration Site Conditions	1 (20.0)	0	1 (14.3)
Chest Pain	1 (20.0)	0	1 (14.3)
Immune System Disorders	1 (20.0)	0	1 (14.3)
Hypersensitivity	1 (20.0)	0	1 (14.3)
Infections and Infestations	2 (40.0)	1 (50.0)	3 (42.9)
Empyema	1 (20.0)	0	1 (14.3)
Gastroenteritis	1 (20.0)	0	1 (14.3)
Nasopharyngitis	0	1 (50.0)	1 (14.3)
Pneumonia	1 (20.0)	0	1 (14.3)
Injury, Poisoning and Procedural Complications	1 (20.0)	0	1 (14.3)
Stab Wound	1 (20.0)	0	1 (14.3)
Investigations	1 (20.0)	0	1 (14.3)
Oxygen Saturation Decreased	1 (20.0)	0	1 (14.3)
Musculoskeletal and Connective Tissue Disorders	1 (20.0)	0	1 (14.3)
Flank Pain	1 (20.0)	0	1 (14.3)
Renal and Urinary Disorders	1 (20.0)	0	1 (14.3)
Dysuria	1 (20.0)	0	1 (14.3)
Respiratory, Thoracic and Mediastinal Disorders	2 (40.0)	0	2 (28.6)
Acute Respiratory Distress Syndrome	1 (20.0)	0	1 (14.3)
Nasal Congestion	1 (20.0)	0	1 (14.3)
Skin and Subcutaneous Tissue Disorders	1 (20.0)	0	1 (14.3)
Ecchymosis	1 (20.0)	0	1 (14.3)

Note: Percentages calculated with the number of subjects in each group as denominator.
Note: At each level of summarization, a subject is counted once if the subject reported one or more events.
Treatment-emergent adverse events (TEAEs) are defined as AEs with onset dates on or after the date of the start of the first dose of study drug therapy and within 30 days after administration of the last dose of study drug therapy

Deaths

There were no deaths reported in this study.

Serious Adverse Events

The incidence of SAEs by SOC and treatment group is summarized in Table 11

Table 11: Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term
(Study JNJ38174942-DORI-PED3003: Intent-to-Treat Analysis Set)

Body System Or Organ Class Dictionary-Derived Term	Doripenem (N=5) n (%)	Cefepime (N=2) n (%)	Total (N=7) n (%)
Total no. subjects with SAE	2 (40.0)	0	2 (28.6)
Infections and Infestations	2 (40.0)	0	2 (28.6)
Empyema	1 (20.0)	0	1 (14.3)
Pneumonia	1 (20.0)	0	1 (14.3)

Note: Percentages calculated with the number of subjects in each group as denominator.
Note: At each level of summarization, a subject is counted once if the subject reported one or more events.

There were 2 SAEs, both in doripenem-treated subjects in the infections and infestations SOC.

Other Significant Adverse Events

Discontinuation of Study Drug Therapy

One doripenem-treated subject was discontinued from IV study drug therapy due to empyema, however, this subject was followed-up for safety at LFU visit and completed the study.

Adverse Drug Reactions

Table 12: Adverse Drug Reactions by ADR Term and Preferred Term
(Study JNJ38174942-DORI-PED3003: Intent-to-Treat Analysis Set)

ADR Derived Term Dictionary-Derived Term	Doripenem (N=5) n (%)	Cefepime (N=2) n (%)	Total (N=7) n (%)
Total no. subjects with ADRs	2 (40.0)	0	2 (28.6)
Diarrhea	1 (20.0)	0	1 (14.3)
Diarrhoea	1 (20.0)	0	1 (14.3)
Hypersensitivity	1 (20.0)	0	1 (14.3)
Hypersensitivity	1 (20.0)	0	1 (14.3)

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

Anaphylaxis, neutropenia, thrombocytopenia, Stevens Johnson Syndrome and toxic epidermal necrolysis (SJS/TEN) have been identified as ADRs during postapproval use of doripenem.

Adverse Events of Special Interest

The following AEs were considered to be of special interest: hemolytic anemia, hepatocellular injury, renal failure/impairment, seizures, thrombocytopenia, and local intolerability and phlebitis.

Subjects at risk for hepatocellular injury were identified as subjects meeting the Hy's high risk (HHR) rule based on past doripenem studies and the definition described in the FDA guidance

Safety summary

The overall exposure of doripenem was small in this study because of the number of subjects enrolled, group) in the safety analysis set, making an assessment of safety limited to single case assessments.

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

2.3. Discussion on clinical aspects by MAH

This was a randomized, double-blind, multicenter study to establish the safety and tolerability of doripenem compared with that of cefepime in hospitalized children 3 months to <18 years of age with suspected bacterial pneumonia including nosocomial pneumonia (NP), ventilator-associated pneumonia (VAP), and community-acquired pneumonia (CAP) including severe CAP.

Secondary objectives were to determine clinical cure rates at the TOC visit, to determine clinical improvement rates at the end-of-treatment for IV study drug therapy (EIV) visit, to determine clinical relapse rates at the LFU visit, and to characterize PK of doripenem based on a sparse PK sampling scheme.

In this study, a total of 7 subjects were randomly assigned to study drug therapy; 5 subjects (71.4%) were randomized to the doripenem treatment group and 2 subjects (28.6%) to the cefepime treatment group. All 7 subjects were included in the ITT and CITT analyses sets. In the ITT analysis set, 6 subjects were male, and 1 was female. All subjects were white; the mean age of these subjects was 5 years: 5.2 years for the doripenem treatment group and 4.5 years for the cefepime treatment group. The median duration of studydrug therapy (IV only or IV and oral) was 14 days for doripenem group and 13.5 days for cefepime group. The median duration for IV only therapy was 9 days for doripenem group and 9.5 days for cefepime group.

All 7 subjects who were randomized into the study were treated and completed the study. The CITT analysis set included 5 doripenem and 2 cefepime subjects. At least 1 susceptible pneumonia pathogen was isolated from the LRT culture in 2 doripenem-treated subjects and from none of the cefepime-treated subjects. Therefore, the MITT analysis set consisted of only 2 doripenem-treated subjects. The clinical cure rate at the TOC visit in the CITT analysis set was numerically lower for subjects in the doripenem group compared to the cefepime group (3 out of 5 vs. 2 out of 2 [60% vs. 100%]). The 2 subjects treated with doripenem in the MITT analysis set were both cured at the TOC visit.

There were no new or unexpected safety findings identified in this study. The laboratory results were comparable between treatment groups. There were no reports of TEAEs of special interest or deaths. One subject was discontinued from study drug because of a TEAE of empyema; however, the subject was followed up for safety and completed the study.

The major limitation of the study was limited enrollment which precludes a meaningful conclusion about the efficacy and safety of doripenem compared with cefepime.

No specific benefits or special precautions can be derived from this limited data.

3. Rapporteur's Overall Conclusion AND RECOMMENDATION

Overall conclusion

The outlined study protocol can be considered satisfactory.

The major limitation of the study was limited enrollment, which precludes a meaningful conclusion about the efficacy and safety of doripenem compared with cefepime for the pediatric population under study.

Doripenem administered as 20 mg/kg per dose (up to a maximum of 500-mg dose) as 1-hour infusion in subjects 3 months to <18 years of age was considered generally safe and well

tolerated 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 1 g (or equivalent mg/kg) doses.

Safety data do not indicate any new or significant safety issues deviating from the current safety profile of doripenem.

The submitted data is not sufficient to draw any conclusions regarding the efficacy and safety of doripenem compared with cefepime.

No specific benefits or special precautions can be derived from these limited data.

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.

Recommendation

x Fulfilled –

No further action required

4. ADDITIONAL CLARIFICATIONS REQUESTED

Not applicable