27 June 2019
EMA/CHMP/455556/2019
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Invented name: Zinforo

International non-proprietary name: ceftaroline fosamil

Procedure No. EMEA/H/C/002252/II/0041

Marketing authorisation holder (MAH): Pfizer Ireland Pharmaceuticals

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

Table of contents

List of abbreviations

ABSSSI	Acute bacterial skin and skin structure infection
AE	Adverse event
AUC24	Area under the concentration-time curve from 0 to 24 hours
CABP	Community-acquired bacterial pneumonia
CAP	Community-acquired pneumonia
CBC	Complete blood count
CDC	Centers for Disease Control
CI	Confidence interval
Cmax, ss	Steady-state maximum concentration
CNS	Central nervous system
CRF	Case Report Form
CRO	Contract research organization
CRP	C-reactive protein
CSF	Cerebrospinal fluid
CSR	Clinical study report
cSSTI	Complicated skin and soft tissue infection
CT	Computed tomography
CTD	Common Technical Document
CXR	Chest radiograph
CV	Curriculum vitae
DCT	Data Collection Tool
DSMB	Data and Safety Monitoring Board
EDP	Exposure during pregnancy
EMA	European Medicines Agency
EOT	End-of-Therapy
ESBL	Extended-spectrum β-lactamase
EU	European Union
FDA	Food and Drug Administration
FPFV	First patient first visit
GCP	Good Clinical Practice
HIV	Human immunodeficiency virus
IB	Investigator's Brochure

ICD	Informed consent document
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IP	Investigational product
IRB	Institutional Review Board
ITT	Intent-to-treat
IV	Intravenous
IXRS	Interactive Response System
JNDA	Japanese new drug application
LLOQ	Lower limit of quantification
LOS	Late-onset sepsis
LPLV	Last patient last visit
LTFU	Lost to follow-up
MedDRA	Medical Dictionary for Regulatory Activities
MIC	Minimum inhibitory concentration
Micro-ITT	Microbiological intent-to-treat
MITT	Modified intent-to-treat
MRI	Magnetic resonance imaging
MRSA	Methicillin-resistant Staphylococcus aureus
n	Number of patients in the category or analysis
N	Number of patients in the cohort
NEC	Necrotizing enterocolitis
PBP	Penicillin-binding protein
PCR	Polymerase chain reaction
PCS	Potentially clinically significant
PDCO	European Paediatric Committee
PIP	Paediatric Investigation Plan
PK	Pharmacokinetics
PRSP	Penicillin-resistant Streptococcus pneumoniae
PT	Preferred term
PTA	Probability of target attainment
q#h	every (number) hours
ROW	Rest of World

SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard deviation
SFU	Safety Follow-up
SmPC	Summary of Product Characteristics
SOC	System organ class
TE	Treatment-emergent
TOC	Test-of-Cure
ULN	Upper limit of normal (standard reference range)
US	United States

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Pfizer Ireland Pharmaceuticals submitted to the European Medicines Agency on 17 October 2018 an application for a variation.

The following variation was requested:

Variation requested		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of Indication to include paediatric patients from birth to less than 2 months old for Zinforo; as a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated based on results from study D3720C00009 (C2661002) an open-label, multicentre study to evaluate the safety, tolerability, pharmacokinetics, and efficacy of ceftaroline in neonates and young infants with late-onset sepsis. The Package Leaflet is updated in accordance. The RMP (v 17.0) has also been submitted.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0176/2018 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the P/0176/2018 was completed.

The PDCO issued an opinion on compliance for the PIP P/0176/2018.

Information relating to orphan market exclusivity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The applicant did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Alar Irs Co-Rapporteur: N/A

Timetable	Actual dates
Submission date	17 October 2018

Timetable	Actual dates
Start of procedure:	1 December 2018
CHMP Rapporteur Assessment Report	28 January 2019
CHMP Co-Rapporteur Assessment Report	28 January 2019
PRAC Rapporteur Assessment Report	28 January 2019
PRAC members comments	6 February 2019
Updated PRAC Rapporteur Assessment Report	8 February 2019
PRAC Outcome	14 February 2019
CHMP members comments	18 February 2019
Updated CHMP Rapporteur(s) (Joint) Assessment Report	25 February 2019
Request for supplementary information (RSI)	28 February 2019
PRAC Rapporteur Assessment Report	3 June 2019
PRAC members comments	5 June 2019
CHMP Rapporteur Assessment Report	14 June 2019
PRAC Outcome	14 June 2019
CHMP members comments	17 June 2019
Updated CHMP Rapporteur Assessment Report	20 June 2019
Opinion	27 June 2019

2. Scientific discussion

2.1. Introduction

Ceftaroline fosamil is a beta-lactam antibiotic that inhibits bacterial cell wall biosynthesis by binding to one or more penicillin-binding proteins (PBP). As a results built up of bacterial cell wall is disturbed and that leads to cell death. Ceftaroline fosamil exhibits unique properties that distinguish it from other β lactams, due to its high affinity for PBP2a in MRSA and PBP2x in PRSP that contribute to its potent antibacterial activity against these organisms.

Ceftaroline fosamil is currently approved for adults and children above the age of 2 months for the treatment of complicated skin and soft tissue infections (cSSTI) and community acquired pneumonia (CAP).

The paediatric approval for the above mentioned age groups was granted in the EU in June 2016.

This application is to extend the approved indications to children aged from birth to less than 2 months of age and includes the appropriate dose recommendations for this age subgroup. Both cSSTI and CAP are relatively rare in children aged less than 2 months; neonates are often affected by the late onset neonatal sepsis (LOS), disease with high mortality and disability rates.

Data on prevalence of cSSTI in neonates are hectic and appropriate epidemiological studies are still scarce. Superficial skin infections have been described but likely do not need systemic antibacterial treatment. Despite this, in hospitalised patients antibacterial treatment is usually employed.

Another group of neonates with skin and soft tissue infections are those admitted to neonatal intensive care unit and having surgical wounds or indwelling catheters. Similar to adults, the SSTI are mostly caused by S.aureus, but may be caused by Gram negative microorganisms if occurring in perianal area. Coagulase

negative staphylococci (CoNS) that do not cause cSSTI in adults and older children may be identified as causative agents, especially if cSSTI is related to indwelling catheters. The rates of infections caused by MRSA depend on the geographical location, similar to adults. Worldwide most CoNS have acquired mecA gene and thus are resistant to classical staphylococcal antibiotics like oxacillin and first/second generation cephalosporins.

CAP is rare in neonates as well. However, if it occurs, then it is mostly caused by group B streptococci, followed by S.aureus and E.coli. This is in contrast to adults and older children in whom Streptococcus pneumonia and Mycoplasma dominate (Pediatr Infect Dis J 2012;00: e78–85).

There are no specific guidelines for treatment of cSSTI in neonates. Therefore recommendations similar to older children should apply. Antistaphylococcal beta-lactams are most commonly recommended and used in case of methicillin susceptible S.aureus (MSSA).

Vancomycin or clindamycin or trimethoprim/sulfamethoxasol are recommended if MRSA is suspected or confirmed (Clinical Infectious Diseases 2014;59(2):e10–52; Arch Dis Child. 2016 Jan;101(1):72-6). Surgical treatment is employed similar to adults and older children.

Ampicillin + aminoglycoside or alternatively third generation cephalopsorins are recommended for treatment of CAP in neonates (The Paediatric Infectious Disease Journal. 31(6):e78–e85). In case of staphylococcal pneumonia, antistaphylococcal penicillins are used.

Ceftaroline fosamil as an agent with the antibacterial activity against S.aureus, CoNS and non-ESBL producing Enterobactriaceae is an alternative antibiotic for treatment of cSSTI and CAP in neonates.

2.2. Non-clinical aspects

2.2.1. Introduction

The nonclinical pharmacology, pharmacokinetics, and toxicology profile of ceftaroline fosamil was described and assessed in the initial marketing authorization application. Subsequently, addenda to the nonclinical summaries (additional pharmacology information and juvenile toxicity studies conducted to support the paediatric development program) were submitted and assessed by CHMP in 2015. They are summarised below:

Table 1 Toxicity studies in juvenile rats using ceftaroline fosamil

Study type and duration	Route of administration	Species	Study number (reference number)	GLP compliant
Dose range finding Juvenile toxicity in neonatal rats/14 days	Intravenous	Rat	20011802 (3011LR)	No
Juvenile toxicity in neonatal rats/14 days	Intravenous	Rat	20011803 (3012LR)	Yes

Updated *in vitro* susceptibility data were also submitted and assessed by CHMP in 2015, in the initial paediatric extension of indication.

No new non-clinical data have been submitted in this application, which was considered acceptable by the

CHMP.

2.2.2. Pharmacology

There are no additional in vitro microbiology studies performed for the current submission, which was considered acceptable by CHMP.

In summary, the *in vitro* activity of ceftaroline fosamil has been reported against clinically important community-acquired pneumonia (CAP) and complicated skin and soft tissue (cSSTI) pathogens, relevant to the Zinforo prescribing information.

Ceftaroline fosamil activity was assessed against Gram-positive and Gram-negative bacteria isolated from adult and paediatric infected patients. Overall, susceptibility to ceftaroline fosamil was similar between isolates from paediatric and adult age groups for the relevant pathogens causing skin and respiratory infections. However, susceptibility varied ±1 doubling dilution in the MIC_{90} values for *S. aureus* (MRSA) depending on the geographic region. MRSA isolates from children were generally more susceptible to ceftaroline fosamil than adult isolates by one doubling dilution.

The fastidious Gram-positive (*S. pneumoniae*, β-haemolytic streptococci) and Gram-negative (*Haemophilus* species) isolates obtained from both age groups were highly susceptible to ceftaroline fosamil when assessed using established interpretative criteria on susceptibility.

Against *Enterobacteriaceae* ceftaroline fosamil is active only against non-ESBL-producing strains. Isolates from adult and paediatric patients showed comparable susceptibilities across different geographic regions.

The MAH has concluded that ceftaroline fosamil is equally active against adult and paediatric isolates that are clinically important in the two indicated infection types. CHMP agreed to this conclusion. During the assessment, CHMP requested the MAH to provide *in vitro* data about the microorganisms relevant for neonates (CoNS and non-ESBL producing *Enterobacteri*a). The MAH has provided MIC distribution data for CoNS and non-ESBL Enterobacteriaceae which showed good susceptibility of these microorganisms to ceftaroline. These data are reassuring and suggest that ceftaroline could potentially be used for treatment of infections caused by abovementioned microorganisms.

2.2.3. Pharmacokinetics

No additional nonclinical pharmacokinetic data were submitted for assessment, which was considered acceptable by CHMP.

The originally intended doses of ceftaroline fosamil proposed by the MAH in paediatric patients with normal renal function and mild renal impairment are 12 mg/kg (up to a maximum dose of 400 mg) administered every 8 hours as a 1 hour infusion to paediatric patients ≥2 years and 8 mg/kg ceftaroline fosamil every 8 hours as a 1 hour infusion in children 2 months to <2 years.

Ceftaroline fosamil was given to male and female neonatal rats by slow intravenous bolus dose for 14 days from PND 7 to 21. Ceftaroline fosamil was well tolerated, no new target organs were identified and the NOAEL was the highest dose tested (270 mg/kg).

Exposure levels ($AUC_{(0-t)}$) of ceftaroline fosamil tested in the juvenile rat at 270 mg/kg/day were approximately 2 to 3-fold higher than the predicted median steady state $AUC_{(0-24)}$ values of ceftaroline fosamil (based on simulations) in patients with mild renal impairment.

The maximum plasma levels of ceftaroline fosamil tested in the juvenile rat at 270 mg/kg/day were approximately 20 to 28-fold higher than the predicted median steady state C_{max} values of ceftaroline fosamil (based on simulations) in patients with mild renal impairment.

2.2.4. Toxicology

Other toxicity studies

Ceftaroline fosamil: 14 day intravenous dose range finding toxicity study in the neonatal rat (study number: 20011802 (3011LR))

Ceftaroline fosamil was administered once daily to neonatal Sprague-Dawley rat pups (Crl:CD[SD]) from Post Natal Day (PND) 7 to 21 via an intravenous (bolus) injection (lateral tail vein) at 0, 30, 90 or 270 mg/kg to groups of 4 males and 4 females (main study) and 24 males and 24 females (toxicokinetic [TK] study) (20011802 (3011LR)). Controls were given 39.5 mg/mL of L-Arginine in 0.9% (w/v) Sodium Chloride for Injection. Dams were not given the test or control articles. Clinical signs, body weights, body weight changes, urine analysis, toxicokinetic parameters (ceftaroline, ceftaroline fosamil, or ceftaroline M-1 metabolite [primary inactive metabolite]), organ weights, and gross and microscopic observations were measured/conducted.

There were no test article-related clinical signs, however injection site reactions occurred at all doses, including controls. Body weights and body weight gains were not affected at any dose. Urine analysis parameters were comparable among the doses. There were no test article-related gross lesions or microscopic findings, or any changes in organ weights at any dose that were considered related to ceftaroline fosamil (brain, paired kidneys and spleen).

Table 2 Summary of ceftaroline fosamil and M1 Toxicokinetic Results

Ceftaroline Fosamil				
Dose mg/kg/day	**Day**	**T_{max} (h)**	**C_{max} (ng/mL)**	**$AUC_{(0-t)}$ (ng.h/mL)**
30	PND 7	0.083	5620	1420
30	PND21	0.083	1450	60.2
90	PND 7	0.5	1220	254
90	PND21	0.083	7870	327
270	PND 7	0.5	7500	5320
270	PND21	0.5	68.2	320
Ceftaroline				
Dose mg/kg/day	**Day**	**T_{max} (h)**	**C_{max} (ng/mL)**	**$AUC_{(0-t)}$ (ng.h/mL)**
30	PND 7	0.083	35000	99600
30	PND21	0.083	73400	46200
90	PND 7	0.083	107000	251000
90	PND21	0.083	229000	134000
270	PND 7	0.083	370000	902000
270	PND21	0.083	829000	436000
M-1 metabolite				
Dose mg/kg/day	**Day**	**T_{max} (h)**	**C_{max} (ng/mL)**	**$AUC_{(0-t)}$ (ng.h/mL)**
30	PND 7	1.5	2550	16400
30	PND21	0.5	6860	12100
90	PND 7	1.5	6040	52300
90	PND21	0.5	18500	37200
270	PND 7	0.5	21400	158000

Table 3 Summary of Toxicokinetic Results in Combined Male and Female

Dose mg/kg/day	Day	T_{max} (h)	C_{max} (ng/mL)	AUC $_{(0-t)}$ (ng.h/mL)
270	PND21	0.5	47400	89000

Ceftaroline fosamil: 14 day intravenous toxicity study in the neonatal rats with a 4-week recovery period (20011803 (3012LR))

Ceftaroline fosamil was given once daily to neonatal Sprague-Dawley (Crl:CD[SD]) rat pups from PND 7 to 21 via an intravenous injection at 30, 90 or 270 mg/kg to groups of 20 males and 20 females (main and recovery study) and 36 males and 36 females (TK study) (20011803 (3012LR)). Controls were given 35.5 mg/mL of L-arginine in 0.9% (w/v) sodium chloride for injection.

Dams were not dosed during this study, clinical signs, body weight, body weight changes, functional observational battery (FOB), urine analysis, haematology, clinical chemistry, organ weights, and gross and microscopic observations were investigated.

There were no test article-related deaths during this study. Morbidity and/or mortality occurred in 7 rats (3 main and 4 satellites). The premature decedents occurred in the control group and at 30 and 90 mg/kg (2, 3 and 2 rats respectively). In these seven animals, four were related to an injury (i.e., broken limb at 30 mg/kg, laceration on the chest at 30 mg/kg, laceration on the back at 0 mg/kg, or de-sheathing of the tail at 90 mg/kg), one was considered secondary to the intravenous dosing procedure (i.e., an embolism in the lungs), and two (one at 0 mg/kg and one at 30 mg/kg) had no known cause of death. All other animals survived to scheduled euthanasia on PND 22 (end of dose period) or PND 50 (end of recovery period).

Injection site reactions (swelling, discoloration or ulceration) were seen at all doses, including the controls; however, these injection site reactions were attributed to the route of administration. At the end of the dosing and recovery periods, body weight gains in both sexes were comparable with controls.

There were no test article-related effects on clinical pathology parameters (haematology and urine analysis) at the end of the dosing or recovery periods. There were no test article-related effects on organ weights (brain, paired kidneys and spleen) at the end of the dosing and recovery periods. There was an equivocal test article-related increase in the incidence of cysts/pitted surfaces of the kidneys in both sexes at PND 50.

Cysts were lined by a single layer of epithelium with a lumen size at least the diameter of two tubules in the region and involved a small area of the kidney. Minimal fibrosis occasionally encircled the cysts and, due to of its focal nature, was considered not to be of toxicological concern.

Table 4 Summary of Microscopic Findings (PND 22)

	Males				Females			
Group	1	2	3	4	1	2	3	4
Dose (mg/kg)	0	30	90	270	0	30	90	270
No. rats examined	10	10	10	10	10	10	10	10
Kidney (No. Examined)	10	10	10	10	10	10	10	10
Cyst	(2)[a]	(2)	(7)	(5)	(5)	(4)	(5)	(4)
Fibrosis	(0)	(0)	(1)	(0)	(2)	(1)	(0)	(0)
Minimal	0	0	1	0	2	1	0	0

[a] Numbers in parentheses represent the number of rats with the finding, and numbers without parentheses represent the number of animals with a minimal grade of fibrosis.

Microscopic findings in the kidney, observed at the end of the recovery period (PND 50), were similar in appearance to those observed at PND 22 (i.e., renal cyst with occasional minimal fibrosis).

Table 5 Summary of Microscopic Findings (PND 50)

	Males				Females			
Group	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**
Dose (mg/kg)	**0**	**30**	**90**	**270**	**0**	**30**	**90**	**270**
No. rats examined	**9**	**10**	**9**	**10**	**9**	**10**	**10**	**10**
Kidney (No. Examined)	9	10	9	10	9	10	10	10
Cyst	(2)[a]	(4)	(5)	(7)	(2)	(3)	(3)	(6)
Fibrosis	(0)	(0)	(3)	(4)	(0)	(1)	(3)	(4)
Minimal	0	0	3	4	0	1	3	4

[a] Numbers in parentheses represent the number of animals with the finding, and numbers without parentheses represent the number of animals with a minimal grade of fibrosis.

An increased macroscopic incidence of kidneys with cysts or pitted surfaces was observed at the end of the recovery period (PND 50) in both sexes at all doses (when compared to published background macroscopic and microscopic renal findings in Sprague-Dawley rats).

Microscopically, an increased and variable incidence of renal cysts was present at all doses at PND 22 and PND 55 in rats, including controls (Owen et al 1986). The incidence was also increased when compared to a recent histological review of renal cysts in 45 day old control Sprague Dawley rats (McKay 2012) which revealed an overall incidence of renal cysts of less than 10%. This observation may suggest a possible procedural-related effect in the current study. This is supported by current literature in which it is suggested that glucocorticoids play a key role in nephrogenesis in young rodents and that excess corticosteroids can potentially lead to cystogenesis (McDonald *et al.,* 2011, Gupta *et al.,* 2001, Chan *et al.,* 2010).

The juvenile rats in this study were being dosed during a time period which coincides with active nephrogenesis (PND 1 to PND 11) (Zoetis *et al*., 2003) and so a potential stress-associated effect on tubule development, secondary to the intravenous dosing procedure should be considered. An additional consideration is that all animals received a high volume daily bolus injection of ceftaroline fosamil or the control article. This could also cause altered electrolyte and fluid homeostasis in the kidney and contribute to renal tubule dilatation and cyst formation. This phenomenon has been described in the beagle dog following administration of high oral doses of potent diuretics.

This finding did not fully correlate with the microscopic findings, as cysts were also identified histologically in control rats. As these findings involved only a small portion of the kidney, were present in control, and occurred in the absence of significant changes in renal function or urinary parameters, they were considered not to be adverse.

At the end of the recovery period (PND 50) there was an increase in the incidence of cysts at all doses in males and at 270 mg/kg/day in females. This was accompanied by an increased incidence of pericystic fibrosis at 90 and 270 mg/kg/day (both sexes).

When the males were evaluated on PND 50, the maximum and average values recorded in the forelimb grip test were decreased at 270 mg/kg. Conversely, in females, increased maximum ($p \leq 0.05$) and average values were recorded in the fore- and hind limb grip tests in this same dose group on PND 50. The differences observed in these tests were considered incidental, and not related to the test article as: 1) alterations in movement were not observed in these rats; and 2) opposing observations occurred in males (i.e., decrease in grip strength) and females (i.e., increase in grip strength). There were no other test article-related effects on neurobehavioral endpoints.

A significant elevation ($p \leq 0.05$) of blood urea nitrogen (BUN) was observed on PND 22 in males at 270 mg/kg. As individual variation was large and there was no correlation of higher values with cyst occurrence, this was considered not to be of toxicological significance. There were no other test article-related effects on clinical chemistry endpoints.

The NOAEL was considered to be 270 mg/kg in juvenile, suckling rats.

Table 6 Summary of ceftaroline fosamil and M1 Toxicokinetic Results

Ceftaroline Fosamil				
Dose mg/kg/day	**Day**	**T_{max} (h)**	**C_{max} (ng/mL)**	**$AUC_{(0-t)}$ (ng.h/mL)**
30	PND 7	NR	NR	NR
30	PND21	0.083	7800	3140
90	PND 7	NR	NR	NR
90	PND21	NR	NR	NR
270	PND 7	NR	NR	NR
270	PND21	NR	NR	NR
Ceftaroline				
Dose mg/kg/day	**Day**	**T_{max} (h)**	**C_{max} (ng/mL)**	**$AUC_{(0-t)}$ (ng.h/mL)**
30	PND 7	0.083	49600	92500
30	PND21	0.083	85900	71800
90	PND 7	0.5	131000	325000
90	PND21	0.083	201000	140000
270	PND 7	0.083	323000	1020000
270	PND21	0.083	571000	419000
M-1 metabolite				
Dose mg/kg/day	**Day**	**T_{max} (h)**	**C_{max} (ng/mL)**	**$AUC_{(0-t)}$ (ng.h/mL)**
30	PND 7	4	1820	14300
30	PND21	0.5	6090	10700
90	PND 7	1.5	8180	47500
90	PND21	0.5	17300	28400
270	PND 7	1.5	19200	156000
270	PND21	0.5	41100	73300

NR: No result as long term stability of 28 days was exceeded.

2.2.5. Ecotoxicity / environmental risk assessment

The MAH has submitted an Environmental Risk Assessment (ERA) as part of the application.

In accordance with the SmPC, the maximum daily dose of ceftaroline fosamil is 1200 mg/day. For infections caused by *S. aureus* in adults, the maximum dose may be increased to 1800 mg/day. After administration, ceftaroline fosamil is converted to microbiologically active ceftaroline in the body. Following administration 87.5 % of the dose was excreted in the urine and 5.95 % in faeces. About 64 % of the dose was excreted in urine as ceftaroline fosamil, in faeces ceftaroline fosamil was detected only 0.05 %. Ceftaroline fosamil was not detected in urine or faeces in humans.

The MAH has provided its Phase I assessment. Screening for persistence, bioaccumulation and toxicity (PBT) was performed. At all environmentally relevant pHs ceftaroline fosamil has $logD_{ow}$ <0, i.e. less than trigger value 4.5. The study data have been already provided during the initial marketing authorization application. Further PBT screening is not required.

Further, data for F_{pen} refinement have been provided. Patient consumption of the prodrug in Slovenia has been used to calculate the market penetration factor. Based on historical data from 2013-2017 Slovenia was the EU country with the highest per capita use of cetraroline fosamil. The maximum annual consumption from all products used in Slovenia was 1.12 kg in 2015. Based on existing data the proposed new indication

is expected to increase overall consumption of ceftaroline fosamil by less than 3%: for CAP increase of 0.0074%, and for cSSTi ca 2.354 % occurs. Taking into account the predicted future consumption in Slovenia is not expected to exceed 1.15 kg per year, and dose 1200 mg/inh/d, refined F_{pen} is 0.000113% (population of Slovenia taken 2.064 million).

Considering the conversion from ceftaroline fosamil to ceftaroline in the body, PEC_{sw} (using refined F_{pen} value) is 0.00068 µg/L (phase II trigger value is 0.01 µg/L), the MAH has concluded that a Phase II assessment is not required. CHMP agreed to this conclusion.

2.2.6. Discussion on non-clinical aspects

Exposure levels ($AUC_{(0-t)}$) of ceftaroline fosamil tested in the juvenile rat at 270 mg/kg/day were approximately 2 to 3-fold higher than the predicted median steady state $AUC_{(0-24)}$ values of ceftaroline fosamil (based on simulations) in paediatric patients with mild renal impairment. The maximum plasma levels of ceftaroline fosamil tested in the juvenile rat at 270 mg/kg/day were approximately 20 to 28-fold higher than the predicted median steady state C_{max} values of ceftaroline fosamil (based on simulations) in paediatric patients with mild renal impairment.

Therefore, in the studies number: 20011802 (3011LR) and 20011803 (3012LR) the pharmacokinetics and toxicity of ceftaroline fosamil and the major metabolite M1 were assessed in the early life of rats (PND 7 - 50), which in humans corresponds to the term newborn infants. Studies showed that ceftaroline fosamil and metabolite M1 do not cause significant toxicological changes. CHMP agreed that no additional non-clinical toxicology studies are required. Of note, section 5.3 of Zinforo SmPC already includes a description of the juivenile toxicity data: "*Juvenile toxicity Intravenous bolus dosing of ceftaroline fosamil to suckling rats from post-natal day 7 to 20 was well tolerated at plasma exposures approximately 2-fold higher than those for paediatric patients. Renal cortical cysts were observed in all groups, including controls, on PND50. The cysts involved a small portion of the kidney and occurred in the absence of significant changes in either renal function or urinary parameters. Therefore, these findings were not considered to be adverse.*"

ERA

As previously discussed, during the initial marketing authorization application in 2013, a full ERA programme was performed. While using default $F_{pen,}$ value PEC_{sw} was 6 µg/L. The provided study results on physical-chemical properties, fate, and effects resulted in low risk levels: PEC/PNEC value for surface water was 0.025, for ground water 0.003, and for sewage treatment plant microorganisms 0.001. The lowest PNEC value is for the *Cyanobacterium Anabaena* flos-aquae, based on the lowest No Observed Effect Concentration (NOEC): 1.2 µg/L. An assessment factor of 10 is applied, in accordance with EMA guidance, resulting in PNEC = 1.2 µg/L /10 = 0.12 µg/L.

Using PEC_{sw} for increased consumption (provided above), the PEC/PNEC value for surface water is 0.00068 / 0.12 = 0.00567.

CHMP noted that the MAH also published the environmental risk assessment data on its website. The PEC/PNEC ratio is currently indicated as 2.4×10^{-4}, which is a lower prevalence/consumption data ratio than that used than in the ERA submitted for assessment. It is recommended that this information is updated on the MAH website.

2.2.7. Conclusion on the non-clinical aspects

Two juvenile toxicity rat studies were conducted in support of the use of Zinforo in paediatric patients aged from 2 months to less than 18 years with CAP or cSSTI and were submitted and assessed by CHMP in an earlier regulatory procedure. To summarise, in the non-GLP dose range finding study ceftaroline fosamil

was given once daily to neonatal Sprague-Dawley rat pups from Post Natal Day (PND) 7 to 21 via an intravenous injection at 0, 30, 90 or 270 mg/kg. In this study ceftaroline fosamil was well tolerated and did not result in any mortality or clinical signs. There were no apparent changes in body weight, body weight gains, organ weights (brain, paired kidneys and spleen) or urine analysis parameters. There were no gross and microscopic findings considered related to ceftaroline fosamil at any dose.

Ceftaroline fosamil was given once daily to neonatal Sprague-Dawley (Crl:CD[SD]) rat pups from PND 7 to 21 via an intravenous injection at 30, 90 or 270 mg/kg (GLP study). Transient reductions in body weight gains occurred in both sexes at all doses at the start of the dosing period; however, these reductions did not persist. At the end of study, there were no relevant test article-related effects on clinical signs, body weight, neurobehavioral parameters, clinical pathology parameters or organ weights.

Exposure levels (AUC_{0-t}) of ceftaroline fosamil tested in the juvenile rat at 270 mg/kg/day were approximately 2 to 3-fold higher than the predicted median steady state $AUC_{(0-24)}$ values of ceftaroline fosamil (based on simulations) in paediatric patients with mild renal impairment. The maximum plasma levels of ceftaroline fosamil tested in the juvenile rat at 270 mg/kg/day were approximately 20 to 28-fold higher than the predicted median steady state C_{max} values of ceftaroline fosamil (based on simulations). Exposures at 30 and 90 mg/kg/day were at or below the predicted clinical exposures.

There were observations of microscopic renal cysts in male rats at 90 mg/kg (PND 22) and in both sexes at (PND 55) there were considered possibly test article-related, but not adverse, due to the small area involved, presence in control, normal morphology of the overall kidney, and lack of changes in renal function or urine parameters. Based on the results of this study, CHMP considered 270 mg/kg to be the No Observed Adverse Effect Level (NOAEL).

However at the end of the recovery period (PND 50) there was an increase in the incidence of cysts at all doses in males and at 270 mg/kg/day in females. This was accompanied by an increased incidence of pericystic fibrosis at 90 and 270 mg/kg/day (both sexes). Since this could indicate a progression of these effects, which were not present in the controls and therefore cannot be attributed to procedural factors, and considering that the kidney has been identified as the primary target organ of toxicity in adult rats and monkeys, and that the extension of the indication sought includes very young children (from birth to 2 months of age) the MAH was asked by CHMP to further discuss the renal findings in juvenile rats, and to justify the conclusion that these findings are not adverse.

The MAH clarified that overall, the cysts involved only a small area of the kidney and the fibrosis was focal and minimal in nature, both occurred in the absence of significant changes in renal function or urinary parameters and they did not appear to have any significant implications for the animals (no adverse clinical signs; only transient effects were noted on body weight gain and no significant changes were observed in clinical pathology or organ weights. It is therefore considered that they are considered not to be adverse. CHMP agreed to this position.

Therefore, in the studies number: 20011802 (3011LR) and 20011803 (3012LR) the pharmacokinetics and toxicity of ceftalorine and the major metabolite M1 were assessed in the early life of rats (PND 7 - 50), which in humans corresponds to the term newborn infants. Studies showed that ceftaroline fosamil and metabolite M1 do not cause significant toxicological changes. CHMP agreed that no additional non-clinical toxicity studies are required.

In vitro microbiology

There were no additional *in vitro* microbiology studies performed for the current application. The relevant data has been reported and assessed by CHMP in the frame of the previous paediatric extension of indication application (II/022). At CHMP request, additional data about the microorganisms relevant to the neonates were submitted and assessed.

ERA

According to the guideline EMA/CHMP/44609/2010 “Questions and answers on 'Guideline on the environmental risk assessment of medicinal products for human use”, in Phase I it is allowed to perform PEC_{sw} refinement based on prevalence data.

In the same document in answer to Question 2 “What is required for an ERA for a type II variation or an extension application?”, it is stated that the submission of a new ERA is needed for a type II variation or a line extension if an increase in environmental exposure is expected. For these types of applications, the environmental data previously submitted in the original dossier of the same MAH can be used. Nevertheless, the ERA dossier may need to be updated. There is no unique value of what constitutes a significant increase. This will be assessed on a case-by-case basis.

CHMP noted that in the case of the present application, there is an increase in the overall consumption of ceftaroline fosamil, but by less than 3%. When considering the data provided in the original ERA dossier (PEC/PNEC value for surface water was 0.025), it appears that due to using actual prevalence data, the updated PEC/PNEC value for surface water is 0.00567, i.e. less than initially indicated. As the outcome of ERA is also not changed (“*No environmentally related labels are proposed for ceftaroline fosamil*”), there is no need to further update the dossier.

CHMP agreed that the updated data submitted in this application show that the extended indication does not lead to a significant increase in environmental exposure further to the use of ceftaroline fosamil (Zinforo). Considering the available data, Zinforo is not expected to pose a risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Study Number	Study Design and Objective	Dose/Route, Regimen	Number of Subjects	Duration of Treatment
P903-15	Multicentre, open-label, non-comparative, single dose study To evaluate PK and safety of ceftaroline fosamil in adolescents	Ceftaroline fosamil 8 mg/kg, single dose, IV for subjects weighing <75 kg (< 165.4 lb) Ceftaroline fosamil 600 mg, single dose, IV for subjects weighing ≥75 kg (≥ 165.4 lb)	9 enrolled: Ceftaroline (N = 9)	Single dose (1 day)
P903-21 (D3720C00006)	Open-label, sequential, single-dose To evaluate the PK of a single-dose of ceftaroline fosamil in children ages birth to younger than 12 years with suspected or confirmed systemic infection.	Ceftaroline fosamil IV. Dose by cohort (infusion time): 1: 10 mg/kg (1-h) 2: 15 mg/kg (1.5 h) 3: 12 mg/kg (1 h) for subjects ≥5 months) or 8 mg/kg (1 h) for subjects ≥28 days to <5 months 4: 8 mg/kg (1 h) 5: 8 mg/kg (1 h)	Overall: 53 Cohort 1: 10 Cohort 2: 8 Cohort 3: 12 (9 in 3A, 3 in 3B) Cohort 4: 12 (6 in 4A, 6 in 4B) Cohort 5: 11 (5 in 5A, 6 in 5B)	Single dose
P903-23 (D3720C00004)	Randomized, observer blinded, active-controlled, parallel group. Safety and tolerability in paediatric subjects aged 2 months to<18 years with complicated skin and soft tissue infections (cSSTI).	Ceftaroline group: ceftaroline fosamil IV infused over 60 minutes every 8 hours (q8h) as follows: Children ≥6 months: 12 mg/kg for subjects weighing ≤33 kg or 400 mg for subjects weighing >33 kg Children < 6 months: 8 mg/kg. Comparator group: IV vancomycin 15 mg/kg infused over 60 minutes q6h or IV cefazolin 75 mg/kg/day divided q8h infused over 60 minutes. And Optional aztreonam 30 mg/kg q8h infused over 60 minutes. Subjects may have been switched from IV to open label oral study drug (cephalexin 25 mg/kg q6h, clindamycin 10 mg/kg q8h, or linezolid [600 mg q12h [Cohort 1] or 10 mg/kg q8h [Cohorts 2, 3, and 4]) on or after Study Day 4.	ITT population N=154 Ceftaroline fosamil (N=110) and comparator (N=53)	5 to 14 days
P903-24 (D3720C00013)	Randomized, observer blinded, active-controlled, parallel group. Safety and tolerability in paediatric subjects aged 2 months to <18 years with complicated community acquired pneumonia (CAP)	Cohorts: 1: 12 to <18 years 2: 6 to <12 years 3: ≥24 months to <6 years 4: ≥2 months to <24 months	ITT population N=40 Ceftaroline fosamil (N=30) and comparator (N=10)	5 to 21 days
P903-26 (D3720C00009/ C2661002)	Open-label, multicentre, multi-national and single treatment arm. To evaluate the safety, tolerability, PK and efficacy of ceftaroline plus ampicillin plus optional aminoglycoside in term and pre-term neonates with late onset sepsis.	Ceftaroline fosamil 4 mg/kg or 6 mg/kg IV over 60 (±10) minutes q8h (±1 hour)	Ceftaroline fosamil (N=11)	2-14 days
P903-31 (D3720C00007)	Randomized, observer blinded, active-controlled, parallel group. Safety and tolerability in paediatric subjects aged 2 months to <18 years with CAP requiring hospitalization	Ceftaroline group: ceftaroline fosamil IV infused over 60 minutes every 8 hours (q8h) as follows: Children ≥6 months: 12 mg/kg for subjects weighing ≤33 kg or 400 mg for subjects weighing >33 kg Children < 6 months: 8 mg/kg. Comparator group: IV ceftriaxone 75 mg/kg/day (up to 4 g/day), infused over 30 minutes q12h. Subjects may have been switched from IV to open label oral study drug (amoxicillin clavulanate up to 90 mg/kg/day q12h on or after Study Day 4.	ITT population N=161 Ceftaroline fosamil (N=122) and ceftriaxone (N=39)	5 to 14 days

2.3.2. Pharmacokinetics

This application contains 2 new pharmacokinetic/clinical studies and a population pharmacokinetic analysis:

- **Study D3720C00006 (P903-21)**, an open-label, multicentre, sequential, single-dose, prospective study of ceftaroline fosamil pharmacokinetics (PK) in subjects younger than 12 years with a suspected or confirmed bacterial infection.

- **Study D3720C00009 (C2661002)**, an open-label, multicentre study to evaluate the safety, tolerability PK, and efficacy of ceftaroline fosamil in neonates and young infants (age 7 to <60 days) with late-onset sepsis (LOS).
- **PMAR-EQDD-C266b-Other-809**, Population Pharmacokinetics Evaluation of ceftaroline fosamil data from Study C2661002 Using A Predictive Check (Simulation) Approach.

No new basic pharmacology, biopharmaceutical nor clinical pharmacology studies have been submitted. CHMP considered this to be acceptable.

Special populations

Selection of Doses in Study D3720C00006 (P903-21)

The safety, effectiveness, and pharmacokinetics of ceftaroline fosamil at a dose of 600 mg every 12 hours (q12h) were established in adults with normal renal function or mild renal impairment.

In adolescent subjects (12 to 17 years; Study P903-15) with normal renal function who received 8 mg/kg ceftaroline fosamil (or 600 mg for subjects weighing > 75 kg), the mean values for C_{max} and AUC for ceftaroline fosamil were about 10% and 23% less, respectively, than the values observed in adults following administration of a 600-mg dose of ceftaroline fosamil.

In Study D3720C00006 (P903-21), at a dose of 10 mg/kg, the predicted ceftaroline fosamil AUC and C_{max} for children 6 to 11 years of age with normal renal function were within 10% and 30%, respectively, of the predicted AUC and C_{max} in adults dosed with 600 mg ceftaroline fosamil every 12 hours (q12h).

Because ceftaroline fosamil is mainly cleared via renal excretion, and renal function in children (adjusted for body size) is at adult levels by the age of 2 years, the dose in subsequent cohorts of descending age was modified to achieve appropriate exposure.

After at least 4 evaluable subjects (defined as subjects who received the entire dose of ceftaroline fosamil and from whom at least 3 PK samples were collected) were enrolled in each cohort (up to and including Cohort 3 [young infants and toddlers ages ≥ 28 days to < 2 years]), PK samples from these subjects were analyzed to obtain plasma concentrations and the data were added to the population PK model.

The dosing regimens (a single dose administration) evaluated were as follows:

- Cohort 1 (≥ 6 years to < 12 years): 10 mg/kg (up to 600 mg for subjects ≥ 60 kg) as a 1-hour infusion
- Cohort 2 (≥ 2 to < 6 years): 15 mg/kg as a 1.5-hour infusion
- Cohort 3 (≥ 28 days to < 2 years): ≥ 5 months: 12 mg/kg as a 1-hour infusion; < 5 months: 8 mg/kg as a 1-hour infusion
- Cohort 4 (term [gestational age ≥ 38 weeks] neonates < 28 days) and Cohort 5 (preterm [gestational age 32 to 37 weeks] neonates ages < 28 days): 8 mg/kg as a 1-hour infusion

Selection of Doses in Study D3720C00009 (C2661002)

Study D3270C00009 was an open label, single-arm steady state study with no randomization. At least 24 patients with LOS were to be enrolled and treated within 3 age cohorts of 8 patients each: young infants aged >28 days to <60 days, term neonates aged 7 to ≤28 days, and preterm neonates aged 7 to ≤28 days.

Patients treated under protocol editions 1 and 2 were dosed with ceftaroline fosamil 4 mg/kg as a 60 minute infusion every 8 hours (q8h). This initial dosing regimen was based on the exposure observed in adolescent patients in Study P903-15, single-dose safety study and PK data in patients from birth to <12 years in Study

P903-21, and predicted exposures from a population PK model. After updating the population PK model with additional paediatric data (described below), the ceftaroline fosamil dose was adjusted to 6 mg/kg as a 60 minute infusion q8h in protocol version 3. All patients treated under protocol edition 3 forward received ceftaroline fosamil 6 mg/kg q8h.

The dosing regimen for ceftaroline fosamil (6 mg/kg q8h as a 60 [±10] minute infusion) was chosen based on a population PK model updated with PK data from 3 multiple-dose safety and efficacy studies in children aged 2 months to <18 years (Studies P903-23, P903-31 and P903-24). These data were used in conjunction with adult patient and healthy volunteer data and data from single-dose ceftaroline fosamil PK studies conducted in children from neonates to <18 years. The ceftaroline fosamil population PK model incorporated allometric scaling for body weight and maturation of renal function. This model was used in Monte Carlo simulations to choose and justify the dose regimens for children aged 2 months to 18 years, now included in the European Summary of Product Characteristics (SmPC).

CHMP noted that the dose selection in infants less than 2 months of age seemed well justified and agreed that a stepwise modification of the final ceftaroline fosamil dose based on the cumulating evidence from the clinical PK studies and modelling and simulation are clearly explained and supported by data.

Summary of PK results of study D3720C00006 (P903-21)

A single dose paediatric PK study (Study P903-21) enrolled 23 neonates (11 preterm GA 32 to 37 weeks and 12 term neonates ≤28 days) receiving a dose regimen of ceftaroline fosamil 8 mg/kg as a 1 hour infusion. The young infant cohort in that study comprised ages >28 days to <2 years (n=12) and did not enroll any subjects between the ages of >28 and ≤60 days.

In Study D3720C00006 (P903-21), after ≥4 evaluable subjects had been enrolled in a cohort (up to and including Cohort 3), PK samples from these subjects were analyzed for ceftaroline fosamil and ceftaroline fosamil (prodrug) concentrations. Because this study used a sparse sampling strategy, PK parameters were not calculated for each subject by noncompartmental analysis. Plasma concentration data for ceftaroline fosamil and ceftaroline fosamil were pooled with data from other studies in adults and adolescent subjects in a population PK analysis.

Ceftaroline fosamil was measureable in all PK samples collected from all subjects. The doses used in this study achieved ceftaroline fosamil exposures in paediatric subjects that exceeded the minimum concentration required to inhibit the growth of 90% of organisms (MIC_{90}) for ceftaroline fosamil against *S. aureus* for more than 50% of an 8-hour dosing interval. The values of T<MIC were taken from preclinical studies. Findings based on ceftaroline fosamil concentrations in the plasma samples taken at the end of the ceftaroline fosamil infusion suggest that ceftaroline fosamil was cleared more slowly by the youngest subjects (term and preterm neonates < 28 days), consistent with immature renal function in this younger age range and that maturation of renal function may impact ceftaroline fosamil clearance in the youngest subjects.

Ceftaroline fosamil plasma concentrations were variable, and were typically only measureable in plasma samples taken at the end of the ceftaroline fosamil infusion or 15 to 45 minutes after the end of infusion. This is expected based on the rapid conversion of ceftaroline fosamil to ceftaroline fosamil in plasma. Eight subjects had no measureable ceftaroline fosamil in any of their plasma samples; however, all of these subjects had significant ceftaroline fosamil and ceftaroline fosamil M-1 levels that were consistent with appropriate dosing of ceftaroline fosamil. Two subjects did not have the first 2 PK samples collected and did not have measureable ceftaroline fosamil in the last 2 PK samples.

Ceftaroline fosamil M-1 was measureable in all plasma samples collected from all subjects. Results were consistent with data in healthy adult subjects and reflective of the longer $T_{1/2}$ of ceftaroline fosamil M-1 compared to ceftaroline fosamil.

Summary of PK results of Study D3720C00009 (C2661002)

In Study D3720C00009 (C2661002), patients were randomly assigned (1:1) at enrollment to 1 of 2 PK sampling schedules; 2 samples were to be collected at steady-state. Patients were randomly assigned (1:1) at the time of enrolment to one of the PK sample collection schedules:

• PK Schedule 1: at the end of the ceftaroline fosamil infusion (±5 minutes) and 3 to 4 hours after the end of the infusion;

• PK Schedule 2: 15 minutes to 2 hours after the end of the ceftaroline fosamil infusion and 5 to 7 hours after the end of the infusion (before the start of the next infusion).

At the time of early study closure, eleven (11) patients were enrolled in the study and received study treatment: 4 (36.4%) patients were in Cohort 1 (young infants), 5 (45.5%) in Cohort 2 (term neonates), and 2 (18.2%) in Cohort 3 (preterm neonates). All enrolled patients completed the study.

All patients (N=11) contributed at least 1 PK sample for a total of 19 plasma samples; 8 patients contributed 2 samples and 3 patients contributed 1 sample each. No cerebrospinal fluid (CSF) samples were collected from any patients in the study. Ceftaroline fosamil was measurable (> lower limit of quantification [LLOQ]) in only 3 plasma samples while ceftaroline fosamil and ceftaroline fosamil M-1 (inactive metabolite) were measurable in all 19 plasma samples.

The sparse ceftaroline fosamil plasma concentrations were evaluated using graphical analysis, comparing with plasma concentration data from previous ceftaroline fosamil studies in paediatric patients aged from birth to <2 years old, and by using a predictive check (simulation) approach.

CHMP noted that a sparse strategy was used to collect PK samples and agreed to this approach, considering the vulnerability of the study population, the relatively rare clinical indication, and the availability of PK data in older infants.

2.3.3. Pharmacodynamics

Mechanism of action

(PBP), which inhibits their function and produces the death of bacteria. Ceftaroline fosamil exhibits unique properties that distinguish it from other β-lactams due to its high affinity for PBP2a in MRSA and PBP2x in PRSP that contribute to its potent antibacterial activity against these organisms.

As with other β-lactam antibiotics, the percentage of time that free drug concentrations are above the minimum inhibitory concentration (MIC) of the bacteria during a dosing interval (%*f*T>MC) has been shown to be the PK/(PD) index associated with efficacy of ceftaroline fosamil in the murine thigh and lung infection models. In these models, median values of 36% and 44% *f*T>MIC were associated with 1-log kill of *S. aureus* and *S. pneumoniae*, respectively.

CHMP noted that no new studies have been conducted in regard to this application, and this was considered acceptable. The appropriateness of the PD targets of 36% and 44% of fT>MIC was discussed and the MAH was asked to perform further simulations by using microorganisms that are relevant for neonates (CoNS and non-ESBL producing enterobacteria) and fT>MIC values of 60% and 100%, to address some concern that higher PDT may be needed for preterm neonates, which is a special vulnerable and relatively immune deficient population. The additional analyses performed by the MAH (simulations made using MIC values of 0.5 mg/L and 1 mg/L) have shown that the required PTA was above 90% for 60% fT>MIC; CHMP considered this to be acceptable; if 100% fT>MIC was considered, the PTA was well below 90%. It cannot be excluded

that, as for adults and older paediatric age groups, a higher dose may need to be considered in case of skin infections produced by pathogens with higher MICs.

2.3.4. PK/PD modelling

The dosing regimen for ceftaroline fosamil (6 mg/kg q8h as a 60 [±10] minute infusion) was chosen based on a population PK model updated with PK data from 3 multiple-dose safety and efficacy studies in children aged 2 months to <18 years (Studies P903-23, P903-31 and P903-24). The ceftaroline fosamil population PK model incorporated allometric scaling for body weight and maturation of renal function.

This model was also used in the Monte Carlo simulations to choose and justify the dose regimens for children aged 2 months to 18 years, at the time of approval in the EU.

The same model was used to predict doses for children <2 months of age, including preterm neonates (with a postmenstrual age of 28 to 41 weeks). Postmenstrual age is defined as gestational age plus chronological age. Various dosing regimens were simulated using body weights for each simulated patient based on age in accordance with either Centres for Disease Control and Prevention (CDC) growth charts for neonates that were born to term or in accordance with intrauterine growth curves for preterm to term neonates (gestational age 32-40 weeks). One hundred simulations were performed for each dose with 600 (300 male and 300 female) patients from each age group. The age groups were categorized as follows: 28 to <30, 30 to <32, 32 to <34, 34 to <36, 36 to <38, 38 to <40 postmenstrual weeks; 0 to <1, 1 to <2, 2 to <6, 6 to <12, 12 to <18, 18 to <24 months.

Using the updated model, several dose regimens were assessed and a dose of 6 mg/kg ceftaroline fosamil q8h as a 60-minute infusion was predicted to achieve >90% probability of target attainment (PTA) for MICs ≤2 mg/L. Predicted ceftaroline fosamil exposures (based on steady-state maximum concentration [$C_{max, ss}$] and area under the concentration-time curve from 0 to 24 hours [$AUC_{24,ss}$]) in paediatric patients younger than 2 months old and of gestational age 32-48 weeks dosed with 6 mg/kg q8h as a 60-minute infusion do not appreciably exceed ceftaroline fosamil exposures in adults dosed with the currently approved ceftaroline fosamil regimen of 600 mg every 12 hours (q12h). The median ceftaroline fosamil C_{max} values in paediatric patients in this age range dosed with the proposed regimen (6 mg/kg q8h) were predicted to be less than the median ceftaroline fosamil value in adults dosed with 600 mg q12h. Median steady-state ceftaroline fosamil AUC_{24} values in paediatric patients younger than 2 months old and of gestational age 32-48 weeks dosed with the proposed regimen were predicted to be no more than 17% higher than the median adult value.

Based on these findings, the updated model was used to optimize the dose for neonates and young infants (6 mg/kg q8h as a 60-minute infusion) in Study D3720C00009 (C2661002).

PK Modelling and Simulation (PMAR-EQDD-C266b-Other-809)

After completion of Study C2661002, PK data from that study were assessed in population PK modelling and simulation analyses.

The updated population PK model described previously to support the approved paediatric doses for children >2 months (CPT-MS-08), and to select the doses for the neonatal study (Study C2661002), including the change of dose from 4 mg/kg to 6 mg/kg, was utilized for these analyses. A pooled Pop PK analysis data set for the 10 adult Phase 1 studies, 6 adult Phase 2/3 studies, 2 paediatric Phase 1 studies, and 3 paediatric Phase 2/3/4 studies was available from the analysis for CPT-MS-08.

Only data from paediatric subjects aged <2 years old were extracted from this data set for use in the current analysis. A total of 87 paediatric subjects <2 years of age contributing 59 ceftaroline fosamil and 227 ceftaroline fosamil plasma concentrations were available in the previous Pop PK data set for the CPT-MS-08 report.

A single dose paediatric PK study (Study P903-21) enrolled 23 neonates (11 preterm GA 32 to 37 weeks and 12 term neonates ≤28 days) receiving a dose regimen of ceftaroline fosamil 8 mg/kg as a 1 hour infusion. The young infant cohort in that study comprised ages >28 days to <2 years (n=12) and did not enrol any subjects between the ages of >28 and ≤60 days. The other paediatric studies enrolled subjects aged 2 months and above. However, the data from this age cohort remain relevant for comparison of model predictions with the observed data from Cohort 1 of Study C2661002, as the relevant covariates of size and renal function are continuous in the Pop PK model and thus allow interpolation.

The lower limit of quantification (LLOQ) of the ceftaroline and ceftaroline fosamil plasma concentrations in all the paediatric studies was 0.05 mg/mL. Plasma ceftaroline and ceftaroline fosamil samples below limit of quantification (BLQ) were excluded from graphical and Pop PK analyses.

Simulation was conducted using the parameter estimates from the previous Pop PK final model, with all covariate effects maintained (allometric scaling by weight, body surface area (BSA)-normalised creatinine clearance (CLcr), age (maturation), population (patients)). Only inter-individual and residual random effects were used. Assessment was based on the median and 90% prediction interval (PI) constructed from a simulation with 1000 subproblems, and overlaid with the observed ceftaroline fosamil plasma concentration-time data from Study C2661002. It should be noted that concentrations were normalised to 6 mg/kg for 3 subjects (1 subject in each cohort) who received the lower dose of 4 mg/kg prior to protocol amendment 2.

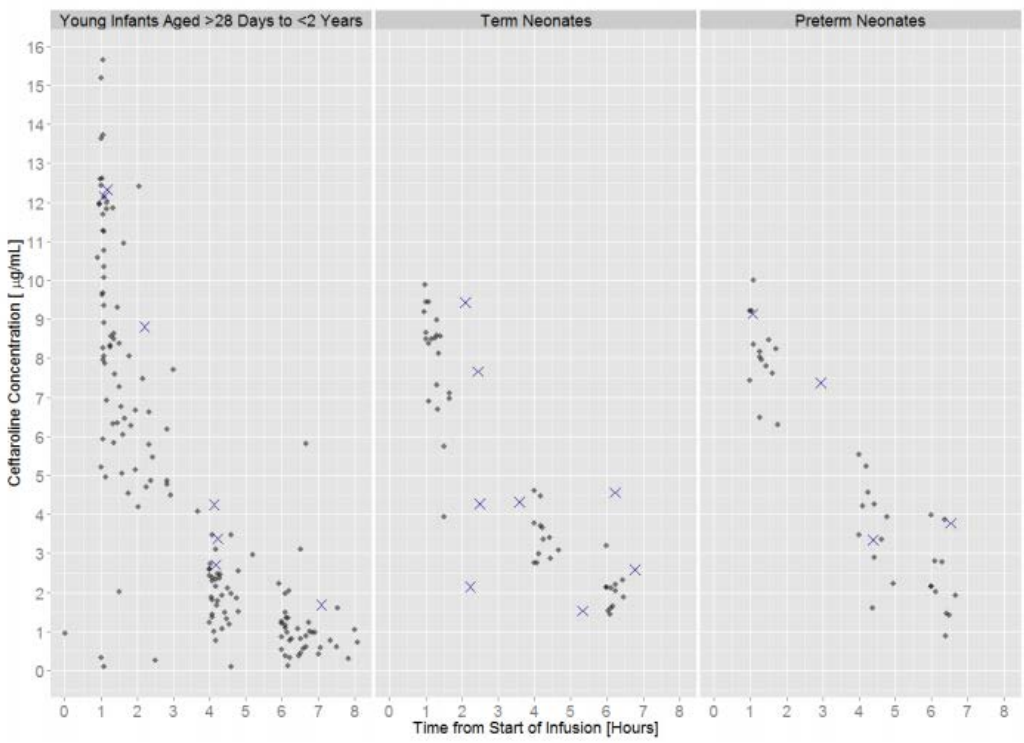
Due to early study closure, a total of 11 subjects (originally planned for 24 subjects) contributed 3 ceftaroline fosamil and 19 ceftaroline fosamil non-BLQ plasma concentrations to the final data of Study C2661002. All 11 subjects received at least 1 dose of ceftaroline fosamil and had at least 1 PK sample.

Results from PK modeling and simulation

Graphical data analysis was conducted with R (version 3.2.2) and R libraries (such as ggplot2 version 1.0.1, dplyr version 0.4.3). The sparse steady-state ceftaroline fosamil plasma concentrations (normalised to 6 mg/kg) obtained from the neonatal Study C2661002 are consistent with concentrations observed in the earlier paediatric studies (Studies P903-21, P903-23, P903-24, and P903-31).

The following figure shows the dose-normalised ceftaroline fosamil plasma concentrations from Study C2661002, overlaid with the concentration-time data included in the previous Pop PK data set for similar age cohorts. The observed data (normalised to 6 mg/kg) from the neonatal Study C2661002 are consistent with concentrations observed in the earlier paediatric studies (Studies P903-21, P903-23, P903-24, and P903-31), which provides support for the use of the predictive check approach.

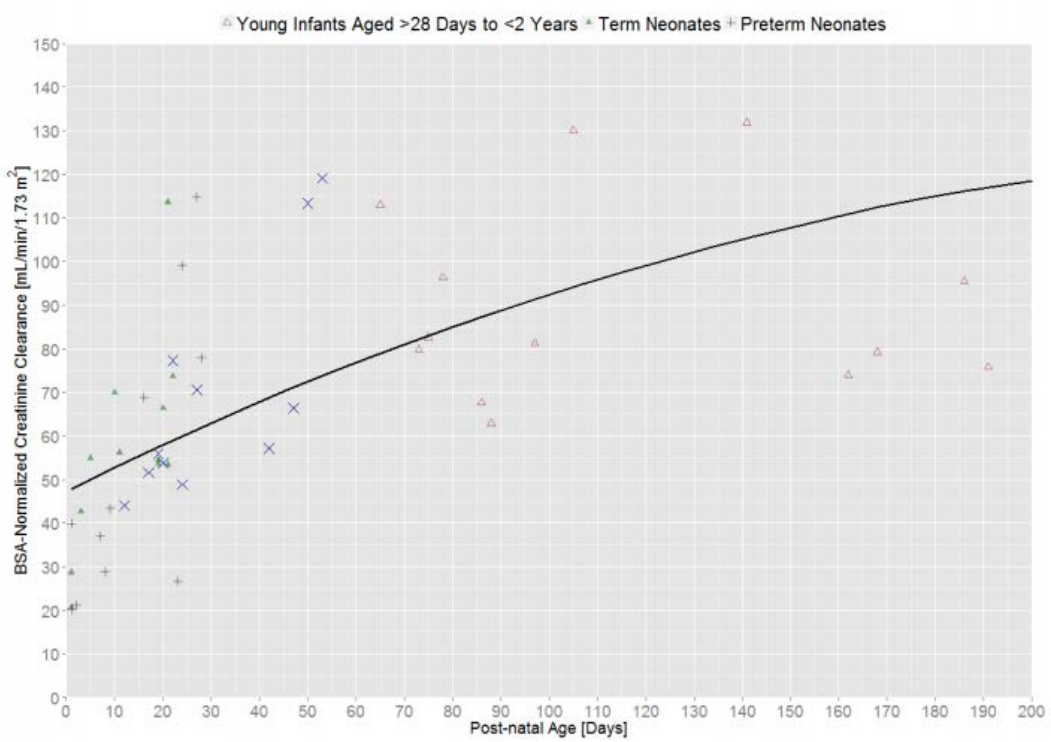
Figure 1 Ceftaroline fosamil Plasma Concentration (normalized to 6 mg/kg) versus Time from Start of Infusion, by Age Cohort for Paediatric Subjects from Birth to <2 Years of Age Included in the Previous Population Pharmacokinetic Dataset (Report CPT-MS-08), Overlaid with Data from Study C2661002 (blue X).



ePharmacology artifact ID RA14823003.
Preterm neonates defined as gestational age ≥34 to <37 weeks in Study C2661002 and 32 to 37 weeks in Study P903-21. Term neonates defined as gestational age ≥37 weeks in Study C2661002 and ≥38 weeks in Study P903-21. Young infants group included subjects aged >60 days to <2 years; no subjects aged >28 to ≤60 days in previous paediatric studies.

The following figure shows a non-linear relationship (consistent with the modified Rhodin maturation function) of nCRCL and post-natal age in days, with the x-axis limited to 200 days. In general, the nCRCL from the 11 paediatric subjects in Study C2661002 lie within the distribution of the prior data. This supports the continuous size and the renal maturation function in the Pop PK model and thus supports interpolation / extrapolation.

Figure 2 Relationship of BSA-normalised Creatinine Clearance and Post-natal Age (limited to Day 200) for Subjects Aged <2 Years in Study C2661002 (blue X) and Previous Paediatric Studies (Studies P903-21, P903-23, P903-24, and P903-31).

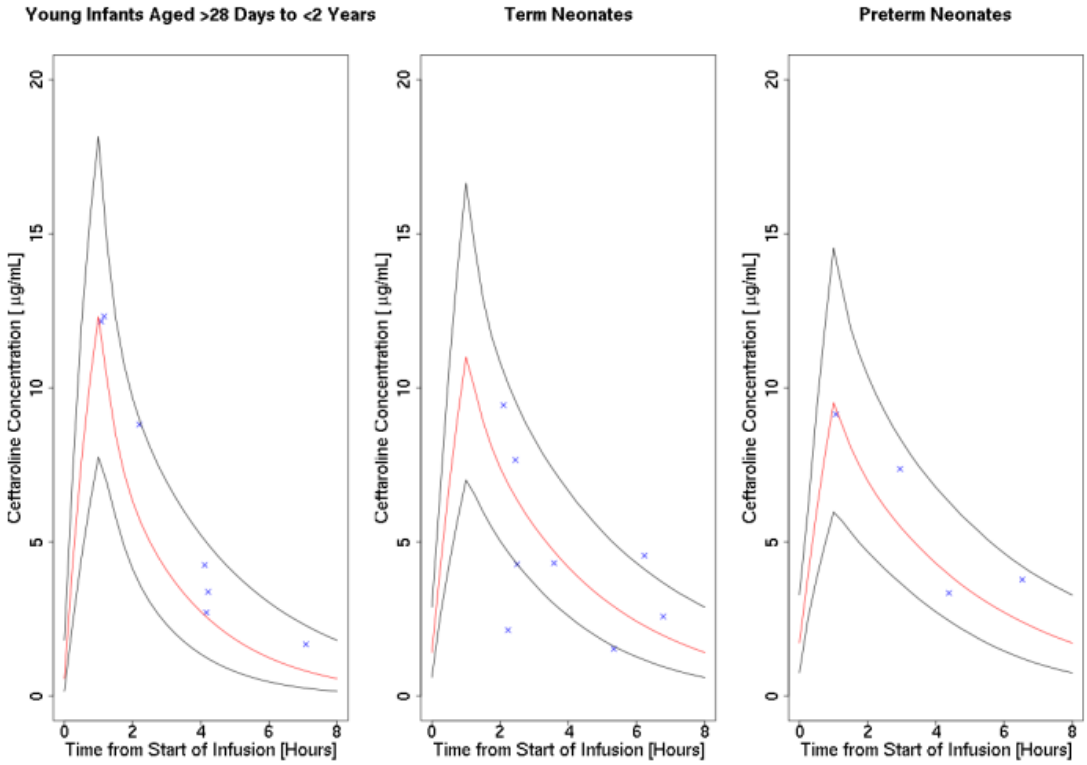


ePharmacology artifact ID RA14823699.
Black line is the loess smooth line.
Preterm neonates (+) defined as gestational age ≥34 to <37 weeks in Study C2661002 and 32 to 37 weeks in Study P903-21. Term neonates (▲) defined as gestational age ≥37 weeks in Study C2661002 and ≥38 weeks in Study P903-21. Young infants group (△) included subjects aged >60 days to <2 years; no subjects aged >28 to ≤60 days in previous paediatric studies.

Simulations of individual profiles (87 paediatric subjects from birth to <2 years old [of which 52 subjects were from the safety / efficacy studies] from the previous Pop PK data set) with 1000 sub-problems were performed. The Pop PK analysis was performed using a nonlinear mixed effects modelling methodology as implemented in the NONMEM software system, version 7.3.0. All subjects assumed a dose regimen of ceftaroline fosamil 6 mg/kg q8h IV infusion given over 1 hour for 14 days.

The following figure shows the median and 90% PIs of ceftaroline fosamil steady-state plasma concentrations versus time after start of infusion obtained from a simulation of 1000 subproblems with the 87 paediatric subjects from birth to <2 years old (of which 52 subjects were from the safety / efficacy studies) from the previous Pop PK data set, assuming a dose regimen of ceftaroline fosamil 6 mg/kg q8h IV infusion given over 1 hour for 14 days.

Figure 3 Median (red line) and 90% Prediction Intervals (black lines, 5th and 95th percentile) by Cohort for Ceftaroline fosamil based on 1000 Simulations (6 mg/kg q8h, 1 hour infusion at steady-state) Overlaid with Observed Data (normalized to 6 mg/kg) from Study C2661002 (blue X).



ePharmacology artifact ID RA14828194.
In Study C2661002, preterm neonates defined as gestational age ≥34 to <37 weeks, term neonates defined as gestational age ≥37 weeks.

All of the observed steady-state ceftaroline fosamil plasma concentrations (normalised to 6 mg/kg) from the neonatal Study C2661002 laid within the 90% PI with the exception of 2 observations in the full-term neonate cohort. These samples were collected at approximately 2 hours and 6 hours after the start of the same infusion from the same subject (ID = 9046005) and have most likely been inadvertently switched when labeled with collection times, as there is no plausible biological explanation for increasing drug concentrations after end of infusion. A switch of time for the values brings both these values into the predicted range.

Predicted ceftaroline fosamil exposures (maximum concentration at steady-state (C_{maxSS}) and area under the plasma concentration-time curve over 24 hours at steady-state (AUC_{24SS})) in paediatric subjects aged <2 months with normal renal function or mild renal impairment dosed with ceftaroline fosamil 6 mg/kg q8h as a 1 hour (or a 5 minute) IV infusion are similar to and do not exceed ceftaroline fosamil exposures (C_{maxSS}) in adults dosed with the approved ceftaroline fosamil regimen of 600 mg every 12 hours (q12h).

Target attainment simulations

Ceftaroline fosamil steady-state PK exposure and PTA simulations for paediatric subjects with normal renal function or mild renal impairment had been performed previously for a wide range of mg/kg doses administered q8h; 2 to 14 mg/kg over l hour infusion, and 2 to 18 mg/kg over 2 hour infusion in the CPT-MS-08 report, and 2 to 14 mg/kg over 5 minute infusion in the CPT-MS-08 addendum, for MIC value of 0.125, 0.25, 0.5, 1, 2, 4, and 8 mg/L. Simulations for paediatric subjects with moderate and severe renal functions were also available in the CPT-MS-08 report and addendum.

For paediatric patients ≤2 years old, the renal maturation function (fractional change in clearance due to maturation (FPMA)) was adjusted to allow for the simulation of mild, moderate, and severe renal impairment. The FPMA was scaled from 0.625 (50/80) to 0.988 (79/80) for mild renal impairment, 0.375 (30/80) to 0.613 (49/80) for moderate renal impairment, and 0.125 (10/80) to 0.363 (29/80) for severe renal impairment. (The divisor for the scaling was set to 80 because this represents the lowest nCRCL that was classified as normal renal function. The dividend for the scaling was set to the upper and lower bounds of creatinine clearance denoting mild (50/80–79/80), moderate (30/80–49/80), and severe (10/80–29/80) renal impairment.) This resulted in paediatric patients ≤2 years old that had the same renal maturation pattern with respect to PMA as those with normal renal function but a lower fractional increase in renal function due to maturation at any given value of PMA. To support the dosing regimens for neonates and young infants up to 2 months of age with LOS, ceftaroline fosamil steady-state PK exposure and PTA simulations for 4 mg/kg and 6 mg/kg (maximum of 400 mg) q8h IV infusions given over 1 hour or 5 minutes for subjects with normal renal function and mild renal impairment were summarized from the previous reports (CPT-MS-08 and Addendum).

Table 7 Median (90% PI) Ceftaroline fosamil CmaxSS and AUC_{24SS} by Age and Duration of IV Infusion for Normal Renal Function Following 6 mg/kg q8h Dosing to Steady-State for Ceftaroline fosamil in Paediatric Patients Based on Simulations

			CmaxSS (mg/L)				AUC24SS (mg·h/L)			
Age Group	Weight (kg)		1 hour infusion		5 minute infusion		1 hour infusion		5 minute infusion	
Adults 600 mg q12h	77.6	(52.5,105)	20.9	(11.7,36.8)	26.5	(13.8,52.0)	97.3	(58.9,165)	97.2	(58.6,164)
18-<24 months	11.7	(9.81,14.1)	14.1	(8.83,21.8)	19.8	(11.0,35.6)	80.3	(52.0,125)	80.4	(51.8,124)
12-<18 months	10.4	(8.60,12.7)	14.3	(8.97,22.1)	19.8	(11.0,35.4)	84.4	(54.3,131)	84.4	(54.2,131)
6-<12 months	8.43	(6.55,10.7)	14.6	(9.11,22.5)	19.8	(11.2,35.9)	90.6	(58.0,140)	91.0	(58.5,141)
2-<6 months	5.75	(4.12,7.66)	14.4	(8.98,22.2)	18.8	(10.6,33.3)	101	(64.8,155)	100	(65.2,156)
1-<2 months	4.69	(3.63,5.77)	14.1	(8.75,21.7)	17.8	(10.2,30.8)	105	(67.7,161)	105	(68.3,163)
0-<1 months	3.88	(2.91,4.75)	13.4	(8.40,20.7)	16.4	(9.52,28.5)	108	(69.7,167)	108	(70.0,165)
GA 38-<40 weeks	3.40	(2.55,4.24)	12.8	(7.89,20.0)	14.9	(8.81,25.4)	114	(73.8,176)	114	(74.3,175)
GA 36-<38 weeks	2.87	(2.07,3.75)	12.4	(7.70,19.4)	14.7	(8.75,25.4)	109	(70.8,169)	109	(71.1,169)
GA 34-<36 weeks	2.32	(1.71,3.05)	12.1	(7.54,19.1)	14.5	(8.61,24.8)	104	(67.8,162)	104	(67.2,160)
GA 32-<34 weeks	1.89	(1.38,2.44)	11.9	(7.36,18.6)	14.2	(8.41,24.5)	98.5	(64.2,154)	98.6	(63.1,154)
GA 30-<32 weeks	1.50	(1.05,1.95)	11.4	(7.07,17.9)	14.0	(8.14,24.1)	92.7	(59.8,145)	92.8	(60.4,142)
GA 28-<30 weeks	1.15	(0.779,1.52)	11.1	(6.86,17.5)	13.8	(7.96,24.0)	86.7	(56.4,134)	86.3	(56.3,134)

ePharmacology artifact ID RA14617817. Lines 1–2 substituted.
AUC24SS = area under the plasma concentration-time curve over 24 hours at steady-state; CmaxSS = maximum concentration at steady-state; GA = gestational age; q12h = every 12 hours.
Median (5^{th}, 95^{th}) based on summary of 100 trials and corresponds to median (90% prediction interval).
Adult dose and regimen is listed in first row.

Considering the PK/PD target of 35% and 44% free percent of time above minimum inhibitory concentration (%f T>MIC) for S. aureus and S. pneumoniae, respectively, ceftaroline fosamil 6 mg/kg administered q8h as a 1 hour (or a 5 minute) IV infusion in paediatric subjects aged <2 months with normal renal function or mild renal impairment would achieve >95% PTA for an MIC of up to 2 mg/L. The exception is for preterm neonates with GA 28 to <30 weeks and normal renal function receiving 6 mg/kg administered q8h as a 5 minute IV infusion for the 35% f T>MIC with an MIC of 2 mg/L where >90% PTA would be achieved.

Table 8 Median (90% PI) %fT>MIC by Age and Duration of IV Infusion for Normal Renal Function Following 6 mg/kg q8h Dosing to Steady-State for Ceftaroline fosamil in Paediatric Patients Based on Simulations

Age Group	Weight (kg)		%*f*T>MIC of 1 mg/L				%*f*T>MIC of 2 mg/L			
			1 hour infusion		5 minute infusion		1 hour infusion		5 minute infusion	
Adults 600 mg q12h	77.6	(52.5,105)	64.5	(44.6,93.5)	60.3	(41.3,90.1)	45.0	(29.8,68.6)	42.1	(26.4,65.3)
18-<24 months	11.7	(9.81,14.1)	63.0	(45.7,90.1)	58.0	(39.5,84.0)	43.2	(29.6,63.6)	38.3	(24.7,58.1)
12-<18 months	10.4	(8.60,12.7)	66.7	(47.5,93.8)	60.5	(42.0,88.9)	45.7	(30.9,66.7)	40.7	(25.9,61.8)
6-<12 months	8.43	(6.55,10.7)	71.6	(50.6,97.5)	66.7	(45.7,95.1)	49.4	(33.3,72.8)	44.4	(29.6,67.9)
2-<6 months	5.75	(4.12,7.66)	82.7	(58.0,100)	77.8	(53.1,100)	56.8	(38.3,85.2)	51.9	(34.6,80.2)
1-<2 months	4.69	(3.63,5.77)	88.9	(63.0,100)	84.0	(58.0,100)	61.7	(40.7,90.1)	56.8	(37.0,86.4)
0-<1 months	3.88	(2.91,4.75)	93.8	(67.9,100)	90.1	(62.9,100)	65.7	(44.4,95.1)	61.7	(39.5,91.4)
GA 38-<40 weeks	3.40	(2.55,4.24)	98.8	(77.8,100)	97.5	(71.6,100)	75.3	(49.4,98.8)	69.1	(45.6,97.5)
GA 36-<38 weeks	2.87	(2.07,3.75)	97.5	(74.0,100)	96.3	(68.5,100)	71.6	(46.9,97.5)	66.7	(43.2,95.1)
GA 34-<36 weeks	2.32	(1.71,3.05)	96.3	(70.3,100)	92.6	(64.2,100)	67.3	(44.4,96.3)	63.0	(40.7,92.7)
GA 32-<34 weeks	1.89	(1.38,2.44)	92.6	(66.7,100)	88.3	(60.5,100)	63.0	(41.9,92.7)	58.6	(38.2,87.7)
GA 30-<32 weeks	1.50	(1.05,1.95)	88.6	(61.7,100)	82.7	(56.8,100)	59.3	(38.3,87.7)	54.3	(35.8,82.7)
GA 28-<30 weeks	1.15	(0.779,1.52)	82.7	(58.0,100)	76.5	(53.0,98.8)	54.3	(35.8,81.5)	50.6	(32.1,76.6)

ePharmacology artifact ID RA14657943. Lines 1–2 substituted.
GA = gestational age; %*f*T>MIC = free percent time above minimum inhibitory concentration; q12h = every 12 hours.
Median (5^{th}, 95^{th}) based on summary of 100 trials and corresponds to median (90% prediction interval).
Adult dose and regimen is listed in first row.

Table 9 Median Percent of Subjects with %fT>MIC≥35% for *S. aureus* or 44% for *S. pneumonia* by Age and Duration of IV Infusion for Normal Renal Function Following 6 mg/kg q8h Dosing to Steady-State for Ceftaroline fosamil in Paediatric Patients Based on Simulations

Age Group	%*f*T>MIC≥35% (*S. aureus*)				%*f*T>MIC≥44% (*S. pneumoniae*)	
	MIC of 1 mg/L		MIC of 2 mg/L		MIC of 0.5 mg/L	
	1 hour infusion	5 minute infusion	1 hour infusion	5 minute infusion	1 hour infusion	5 minute infusion
Adults 600 mg q12h	99.7	99.0	83.2	74.3	100	99.7
1-<2 months	100	100	98.8	97.0	100	100
0-<1 months	100	100	99.3	98.3	100	100
GA 38-<40 weeks	100	100	99.7	99.3	100	100
GA 36-<38 weeks	100	100	99.7	99.0	100	100
GA 34-<36 weeks	100	100	99.0	98.3	100	100
GA 32-<34 weeks	100	100	98.7	97.0	100	100
GA 30-<32 weeks	100	100	97.3	95.3	100	100
GA 28-<30 weeks	100	100	95.3	91.3	100	100

ePharmacology artifact ID RA14657973. Lines 1–3 substituted.
GA = gestational age; %*f*T>MIC = free percent time above minimum inhibitory concentration; MIC = minimum inhibitory concentration; q12h = every 12 hours.
Median based on summary of 100 trials. Adult dose and regimen is listed in first row.

The summary statistics of weight and steady-state ceftaroline fosamil PK exposures (C_{maxSS} and $AUC2_{4SS}$) by age group for subjects with mild renal impairment following ceftaroline fosamil 6 mg/kg q8h IV infusions given over 1 hour or 5 minutes were provided. The statistics for adult doses of 600 mg q12h IV infusions given over 1 hour or 5 minutes for subjects with normal renal function are also shown for comparison to the paediatric subjects.

Table 10 Median (90% PI) Ceftaroline fosamil CmaxSS and AUC_{24SS} by Age and Duration of IV Infusion for Mild Renal Impairment Following 6 mg/kg q8h Dosing to Steady-State for Ceftaroline fosamil in Paediatric Patients Based on Simulations

Age Group	Weight (kg)		CmaxSS (mg/L) 1 hour infusion		CmaxSS (mg/L) 5 minute infusion		AUC24SS (mg·h/L) 1 hour infusion		AUC24SS (mg·h/L) 5 minute infusion	
Adults 600 mg q12h	77.6	(52.2,105)	20.9	(11.8,36.5)	26.5	(13.6,52.3)	97.3	(59.0,164)	96.9	(58.8,164)
18-<24 months	11.7	(9.82,14.1)	15.4	(9.57,24.1)	20.7	(11.6,37.2)	100	(62.0,164)	100	(61.9,164)
12-<18 months	10.4	(8.58,12.7)	15.7	(9.78,24.4)	20.8	(11.7,36.8)	105	(64.7,172)	105	(64.5,171)
6-<12 months	8.43	(6.56,10.8)	16.0	(9.94,24.9)	20.9	(12.0,37.3)	113	(69.7,186)	114	(69.5,186)
2-<6 months	5.75	(4.11,7.67)	15.9	(9.83,24.7)	20.0	(11.4,34.9)	126	(77.2,205)	126	(77.9,206)
1-<2 months	4.69	(3.63,5.77)	15.6	(9.70,24.1)	19.0	(11.1,32.7)	132	(80.5,212)	131	(81.1,213)
0-<1 months	3.86	(2.91,4.75)	14.9	(9.24,23.4)	17.7	(10.5,30.1)	135	(83.3,218)	135	(83.0,219)
GA 38-<40 weeks	3.40	(2.56,4.26)	14.3	(8.87,22.5)	16.4	(9.77,27.3)	143	(88.4,232)	143	(87.8,230)
GA 36-<38 weeks	2.86	(2.06,3.77)	13.9	(8.63,22.0)	16.1	(9.59,27.2)	136	(84.4,220)	136	(84.3,221)
GA 34-<36 weeks	2.33	(1.73,3.06)	13.6	(8.40,21.5)	15.8	(9.43,26.5)	130	(80.3,212)	130	(80.4,210)
GA 32-<34 weeks	1.89	(1.38,2.44)	13.2	(8.20,20.8)	15.4	(9.10,26.0)	123	(76.2,202)	123	(75.7,202)
GA 30-<32 weeks	1.50	(1.06,1.95)	12.7	(7.82,20.1)	15.0	(8.89,25.6)	117	(71.1,188)	116	(72.0,188)
GA 28-<30 weeks	1.16	(0.779,1.53)	12.3	(7.55,19.4)	14.7	(8.67,25.3)	108	(66.4,176)	108	(67.0,177)

ePharmacology artifact ID RA14617815. Lines 1–2 substituted.
AUC24SS = area under the plasma concentration-time curve over 24 hours at steady-state; CmaxSS = maximum concentration at steady-state; GA = gestational age; q12h = every 12 hours.
Median (5^{th}, 95^{th}) based on summary of 100 trials and corresponds to median (90% prediction interval).
Adult dose and regimen is listed in first row.

The median AUC_{24SS} values in preterm neonates (GA 28 to <40 weeks) and infants up to <2 months with mild renal impairment given a dose of 6 mg/kg q8h were up to 48% higher than median AUC_{24SS} values in adults with normal renal function given a dose of 600 mg q12h. The median AUC_{24SS} values in adults with mild renal impairment were within approximately 25% of those in adults with normal renal function given a dose of 600 mg q12h.

CHMP noted that the previous pop PK model has been updated using data from the P903-21 study. The updated model was also used to modify dose of ceftaroline fosamil after enrolment of first patients into the study C2661002. As shown by the MAH via graphical data analysis and Visual Predictive Checks, the updated model predicted concentrations are well overlaid with the observed sparse data samples.

The updated model was used to simulate ceftaroline fosamil median AUCss in preterm neonates, term neonates and infants up to 2 months of age, the predicted PK parameters were within the range of 89% to 118% of the adult median values. Similarly, the median %fT>MIC for MICs of 1 mg/L and 2 mg/L were similar to or exceeded median %fT>MIC values in adults.

As discussed above, there was some concern that fT>MIC values >35% for S. aureus may not be sufficient and the MAH was requested to perform similar simulations for relevant microorganisms with fT>MIC values of 60% and 100%, both for patients with normal renal function and for patients with mild renal impairment.

In summary, a dose of ceftaroline fosamil 6 mg/kg administered q8h as a 1 hour infusion to preterm or term neonates (GA: 28 to <40 weeks) and infants up to <2 months provided:

In patients with normal renal function:

- Median ceftaroline AUC24SS that ranged from 107% to 128% of the adult median AUC24SS (adult regimen of 600 mg every 12 hours (q12h) as a 1 hour infusion in patients with normal renal function), median ceftaroline CmaxSS that ranged from 47.5% to 67.0% of the adult median CmaxSS.
- >95% PTA against a PK/PD target of 60% fT>MIC for non-ESBL producing *Enterobacteriaceae* (MIC of 0.5 mg/L) and CoNS (MIC of 1 mg/L) in children of less than 2mo of age.
- PTA against a PK/PD target of 100% fT>MIC for non-ESBL producing *Enterobacteriaceae* (MIC of 0.5 mg/L) ranges between 58-73% for infants aged 0 to <2 months.
- PTA against a PK/PD target of 100% fT>MIC for CoNS (MIC of 1 mg/L) ranges between 13-24% for neonates and infants aged 0 to <2 months.

In patients with mild renal impairment:

- Median ceftaroline AUC24SS that ranged from 133% to 162% of the adult median AUC24SS (adult regimen of 600 mg q12h as a 1 hour infusion in patients with normal renal function), median ceftaroline CmaxSS that ranged from 56.0% to 74.2% of the adult median CmaxSS, and median %fT>MIC for MICs of 0.5 for non-ESBL producing Enterobacteriaceae and 1 mg/ L for CoNS that exceeded median %fT>MIC values in adults.
- >99% PTA against a PK/PD target of 60% fT>MIC for non-ESBL producing Enterobacteriaceae (MIC of 0.5 mg/L) and CoNS (MIC of 1 mg/L) in all age groups.
- <90% PTA against a PK/PD target of 100% fT>MIC for non-ESBL producing Enterobacteriaceae (MIC of 0.5 mg/L) for infants aged 1 to <2 months.
- <90% PTA against a PK/PD target of 100% fT>MIC for CoNS (MIC of 1 mg/L) for neonates with GA ≥36 weeks, and infants aged 0 to <2 months.

In comparison, a dose of ceftaroline fosamil 4 mg/kg administered q8h as a 1 hour infusion to preterm/term neonates (GA 28 to <40 weeks) and infants <2 months provided:
In patients with mild renal impairment:

- Median ceftaroline AUC24SS that ranged from 88.6% to 108% of the adult median AUC24SS (adult regimen of 600 mg q12h as a 1 hour infusion in patients with normal renal function), median ceftaroline CmaxSS that ranged from 37.3% to 49.5% of the adult median CmaxSS, and median %fT>MIC for MICs of 0.5 and 1 mg/L that exceeded median %fT>MIC values in adults.
- >90% PTA against a PK/PD target of 60% fT>MIC for non-ESBL producing Enterobacteriaceae (MIC of 0.5 mg/L) and CoNS (MIC of 1 mg/L) in all age groups.
- <90% PTA against a PK/PD target of 100% fT>MIC for non-ESBL producing Enterobacteriaceae (MIC of 0.5 mg/L) for infants aged 0 to <2 months.
- <90% PTA against a PK/PD target of 100% fT>MIC for CoNS (MIC of 1 mg/L) for all age groups.

In addition, a dose of ceftaroline fosamil 6 mg/kg administered q12h as a 1 hour infusion to preterm or term neonates (GA: 28 to <40 weeks) and infants up to <2 months with mild renal impairment provided:

- Median ceftaroline AUC24SS that ranged from 88.3% to 107% of the adult median AUC24SS (adult regimen of 600 mg q12h as a 1 hour infusion in patients with normal renal function), median ceftaroline CmaxSS that ranged from 44.1% to 68.7% of the adult median CmaxSS, and median %fT>MIC for MICs of 0.5 and 1 mg/L that exceeded median %fT>MIC values in adults.
- >95% PTA against a PK/PD target of 60% fT>MIC for non-ESBL producing *Enterobacteriaceae* (MIC of 0.5 mg/L) in all age groups.
- <90% PTA against a PK/PD target of 60% fT>MIC for CoNS (MIC of 1 mg/L) for infants aged 0 to <2 months; but >95% PTA for neonates (GA 28 to <40 weeks).
- <90% PTA against a PK/PD target of 100% fT>MIC for non-ESBL producing *Enterobacteriaceae* (MIC of 0.5 mg/L) for neonates with GA ≥34 weeks, and infants aged 0 to <2 months.
- <90% PTA against a PK/PD target of 100% fT>MIC for CoNS (MIC of 1 mg/L) for all age groups.

CHMP agreed that according to the data presented the dose 6 mg/kg q8h is adequate. It cannot be excluded that higher doses might be required for patients infected with microorganisms with higher MICs (similar to adults and older children). Simulations for microorganisms with higher MICs (2 mg/L and 4mg/L) would be needed in the future to have a definitive view on the matter.

2.3.5. Discussion on clinical pharmacology

This application contains two clinical studies and population PK analysis using the previously validated model.

Study P903-21 enrolled 23 neonates (11 preterm GA 32 to 37 weeks and 12 term neonates <28 days) receiving a single dose regimen of ceftaroline fosamil 8 mg/kg as a 1 hour infusion. The young infant cohort in that study comprised ages >28 days to <2 years (n=12), but and did not enrol any subjects between the ages of >28 and <60 days.

Study C2661002 was closed prematurely, and at the time of early closure 11 patients were enrolled, received study treatment, and completed the study: 4 patients were in Cohort 1 (young infants aged >28 days to <60 days), 5 in Cohort 2 (term neonates aged 7 to <28 days), and 2 in Cohort 3 (preterm neonates, postmenstrual age of 28 to 41 weeks, aged 7 to <28 days).

Both studies used a sparse sampling strategy, therefore PK parameters were not calculated for each subject by noncompartmental analysis. Therefore, real life sparse PK data are available from 13 (11+2) preterm neonates, 17 (12+5) term neonates, and 4 young infants aged >28 days to <60 days. Considering the vulnerability of the study population, the relatively rare clinical indication, and the availability of PK data in older infants, CHMP agreed that this approach is acceptable.

The dosing regimen for ceftaroline fosamil (6 mg/kg q8h as a 60 [±10] minute infusion) was chosen based on a population PK model updated with PK data from 3 multiple-dose safety and efficacy studies in children aged 2 months to <18 years (Studies P903 23, P903 31 and P903 24). This model was used in Monte Carlo simulations to choose and justify the dose regimens for children aged 2 months to 18 years, now approved in the US and the EU. The same model was used to predict initial doses for children <2 months of age, including preterm neonates (with a postmenstrual age of 28 to 41 weeks), and later change the dose from 4 mg/kg to 6 mg/kg in the study C2661002 via protocol edition 3.

The ceftaroline fosamil population PK model incorporated allometric scaling for body weight and maturation of renal function. Validity of the model was analysed by graphical data check, the observed plasma concentrations from the study C2661002 were overlaid with the model predicted $C_{max24ss}$ and AUC_{24ss}. The model predicted $C_{max24ss}$ and AUC_{24ss} in various age groups of neonates and infants after administration of ceftaroline fosamil 6 mg/kg q8h as 1h infusion were compared with the median adult $C_{max24ss}$ and AUC_{24ss} after administration of ceftaroline fosamil 600mg q12h as 1h infusion. The predicted AUC_{24ss} parameters in neonates and infants were within the range of 89% to 118% of the adult median values. Similarly, the median %fT>MIC for MICs of 1 mg/L and 2 mg/L that were similar to or exceeded median %fT>MIC values in adults. Similar predictions were simulated for various age groups of neonates and infants with mild renal impairment. The median AUC_{24SS} values in preterm neonates (GA 28 to <40 weeks) and infants up to <2 months with mild renal impairment given a dose of 6 mg/kg q8h were up to 48% higher than median AUC_{24SS} values in adults with normal renal function given a dose of 600 mg q12h. Based on the additional simulations submitted by the MAH (see above), the proposed dosing of ceftaroline fosamil 6 mg/mg q8h as 1h infusion, was considered acceptable by CHMP.

2.3.6. Conclusions on clinical pharmacology

The median AUC_{24SS} values in preterm neonates (GA 28 to <40 weeks) and infants up to <2 months with mild renal impairment given a dose of 6 mg/kg q8h were up to 48% higher than median AUC_{24SS} values in adults with normal renal function given a dose of 600 mg q12h. Based on the additional simulations submitted by the MAH (see above), the proposed dosing of ceftaroline fosamil 6 mg/mg q8h as 1h infusion, was considered acceptable by CHMP.

2.4. Clinical efficacy

Table 11. Summary of efficacy studies

Study ID	No. of study centres / locations	Design	Study Posology	Study Objective	Subjs by arm entered / compl.	Duration of treatment	Gender M/F Median age (range)	Diagnosis
D3720C00009 C2661002)	4 centres in the US and Hungary enrolled patients	open-label, single-arm study with no randomization	Ceftaroline fosamil 4 mg/kg or 6 mg/kg IV over 60 (±10) minutes q8h (±1 hour)	safety, tolerability, PK and efficacy of ceftaroline fosamil plus ampicillin plus optional aminoglycoside in term and preterm neonates with late onset sepsis	Ceftaroline fosamil (N=11/11)	2-14 days	11 (6/5) patients The mean age was 30.3 ±14.8 days (median 24.0, range 12-53 days).	Late-onset sepsis (LOS)

2.4.1. Main study

Study P903-26 (D3720C00009/C2661002)

Title of Study: Open-label, Multicentre Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Efficacy of Ceftaroline fosamil in Neonates and Young Infants (7 to <60 days) with Late-Onset Sepsis

Methods

The study design was open-label, multicentre, multi-national and single treatment arm with no randomisation. The patients enrolled were neonates and young infants with late-onset sepsis (LOS). The open-label design allowed for close clinical monitoring by the Investigator. Given the risk to patients and the severity of disease, a placebo-controlled trial was not ethically appropriate.

The study was to be conducted in approximately 30 centres worldwide. At least 24 patients with LOS were to be enrolled and treated within 3 age cohorts of 8 patients each:

Cohort 1: young infants aged >28 days to <60 days of postnatal age

Cohort 2: term neonates (defined as gestational age ≥37 weeks) aged 7 to ≤28 days of postnatal age

Cohort 3: preterm neonates (defined as gestational age ≥34 to <37 weeks) aged 7 to ≤28 days of postnatal age

An external Data and Safety Monitoring Board (DSMB) was used in this study to evaluate the safety of the study at periodic intervals.

CHMP noted that a request to close this study was submitted by the MAH to the EMA through a modification to the agreed Paediatric Investigation Plan (PIP) based on the fact that there was sufficient data available to provide ceftaroline fosamil dosing recommendations for neonates. There was agreement from the Paediatric Committee with early closure of the study with the enrolment of 11 patients. Of note, the same request was submitted to the US FDA and was agreed upon.

Study participants

Eleven (11) patients were enrolled in the study and received study treatment: 4 (36.4%) patients were in Cohort 1 (young infants), 5 (45.5%) in Cohort 2 (term neonates), and 2 (18.2%) in Cohort 3 (preterm neonates). All enrolled patients completed the study.

Patients had to meet all inclusion criteria and not to meet any exclusion criteria to participate in the study.

Main inclusion criteria

- Gestational age ≥34 weeks, chronological age 7 to <60 days at the time of screening.
- Diagnosis of sepsis within 36 hours before enrolment, defined as the presence of at least 2 clinical criteria and at least 1 laboratory criterion in the presence of or as a result of suspected or proven bacterial infection that required IV antibiotic therapy.
- At least 2 of the following clinical criteria: hypothermia or fever; bradycardia or tachycardia or rhythm instability; Urine output 0.5 to 1 mL/kg/h OR hypotension OR mottled skin OR impaired peripheral perfusion; Petechial rash OR sclerema neonatorum; New onset or worsening of apnea episodes OR tachypnea episodes OR increased oxygen requirements OR requirement for ventilation support; Feeding intolerance OR poor sucking OR abdominal distension; Irritability; Lethargy; Hypotonia
- At least 1 of the following laboratory criteria: WBC count ≤4.0 × 10^9/L OR ≥20.0 × 10^9/L; Immature to total neutrophil ratio >0.2; PLT count ≤100 × 10^9/L; CRP >15 mg/L OR procalcitonin ≥2 ng/mL; Hyperglycemia OR Hypoglycemia; Metabolic acidosis.

Main exclusion criteria

- Refractory septic shock within 24 hours before enrolment that did not resolve after 60 minutes of vasopressor therapy
- Moderate or severe renal impairment defined as serum creatinine ≥2 times (2 ×) the upper limit of normal (ULN) for age OR urine output <0.5 mL/kg/h (measured over at least 8 hours) OR requirement for dialysis.

During the course of the study, there were no cases of patients failing to meet all eligibility criteria.

CHMP noted that, although there are no validated inclusion and exclusion criteria of LOS, the criteria selected by the applicant seem to adequately reflect a population with LOS and are considered acceptable.

Treatments

Patients received a combination of:

- IV **ceftaroline fosamil** 4 mg/kg (patients enrolled prior to amendment 2) or 6 mg/kg (after protocol amendment 2) IV over 60 (±10) minutes q8h (±1 hour) and
- IV **ampicillin** for at least 48 hours (after 48 hours, the duration of treatment with ampicillin was at the discretion of the Investigator), plus
- an optional **aminoglycoside** (gentamicin was the preferred aminoglycoside) of choice as empiric therapy for LOS.

The total duration of study therapy was between 48 hours (minimum) and 14 days (maximum). Three patients enrolled prior to amendment 2 (Protocol edition 3) received ceftaroline fosamil at a dose of 4 mg/kg over 60 (±10) minutes q8h (±1 hour). Remaining 8 patients received 6 mg/kg q8h ceftaroline fosamil.

If the presence of an organism that required treatment with ampicillin could not be excluded, then the use of IV ampicillin for the first 48 hours was mandatory. If the results of additional microbiology, PCR or other investigations indicated that ampicillin during the first 48 hours of treatment was not required, then its use was at the discretion of the Investigator.

Nine (9) of the 11 patients received ampicillin with the mean duration of exposure of 4.8 ±2.86 days (median 3.0, range 2-11 days). Patients in Cohort 1 had the shortest mean exposure (3.0 ±0.0 days), while mean exposure in Cohorts 2 (6.0 ±3.74 days) and 3 (5.0 ±2.83 days) was similar.

Aminoglycoside could be started and stopped at any time during the study at the discretion of the Investigator. The use of an aminoglycoside was optional from Baseline through the entire study.

Six (6) patients received aminoglycoside and the mean duration of exposure was 7.7 ±3.78 days (median 7.5, range 3-12 days). Brulamycin, gentamycin, and tobramycin were the aminoglycosides administered to 2 patients each.

CHMP noted that the use of combination therapy is not ideal, but accepted in the patients with LOS. However, concomitant medication may affect safety profile/assessment of ceftaroline fosamil. It was also noted that the sample size of the study was lower than initially planned (24 vs 11, especially in cohort 3 in which only 2 patients out of 8 planned were recruited). And that not all patients received the dose that was proposed to be recommended (6 mg/kg q8h) but received 4 mg/kg q8h. In view of the above, it was agreed that interpretation of these data is difficult.

Objectives

Table 12 Primary Objective:

Primary Objective	Outcome Measure(s):
To evaluate the **safety and tolerability** of ceftaroline fosamil for the treatment of late-onset sepsis (LOS) in neonates and young infants aged 7 to <60 days.	AEs, serious adverse events (SAEs), deaths, clinical laboratory parameters (eg, complete blood count [CBC] with differential, chemistry panel), and vital signs. Safety evaluations were conducted in the Safety Analysis Set.

Table 13 Secondary Objectives:

Secondary Objective	Outcome Measure(s):
To evaluate the **PK** profile of ceftaroline fosamil in neonates and young infants aged 7 to <60 days with LOS.	Concentrations of ceftaroline fosamil, ceftaroline fosamil, and ceftaroline fosamil M-1 in plasma (and if available, concentrations of ceftaroline fosamil and ceftaroline fosamil M-1 in CSF).
To evaluate the **efficacy** of ceftaroline fosamil for the treatment of LOS in neonates and young infants aged 7 to <60 days.	Clinical response at EOT and TOC in the ITT, MITT and Microbiological-ITT (Micro-ITT) Analysis Sets. Per-pathogen and per-patient microbiological response variables at EOT and TOC in the MITT and Micro-ITT Analysis Sets.

Outcomes/endpoints

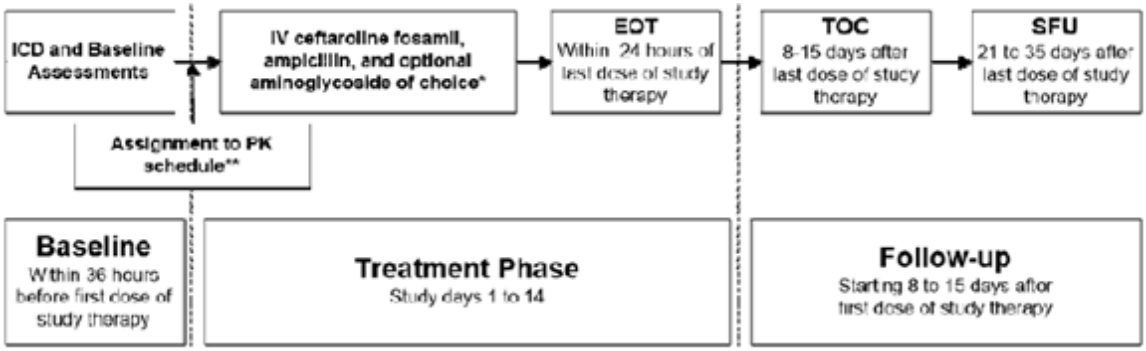
There was no primary efficacy evaluation.

Secondary efficacy outcome measures included clinical response and microbiological response (per-patient and per-pathogen) at End-of-Therapy (EOT) and Test-of-Cure (TOC).Please refer to the Table 4.4.2-3. The clinical outcome was assessed by the Investigator as cure, failure or indeterminate at EOT and TOC. Microbiological response was determined programmatically as favourable (eradication or presumed eradication), unfavourable (persistence or presumed persistence) or indeterminate at EOT and TOC.

Table 14 Study visits

Time points	Time
Baseline	Within 36 hours before first dose of study therapy
EOT	Within 24 hours of last dose of study therapy
TOC	8-15 days after las dose of study therapy
Safety follow-up (SFU)	21 to 35 days after last dose of study therapy

Figure 4. Study P903-26 (D3720C00009/ C2661002) diagram



Abbreviations: EOT = End-of-Therapy, ICD = informed consent document, IV = intravenous, IXRS = Interactive Response System, PCR = polymerase chain reaction, PK = pharmacokinetic, SFU = Safety Follow-up, TOC = Test-of-Cure

*IV ampicillin and an optional aminoglycoside were given as per standard of care. If the presence of an organism that required treatment with ampicillin could not be excluded, then the use of IV ampicillin for the first 48 hours of treatment was mandatory. If the results of additional microbiology, PCR, or other investigations indicated that ampicillin during the first 48 hours of treatment was not required, then its use was at the discretion of the Investigator.
**Patients were randomly assigned to PK schedule using an IXRS.

Table 15 Schedule of Activities

Assessment or Procedure		Baseline[a]	Treatment period					Follow-up	
			Study Days*						
			1	2	3	4-14	EOT[b]	TOC[c]	SFU[d]
	Written informed consent	X							
	Inclusion/exclusion criteria[e]	X							
Clinical	Medical history (including antepartum/ peripartum period)	X							
Clinical	Adverse event review (AEs and SAEs)	X	X	X	X	X	X	X	X
Clinical	Prior and concomitant medications[f]	X	X	X	X	X	X	X	X
Clinical	Length	X							
Clinical	Weight	X	X	X	X	X	X	X	X
Clinical	Physical examination	X	X	X	X	X	X	X	
Clinical	Vital signs and oxygen saturation[g]	X	X	X	X	X	X	X	X
Clinical	Clinical outcome						X	X	
Clinical	Record adjunctive therapeutic procedures (if performed)		X	X	X	X	X	X	
Clinical	CXR, CT scan, or other imaging tests[h]	X[j]							
Laboratory	CBC with differential[i]	X	X[j]				X	X[j]	X[j]
Laboratory	Chemistry panel[i]	X	X[j]				X	X[j]	X[j]
Laboratory	Base excess	X[j]							
Laboratory	CRP and Procalcitonin[i]	X[j]							
Laboratory	Urinalysis	X	X[j]				X	X[j]	
Laboratory	Urine output	X[k]	X	X	X	X[j]			
Laboratory	CSF	X[j]							

PK	Assignment to PK schedule[l]	X							
	PK blood sample[m]				X				
	CSF sample (if collected as per standard of care) and matching blood sample[n]				X				
Micro	Blood culture				X[j]				
	Urine culture				X[j]				
	CSF culture				X[j]				
	Other specimen or tissue cultures				X[j]				
	Administration of study therapy		X	X	X	X			

Baseline microbiological assessments were to be performed preferably before any antibiotics were administered. Blood, urine, CSF and other specimens/tissue samples were collected at Baseline if clinically indicated and performed as part of the patient's regular medical care.

From Baseline through the TOC visit, blood and urine samples were to be repeated per standard of care upon knowledge of a positive result until sterilization was confirmed. CSF or other specimens/tissue samples were to be repeated per standard of care upon knowledge of a positive result.

Table 16 Clinical Outcome Categories at EOT

Outcome	Definition
Clinical Cure	Resolution of all acute signs and symptoms of LOS or improvement to such an extent that no further antibacterial therapy was required.
Clinical Failure	Patients who received ≥48 hours of study treatment and met any of the following criteria: • Discontinuation of study therapy due to insufficient therapeutic effect, including persistence, incomplete clinical resolution, worsening in signs and symptoms of LOS, or isolation of a resistant pathogen that required alternative non-study antibacterial therapy. • Discontinuation of study therapy due to a study therapy-related AE and requirement for alternative non-study antibacterial therapy for LOS. • Death in which LOS was contributory.
Indeterminate	Study data were not available for evaluation of efficacy for any reason, including: • Death in which LOS was clearly non-contributory. • LTFU (lost to follow-up) • Extenuating circumstances precluding classification as a cure or failure. • Diagnosis of CNS infection, osteomyelitis, endocarditis, or NEC (necrotizing enterocolitis) at any time after enrolment. • Received <48 hours of study therapy.

Table 17 Clinical Outcome Categories at TOC

Outcome	Definition
Clinical Cure	Resolution of all acute signs and symptoms of LOS or improvement to such an extent that no further antibacterial therapy was required.
Clinical Failure	Patients who received ≥48 hours of study treatment and met any of the following

	criteria: • Incomplete resolution or worsening of LOS signs or symptoms or development of new signs or symptoms, or isolation of a resistant pathogen requiring alternative non-study antibacterial therapy. • Death in which LOS was contributory.
Indeterminate	Study data were not available for evaluation of efficacy for any reason, including: • Death in which LOS was clearly non-contributory. • LTFU • Extenuating circumstances precluding classification as a cure or failure. • Diagnosis of CNS infection, osteomyelitis, endocarditis, or NEC at any time after enrolment. • Received <48 hours of study therapy.

Sample size

The study was not powered for inferential statistical analysis. The planned sample size (24 patients; 3 cohorts of 8 patients each) was considered adequate to evaluate the safety of ceftaroline fosamil in neonates and young infants with LOS.

Randomisation

This study was with no randomization.

Blinding (masking)

This study was not blinded. The Investigators, pharmacists or designees, study centre personnel, and parent(s)/legally acceptable representative(s) were aware of study treatment being administered.

Statistical methods

Descriptive statistics (number, mean, standard deviation [SD], median, minimum, and maximum) is provided for continuous variables, and frequency distributions (counts and percentages) are shown for categorical variables. All variables are summarized overall and by age cohort.

Patient disposition (enrolment, discontinuations from the study) overall and within each age cohort is provided based on the ITT Analysis Set.

Demographics (age, race, gender), medical and surgical history including antepartum/peripartum period, microbiological assessment of blood, CSF, urine, and other specimens or tissue samples are summarized for the ITT, MITT, and Micro-ITT Analysis Sets.

Efficacy response was analysed using the ITT, MITT and Micro-ITT Analysis Sets.

Proportions of patients with a favourable efficacy response are displayed overall and within each age cohort. The number and percentage of patients classified as a clinical cure at EOT and TOC are tabulated in the ITT, MITT and Micro-ITT Analysis Sets.

The proportion of patients with clinical failure and with indeterminate clinical response was calculated analogously. For the proportion of patients with clinical cure, clinical failure, and indeterminate, indeterminate or missing assessments were included in the denominator for calculation of the proportions for the ITT, MITT and Micro-ITT Analysis Sets.

Microbiological success at EOT and TOC was evaluated. A summary of the microbiological outcome by patient and by pathogen is presented in the MITT and Micro-ITT Analysis Sets.

Table 18 Analysis sets

ITT (Intent-to-treat)	all enrolled patients (11 patients)
MITT (Modified Intent-to-treat) Analysis set	all patients who received any amount of ceftaroline fosamil and who met minimal disease criteria of LOS (8 patients)
Micro-ITT (Microbiological-ITT)	all ITT patients who had 1 or more potentially causative baseline pathogens identified (10 patients)

CHMP noted that the main objective of the study was to describe safety and agreed to describing the observed efficacy results. It was agreed that while no efficacy conclusions can be derived from this study alone, based on the very small sample size, extrapolation of efficacy from adults would be according to existing guidelines and would be acceptable.

Results

Participant flow

Figure 5 Participant flow

Outline of Analysis Sets

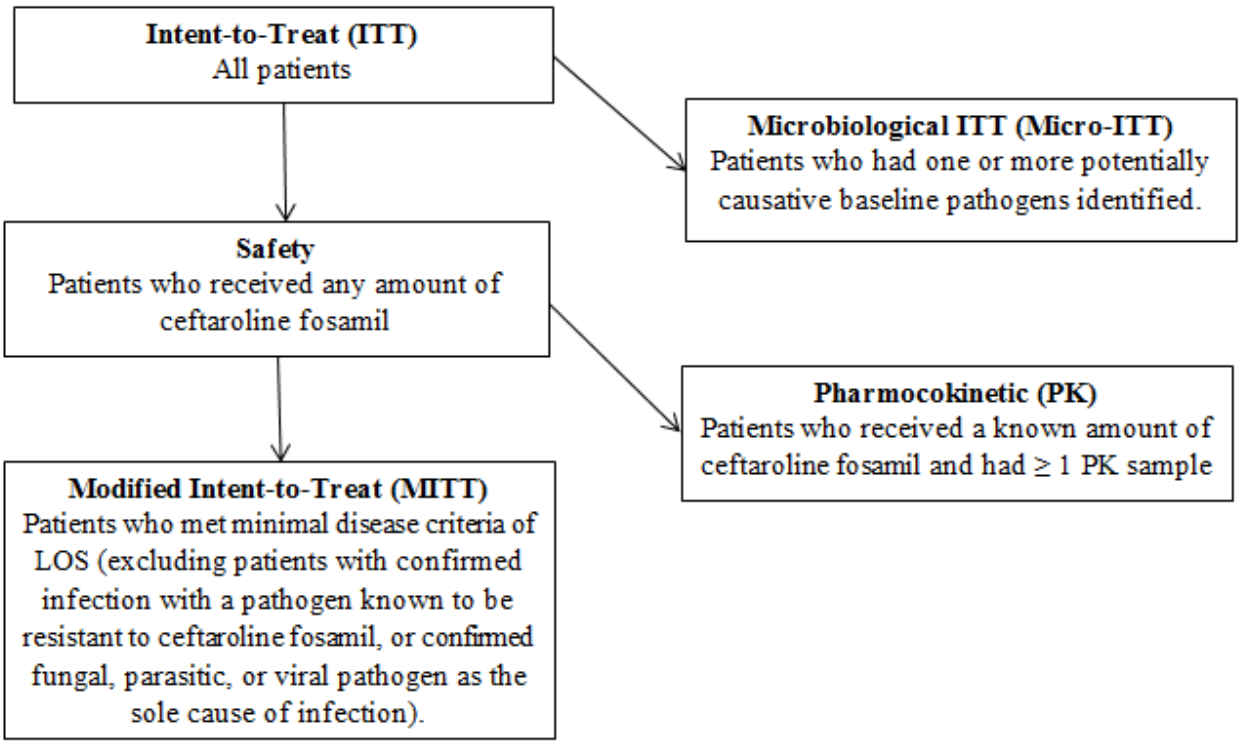


Table 19 Analysis Sets (All Patients)

	Number of Patients			
	Cohort 1 (N = 4)	Cohort 2 (N = 5)	Cohort 3 (N = 2)	Total (N = 11)
Patients included in Intent-to-Treat (ITT) Analysis Set	4	5	2	11
Patients included in Safety Analysis Set	4	5	2	11
Patients included in Modified Intent-to-Treat (MITT) Analysis Set	4	3	1	8
Patients excluded from Modified Intent-to-Treat (MITT) Analysis Set [a]	0	2	1	3
Patients included in Microbiological (Micro-ITT) Analysis Set	3	5	2	10
Patients excluded from Microbiological (Micro-ITT) Analysis Set [b]	1	0	0	1
Patients included in Pharmacokinetic (PK) Analysis Set	4	5	2	11

Please refer to SAP for population definitions.
The following patients were excluded from the MITT analysis set based on their baseline pathogen(s):

- one patient had *E. coli* (urine, MIC >32) resistant to ceftaroline
- one patient had *E. coli* (nose, MIC =16) resistant to ceftaroline and *E. faecalis* (urine) considered a pathogen by the Investigator
- one patient had *E. faecalis* (urine) considered a pathogen by the Investigator

One patient had no baseline microbiology data and was excluded from the Micro-ITT population.
During the site close-out visit at site 9004, after database lock, a new screen failure was discovered. No data was recorded in the CRF for this patient (see Erratum). This patient was not enrolled and is not included in the ITT Analysis Set.

Cohort 1 = Young infants, Cohort 2 = Term neonates, Cohort 3 = Preterm neonates.

CRF = Case Report Form; ITT = Intent-to-Treat; MIC = minimum inhibitory concentration; MITT = Modified Intent-to-Treat; N = number of patients; PK = pharmacokinetic; SAP = statistical analysis plan

Table 20 Patient disposition (All patients)

	Number (%) of patients			
	Cohort 1 (N = 4)	Cohort 2 (N = 5)	Cohort 3 (N = 2)	Total (N = 11)
Patients enrolled[a]	4	5	2	11
Patients who received treatment	4 (100)	5 (100)	2 (100)	11 (100)
Patients who did not receive treatment	0	0	0	0
Patients who completed treatment[b]	2 (50.0)	3 (60.0)	2 (100)	7 (63.6)
Patients who discontinued treatment[b]	2 (50.0)	2 (40.0)	0	4 (36.4)
Other[c]	2 (50.0)	2 (40.0)	0	4 (36.4)

	Number (%) of patients			
	Cohort 1 (N = 4)	Cohort 2 (N = 5)	Cohort 3 (N = 2)	Total (N = 11)
Patients enrolled[a]	4	5	2	11
Patients who received treatment	4 (100)	5 (100)	2 (100)	11 (100)
Patients who did not receive treatment	0	0	0	0
Patients who completed treatment[b]	2 (50.0)	3 (60.0)	2 (100)	7 (63.6)
Patients who discontinued treatment[b]	2 (50.0)	2 (40.0)	0	4 (36.4)
Other[c]	2 (50.0)	2 (40.0)	0	4 (36.4)

	Number (%) of patients			
	Cohort 1 (N = 4)	Cohort 2 (N = 5)	Cohort 3 (N = 2)	Total (N = 11)
Patients who completed study[b]	4 (100)	5 (100)	2 (100)	11 (100)
Patients withdrawn from study[b]	0	0	0	0

Reasons for treatment discontinuation are based on the discontinuation of investigational product CRF page.
Cohort 1 = Young infants, Cohort 2 = Term neonates, Cohort 3 = Preterm neonates
CRF = Case Report Form; ICD = informed consent document; N = number of patients in each age cohort and overall.
a. Informed consent received; note, the ICD signed for 1 patient is not included in this table, see erratum.
b. Patients who completed treatment are defined as patients who did not discontinue ceftaroline prematurely and permanently as indicated on the discontinuation of investigational product CRF page. Percentages are calculated from the number of patients who received treatment.
c. "Other" was selected as the reason for discontinuation of treatment for 4 patients who improved and were discharged home and switched to oral/IV antibacterial therapy per standard of care.

Conduct of the study

Efficacy analyses were conducted in the Intent-to-Treat (ITT), modified-ITT (MITT) and Microbiological-ITT (Micro-ITT) Analysis Sets. The number and percentage of patients with a clinical cure, clinical failure, and indeterminate clinical response at EOT and TOC were tabulated overall, by baseline pathogen, and within each age cohort. A 2-sided 95% confidence interval (CI) for the observed clinical cure rate overall and within each cohort was constructed using the Jeffreys method. Sensitivity analyses were conducted on the overall response excluding indeterminate responses. Microbiological outcome at EOT and TOC was summarized by patient and by pathogen.

All 11 experienced at least 1 important protocol deviation. The most common protocol deviation, experienced by 5 patients, was "lab not done", followed by dosing schedule and antibiotic switch deviations, experienced by 4 patients each. The clinical response for the 4 patients with antibiotic switch deviations was considered indeterminate, thus impacting efficacy evaluation. None of the other investigational product (IP)-related deviations had an impact on the efficacy evaluation and none were considered safety issues.

Baseline data

Demographics

Table 21 Demographic Characteristics (ITT Analysis Set)

Demographic Characteristic	Summary Statistic	Cohort 1 (N = 4)	Cohort 2 (N = 5)	Cohort 3 (N = 2)	Total (N = 11)
Age (days)	N	4	5	2	11
	Mean	48.0	22.0	15.5	30.3
	SD	4.69	3.81	4.95	14.78
	Median	48.5	22.0	15.5	24.0
	Minimum	42	17	12	12
	Maximum	53	27	19	53
Sex n (%)	Female	3 (75.0)	1 (20.0)	1 (50.0)	5 (45.5)
	Male	1 (25.0)	4 (80.0)	1 (50.0)	6 (54.5)
	Total	4 (100)	5 (100)	2 (100)	11 (100)
Race n (%)	White	3 (75.0)	5 (100)	2 (100)	10 (90.9)
	Asian	1 (25.0)	0	0	1 (9.1)
	Total	4 (100)	5 (100)	2 (100)	11 (100)
Ethnic Group n (%)	Hispanic or Latino	0	1 (20.0)	0	1 (9.1)
	Not Hispanic or Latino	4 (100)	4 (80.0)	2 (100)	10 (90.9)
	Total	4 (100)	5 (100)	2 (100)	11 (100)

Source: Table 14.1.2.1.1.1
Percentages are calculated out of patients with non-missing data.
Cohort 1 = Young infants, Cohort 2 = Term neonates, Cohort 3 = Preterm neonates.
ITT = Intent-to-Treat; n = Number of patients in the category or analysis; N = Number of patients in the cohort; SD = Standard deviation.

The mean age was 30.3 ±14.8 days (median 24.0, range 12-53 days).

Gender across all cohorts was nearly evenly divided. Ten (10, 90.9%) patients were White (1 [9.1%] Hispanic or Latino), and 1 (9.1%) patient was Asian.

Table 22 Patient Characteristics at Baseline (ITT Analysis Set)

Demographic Characteristic	Summary Statistic	Cohort 1 (N = 4)	Cohort 2 (N = 5)	Cohort 3 (N = 2)	Total (N = 11)
Age (days)	N	4	5	2	11
	Mean	48.0	22.0	15.5	30.3
	SD	4.69	3.81	4.95	14.78
	Median	48.5	22.0	15.5	24.0
	Minimum	42	17	12	12
	Maximum	53	27	19	53
Sex n (%)	Female	3 (75.0)	1 (20.0)	1 (50.0)	5 (45.5)
	Male	1 (25.0)	4 (80.0)	1 (50.0)	6 (54.5)
	Total	4 (100)	5 (100)	2 (100)	11 (100)
Race n (%)	White	3 (75.0)	5 (100)	2 (100)	10 (90.9)
	Asian	1 (25.0)	0	0	1 (9.1)
	Total	4 (100)	5 (100)	2 (100)	11 (100)
Ethnic Group n (%)	Hispanic or Latino	0	1 (20.0)	0	1 (9.1)
	Not Hispanic or Latino	4 (100)	4 (80.0)	2 (100)	10 (90.9)
	Total	4 (100)	5 (100)	2 (100)	11 (100)

Percentages are calculated out of patients with non-missing data.
Cohort 1 = Young infants, Cohort 2 = Term neonates, Cohort 3 = Preterm neonates.
ITT = Intent-to-Treat; n = Number of patients in the category or analysis; N = Number of patients in the cohort; SD = Standard deviation

The length and weight of the patients in the ITT Analysis Set were as expected for infants in these age groups.

Baseline Medical and Surgical History

The most frequently reported medical history terms were anaemia and pyrexia, both reported for 3 (27.3%) patients, followed by pyelonephritis, irritability, respiratory distress, and caesarean section, all reported for 2 (18.2%) patients.

Baseline Microbiology

Table 23 Summary of Baseline Pathogens (Micro-ITT Analysis Set)

Specimen Type	Baseline Pathogen	Cohort 1 (N = 3)	Cohort 2 (N = 5)	Cohort 3 (N = 2)	Total (N = 10)
Blood	*Enterobacter aerogenes*	1	0	0	1
	Escherichia coli	0	1	0	1
	Staphylococcus epidermidis	0	0	1	1
	Staphylococcus hominis	1	0	0	1
	Streptococcus salivarius group	0	1	1	2
Urine	*Enterobacter aerogenes*	1	0	0	1
	Enterococcus faecalis	0	1	1	2
	Escherichia coli	2	3	0	5
	Klebsiella pneumoniae	0	0	1	1
	Streptococcus agalactiae	0	1	0	1
Other	*Escherichia coli*	0	2	1	3
	Staphylococcus aureus	1	1	1	3

Cohort 1, 1 patient had other - sputum/nose as specimen type. Cohort 2, 2 patients had other - sputum/throat and 1 patient had other - sputum/throat tissue as specimen type. Cohort 3, 1 patient had other - other/nose (*E. coli*) and other - other/throat (*S. aureus*) as specimen types.
Cohort 1 = Young infants, Cohort 2 = Term neonates, Cohort 3 = Preterm neonates.
ITT = Intent-to-Treat; n = Number of pathogens, patients could have multiple pathogens at baseline;
N = number of patients in the cohort.

E. coli was the most commonly identified organism at Baseline within the Micro-ITT Analysis Set, identified in 1 blood sample, 5 urine samples and 3 “other” samples.

The organisms identified at Baseline within the MITT Analysis Set showed a similar pattern; however, the number of *E. coli* isolates was reduced, as 2 isolates (urine, nose) were resistant to ceftaroline fosamil, and the *E. faecalis* isolates were not included because ceftaroline fosamil is not active against this organism.

Numbers analysed

Outcomes and estimation

At both EOT and TOC (MITT analysis set), all patients were classified as either clinical cure (4, 50%) or indeterminate (4, 50%). The 4 patients with indeterminate outcomes had improved clinically and were discharged from the hospital with standard of care antibacterial treatment. Based on the definitions for clinical outcome these patients did not meet the definition for cure or failure.

Clinical response was similar for the ITT and Micro-ITT Analysis Sets (Please refer to the Table 4.4.2-15 and Table 4.4.2-16). Clinical cure rates were 63.6% (7/11) and 70.0% (7/10) in the ITT and Micro-ITT Analysis Sets, respectively. There were no clinical failures at EOT or TOC in any analysis set.

Timepoint	Response	Cohort 1 (N = 4)	Cohort 2 (N = 3)	Cohort 3 (N = 1)	Total (N = 8)
EOT	95% CI of Clinical Cure[a]	(12.3, 87.7)	(3.9, 82.3)	(14.7, 100)	(19.9, 80.1)
	Clinical Cure n (%)	2 (50.0)	1 (33.3)	1 (100)	4 (50.0)
	Clinical Failure n (%)	0	0	0	0
	Indeterminate n (%)	2 (50.0)	2 (66.7)	0	4 (50.0)
TOC	95% CI of Clinical Cure[a]	(12.3, 87.7)	(3.9, 82.3)	(14.7, 100)	(19.9, 80.1)
	Clinical Cure n (%)	2 (50.0)	1 (33.3)	1 (100)	4 (50.0)
	Clinical Failure n (%)	0	0	0	0
	Indeterminate n (%)	2 (50.0)	2 (66.7)	0	4 (50.0)

Clinical response is the derived overall response.
Percentages are based on the total number of patients in the cohort (N).
Cohort 1 = Young infants, Cohort 2 = Term neonates, Cohort 3 = Preterm neonates.
CI = confidence interval; EOT = End-of-Therapy; MITT = Modified Intent-to-Treat; TOC = Test-of-Cure.
a. Confidence intervals (CIs) for rates within cohort are calculated using the Jeffreys method.

All patients in the MITT Analysis Set had a favourable or indeterminate microbiological response at EOT and TOC with the exception of 1 patient with persistent *E. coli* in urine at TOC (MIC = 0.12 mg/L, ESBL negative, clinical cure).

Within the MITT Analysis Set, the per-pathogen microbiological response was favourable for all baseline pathogens with the exception of 1 *E. coli* at TOC (as mentioned above).

The per-patient and per-pathogen microbiological responses were similar between the MITT and Micro-ITT Analysis Sets. There was an additional unfavourable microbiological response in the Micro-ITT Analysis Set for an *E. coli* with a ceftaroline fosamil MIC >32 mg/L at baseline.

A sensitivity analysis of the clinical responses was conducted, which excluded the indeterminate clinical responses. The results for the number of patients experiencing clinical cure at EOT and TOC were unchanged; all patient were cures with no clinical failures in the MITT, ITT and Micro-ITT Analysis Sets.

Table 24 Clinical Response at EOT and TOC – Sensitivity Analysis (MITT Analysis Set)

Timepoint	Response	Cohort 1 (N = 2)	Cohort 2 (N = 1)	Cohort 3 (N = 1)	Total (N = 4)
EOT	95% CI of Clinical Cure[a]	(33.3, 100)	(14.7, 100)	(14.7, 100)	(55.5, 100)
	Clinical Cure n (%)	2 (100)	1 (100)	1 (100)	4 (100)
	Clinical Failure n (%)	0	0	0	0
TOC	95% CI of Clinical[a]	(33.3, 100)	(14.7, 100)	(14.7, 100)	(55.5, 100)
	Clinical Cure n (%)	2 (100)	1 (100)	1 (100)	4 (100)
	Clinical Failure n (%)	0	0	0	0

Clinical response is the derived overall response.
Percentages are based on the total number of patients in the cohort in the population of interest with clinical responses of clinical cure or clinical failure (N). Indeterminate clinical responses are omitted from this analysis.
Cohort 1 = Young infants, Cohort 2 = Term neonates, Cohort 3 = Preterm neonates.
CI = confidence interval; EOT = End-of-Therapy; MITT = Modified Intent-to-Treat; n = number of patients included in analysis; N = number of patients in the cohort; TOC = Test-of-Cure.

a. Confidence intervals (CIs) for rates within cohort are calculated using the Jeffreys method.

Clinical response rates by baseline pathogen were summarized for the Micro-ITT and MITT Analysis Sets. In the Micro-ITT Analysis Set, results at EOT were unchanged at TOC. The clinical response was cure for all baseline pathogens with the exception of *S. agalactiae* (1), *E. aerogenes* (1), and *E. coli* (1), all of which were assessed as indeterminate. For these 3 pathogens, each patient was discontinued from study treatment to allow for hospital discharge, resulting in a clinical outcome of indeterminate (despite improving clinically). There were no clinical failures by baseline pathogen in any analysis set.

Table 25 Clinical response, at EOT and TOC (ITT analysis set)

Timepoint	Response	Cohort 1 (N = 4)	Cohort 2 (N = 5)	Cohort 3 (N = 2)	Total (N = 11)
EOT	95% CI of Clinical Cure [a]	(12.3, 87.7)	(20.9, 90.6)	(33.3, 100)	(34.8, 86.3)
	Clinical Cure n (%)	2 (50.0)	3 (60.0)	2 (100)	7 (63.6)
	Clinical Failure n (%)	0	0	0	0
	Indeterminate n (%)	2 (50.0)	2 (40.0)	0	4 (36.4)
TOC	95% CI of Clinical Cure [a]	(12.3, 87.7)	(20.9, 90.6)	(33.3, 100)	(34.8, 86.3)
	Clinical Cure n (%)	2 (50.0)	3 (60.0)	2 (100)	7 (63.6)
	Clinical Failure n (%)	0	0	0	0
	Indeterminate n (%)	2 (50.0)	2 (40.0)	0	4 (36.4)

[a] Confidence intervals (CIs) for rates within cohort are calculated using the Jeffreys method.

Clinical response is the derived overall response. CI Confidence interval. EOT=End-of-Therapy. TOC=Test-of-Cure.

Percentages are based on the total number of patients in the cohort (N).

Cohort 1=Young infants, Cohort 2=Term neonates, Cohort 3=Preterm neonates.

Table 26 Clinical response, at EOT and TOC (Micro-ITT analysis set)

Timepoint	Response	Cohort 1 (N = 3)	Cohort 2 (N = 5)	Cohort 3 (N = 2)	Total (N = 10)
EOT	95% CI of Clinical Cure [a]	(17.7, 96.1)	(20.9, 90.6)	(33.3, 100)	(39.4, 90.7)
	Clinical Cure n (%)	2 (66.7)	3 (60.0)	2 (100)	7 (70.0)
	Clinical Failure n (%)	0	0	0	0
	Indeterminate n (%)	1 (33.3)	2 (40.0)	0	3 (30.0)
TOC	95% CI of Clinical Cure [a]	(17.7, 96.1)	(20.9, 90.6)	(33.3, 100)	(39.4, 90.7)
	Clinical Cure n (%)	2 (66.7)	3 (60.0)	2 (100)	7 (70.0)
	Clinical Failure n (%)	0	0	0	0
	Indeterminate n (%)	1 (33.3)	2 (40.0)	0	3 (30.0)

[a] Confidence intervals (CIs) for rates within cohort are calculated using the Jeffreys method.

Clinical response is the derived overall response. CI Confidence interval. EOT=End-of-Therapy. TOC=Test-of-Cure.

Percentages are based on the total number of patients in the cohort (N).

Cohort 1=Young infants, Cohort 2=Term neonates, Cohort 3=Preterm neonates.

Per-Patient Microbiological Response

Table 27 Per-patient Microbiological Response at EOT and TOC (Micro-ITT Analysis Set)

Timepoint	Response	Cohort 1 (N = 3)	Cohort 2 (N = 5)	Cohort 3 (N = 2)	Total (N = 10)
EOT	95% CI of Favorable Response[a]	(17.7, 96.1)	(20.9, 90.6)	(6.1, 93.9)	(30.4, 84.7)
	Favorable Response n (%)	2 (66.7)	3 (60.0)	1 (50.0)	6 (60.0)
	Unfavorable Response n (%)	0	1 (20.0)	1 (50.0)	2 (20.0)
	Indeterminate n (%)	1 (33.3)	1 (20.0)	0	2 (20.0)
TOC	95% CI of Favorable Response[a]	(3.9, 82.3)	(9.4, 79.1)	(33.3, 100)	(22.4, 77.6)
	Favorable Response n (%)	1 (33.3)	2 (40.0)	2 (100)	5 (50.0)
	Unfavorable Response n (%)	1 (33.3)	1 (20.0)	0	2 (20.0)
	Indeterminate n (%)	1 (33.3)	2 (40.0)	0	3 (30.0)

Percentages are based on the total number of patients in the cohort (N).
Cohort 1 = Young infants, Cohort 2 = Term neonates, Cohort 3 = Preterm neonates.
Microbiological response is the derived overall response. Favorable responses are Eradication and Presumed Eradication. Unfavorable responses are Persistence and Presumed Persistence.
CI = confidence interval; EOT = End-of-Therapy; ITT = Intent-to-Treat; N = number of patients in each age cohort and overall; n = number of patients with each response within each age cohort and overall; TOC = Test-of-Cure.
a. Confidence intervals (CIs) for rates within cohort are calculated using the Jeffreys method.

Per-patient microbiological response at EOT and TOC was categorized as favourable (eradication or presumed eradication), unfavourable (persistence or presumed persistence), or indeterminate. In the Micro-ITT Analysis Set, 5 (50%) patients had favourable response at TOC. Three (3) patients had a response of indeterminate. Each of these 3 patients was discontinued from study treatment to allow for hospital discharge, resulting in a clinical outcome of indeterminate (despite improving clinically). In the absence of follow-up culture data for these patients, the per-pathogen response was indeterminate by definition. Because the protocol did not require that post-baseline cultures be collected, it is not unexpected that patients who were improving clinically would have no follow-up culture data available. Two patients had an unfavourable response in the Micro-ITT Analysis Set. One of the patients with an unfavourable response had an *E. coli* at baseline in urine that was not susceptible to ceftaroline fosamil (MIC >32 mg/L), but no follow up urine culture was available for this patient at TOC. The other patient had and *E. coli* (urine, MIC = 0.12 mg/L, ESBL negative) that was persistent at TOC. Both of the patients with unfavourable microbiological response were clinical cures at the EOT and TOC assessments.

Per-Pathogen Microbiological Response

Table 28 Microbiological Response at TOC by Baseline Pathogen (Micro-ITT Analysis Set)

Baseline Pathogen	Response	Cohort 1 (N = 3)	Cohort 2 (N = 5)	Cohort 3 (N = 2)	Total (N = 10)
Enterobacter aerogenes	N	1	0	0	1
	Favorable Response n (%)	0	0	0	0
	Unfavorable Response n (%)	0	0	0	0
	Indeterminate n (%)	1 (100)	0	0	1 (100)
Enterococcus faecalis	N	0	1	1	2
	Favorable Response n (%)	0	1 (100)	1 (100)	2 (100)
	Unfavorable Response n (%)	0	0	0	0
	Indeterminate n (%)	0	0	0	0
Escherichia coli	N	2	3	1	6
	Favorable Response n (%)	1 (50.0)	1 (33.3)	1 (100)	3 (50.0)
	Unfavorable Response n (%)	1 (50.0)	1 (33.3)	0	2 (33.3)
	Indeterminate n (%)	0	1 (33.3)	0	1 (16.7)
Klebsiella pneumoniae	N	0	0	1	1
	Favorable Response n (%)	0	0	1 (100)	1 (100)
	Unfavorable Response n (%)	0	0	0	0
	Indeterminate n (%)	0	0	0	0
Staphylococcus aureus	N	1	1	1	3
	Favorable Response n (%)	1 (100)	1 (100)	1 (100)	3 (100)
	Unfavorable Response n (%)	0	0	0	0
	Indeterminate n (%)	0	0	0	0
Staphylococcus epidermidis	N	0	0	1	1
	Favorable Response n (%)	0	0	1 (100)	1 (100)
	Unfavorable Response n (%)	0	0	0	0
	Indeterminate n (%)	0	0	0	0
Staphylococcus hominis	N	1	0	0	1
	Favorable Response n (%)	1 (100)	0	0	1 (100)
	Unfavorable Response n (%)	0	0	0	0
	Indeterminate n (%)	0	0	0	0
Streptococcus agalactiae	N	0	1	0	1
	Favorable Response n (%)	0	0	0	0
	Unfavorable Response n (%)	0	0	0	0
	Indeterminate n (%)	0	1 (100)	0	1 (100)
Baseline Pathogen	Response	Cohort 1 (N = 3)	Cohort 2 (N = 5)	Cohort 3 (N = 2)	Total (N = 10)
Streptococcus salivarius gp	N	0	1	1	2
	Favorable Response n (%)	0	1 (100)	1 (100)	2 (100)
	Unfavorable Response n (%)	0	0	0	0
	Indeterminate n (%)	0	0	0	0

Favorable response rate is defined as the number of patients with a microbiological response at EOT divided by the number of patients with favorable + unfavorable + indeterminate.
Favorable responses are Eradication and Presumed Eradication. Unfavorable responses are Persistence and Presumed Persistence.
Percentages are based on the number of patients with each baseline pathogen within age cohort and overall.
Cohort 1 = Young infants, Cohort 2 = Term neonates, Cohort 3 = Preterm neonates.
EOT = End-of-Therapy; ITT = Intent-to-Treat; TOC = Test-of-Cure; N = number of patients in each age cohort and overall; n = number of patients with each pathogen within each age cohort and overall.

Per-pathogen microbiological response at EOT and TOC was categorized as favourable (eradication or presumed eradication), unfavourable (persistence or presumed persistence), or indeterminate. The per-pathogen microbiological response in the Micro-ITT population at TOC was favourable in all baseline pathogens or indeterminate response at TOC, with the exception of 2 *E. coli*.

The results for the MITT analysis are similar to the Micro-ITT population. All baseline pathogens had a favourable or indeterminate response at TOC, with the exception of 1 *E. coli*. Of note, the second patient with unfavourable microbiological response was not included in the MITT Analysis Set because this patient had a

baseline *E. coli* which was resistant to ceftaroline fosamil (MIC >32 mg/L).

Table 29 Per-pathogen Favorable Microbiological Response Rate at Test-of-Cure by Baseline Pathogen and Baseline Ceftaroline fosamil MIC (Micro-ITT Analysis Set)

	Number of patients with favorable response / number with baseline pathogen and MIC (%)			
Baseline Pathogen MIC (mg/L)	Cohort 1 (N = 3)	Cohort 2 (N = 5)	Cohort 3 (N = 2)	Total (N = 10)
Enterobacter aerogenes				
0.25	0/1 (0)	0	0	0/1 (0)
Enterococcus faecalis				
1	0	1/1 (100)	1/1 (100)	2/2 (100)
Escherichia coli				
0.06	1/1 (100)	1/1 (100)	0	2/2 (100)
0.12	0/1 (0)	0/1 (0)	0	0/2 (0)
16	0	0	1/1 (100)	1/1 (100)
>32	0	0/1 (0)	0	0/1 (0)
Klebsiella pneumoniae				
0.12	0	0	1/1 (100)	1/1 (100)
Baseline Pathogen MIC (mg/L)	Cohort 1 (N = 3)	Cohort 2 (N = 5)	Cohort 3 (N = 2)	Total (N = 10)
Staphylococcus aureus				
0.25	1/1 (100)	1/1 (100)	0	2/2 (100)
Staphylococcus epidermidis				
0.25	0	0	1/1 (100)	1/1 (100)
Staphylococcus hominis				
0.25	1/1 (100)	0	0	1/1 (100)
Streptococcus agalactiae				
0.015	0	0/1 (0)	0	0/1 (0)
Streptococcus salivarius group				
0.03	0	1/1 (100)	0	1/1 (100)
0.06	0	0	1/1 (100)	1/1 (100)

Cohort 1 = Young infants, Cohort 2 = Term neonates, Cohort 3 = Preterm neonates.
ITT = Intent-to-Treat; MIC = minimum inhibitory concentration; N = number of patients in each age cohort and overall.

The numbers of baseline pathogens by MIC are low, but there were high favourable responses against baseline pathogens with low MICs (≤ 1 mg/L). The per-pathogen microbiological response was indeterminate for all baseline pathogens without favourable response, with the exception of an unfavourable response for 2 *E. coli* strains with MICs = 0.12 mg/L and >32 mg/L.

CHMP noted again that, due to the much smaller size of the study than planned (24 vs 11 subjects) due to the fact that ceftaroline fosamil was given in 2 dosages – 4 mg/kg q8h (3 patients) and 6 mg/kg q8h and because not all subjects could be evaluated (out of 11 patients 4 discontinued the study prematurely leaving only 7 patients (2 in cohort 1, 3 in cohort 2 and 2 in cohort 3) fully evaluable) results are difficult to interpreted.

Ancillary analyses

Summary of main study

The following table summarises the efficacy results from the main study supporting the present application. It should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 30. Summary of Efficacy for trial D3720C00009

Title: Open-label, Multicentre Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Efficacy of Ceftaroline fosamil in Neonates and Young Infants (7 to <60 days) with Late-Onset Sepsis			
Study identifier	**D3720C00009 (C2661002)**		
Design	**Open-label, single-arm study**		
	Duration of main phase:		04 Aug 2015 (First patient first visit) 26 Dec 2017 (Last patient last visit) The study was terminated prematurely.
Hypothesis	Exploratory: To evaluate the safety and tolerability of ceftaroline fosamil for the treatment of late-onset sepsis (LOS) in neonates and young infants aged 7 to 60 days		
Treatments groups	Cohort 1: young infants (>28 days to <60 days); 4 patients Cohort 2: term neonates (gestational age ≥37 weeks; aged 7 to ≤28 days); 5 patients Cohort 3: preterm neonates (gestational age ≥34 to <37 weeks; aged 7 to ≤28 days); 2 patients		Ceftaroline fosamil IV 4 mg/kg (based on adolescents dose) or 6 mg/kg (after updating the population PK model, protocol version 3) as a 60-minute (±10 min) infusion q8h (±1 hour) 48 hours (minimum) to 14 days (maximum)+ Ampicillin IV for at least 48 hours + Aminoglycoside
Endpoints and definitions	Primary endpoint		Safety assessments (AEs, SAEs, deaths, clinical laboratory parameters, chemistry panel, and vital signs.
	Secondary endpoint		Clinical response at EOT and TOC in the ITT, MITT and Micro-ITT Analysis sets.
	Secondary endpoint		Microbiological response (per-pathogen and per-patient) at EOT and TOC in the MITT and Micro-ITT Analysis sets.
Database lock	-		
Results and Analysis			
Analysis description	Analysis		

Analysis population and time point description	Clinical response in the MITT (8) at EOT and TOC			
Descriptive statistics and estimate variability	Treatment group	Cohort 1	Cohort 2	Cohort 3
	Number of subject	4	3	1
	EOT and TOC 95% CI of Clinical cure (CIs for rates within cohort, calculated using Jeffreys method)	(12.3, 87.7)	(3.9, 82.3)	(14.7, 100)
	Clinical Cure n (%)	2 (50.0)	1 (33.3)	1 (100)
	Clinical Failure n (%)	0	0	0
	Indeterminate n (%)	2 (50.0)	2 (66.7)	0
	Microbiological response in the Micro-ITT Analysis set at EOT and TOC Analysis set			
	Microbiological response (Micro-ITT Analysis set) at EOT 95% CI of Favourable Response	(17.7, 96.1)	(20.9, 90.6)	(6.1, 93.9)
	Favourable Response n (%)	2 (66.7)	3 (60.0)	1 (50.0)
	Unfavourable Response n (%)	0	1 (20.0)	1 (50.0)

	Indeterminate n (%)	1 (33.3)	1 (20.0)	0
	Microbiological response (Micro-ITT Analysis set) at TOC 95% CI of Favourable Response	(3.9, 82.3)	(9.4, 79.1)	(33.3, 100)
	Favourable Response n (%)	1 (33.3)	2 (40.0)	2 (100.0)
	Unfavourable Response n (%)	1 (33.3)	1 (20.0)	0
	Indeterminate n (%)	1 (33.3)	2 (40.0)	0

2.4.2. Discussion on clinical efficacy

According to existing guidelines, no appropriately powered efficacy studies are requested in children from birth to less than 2 months of age, as efficacy can be extrapolated from adults and older children provided that similar exposure is achieved in this paediatric age group. The applicant conducted one study that included patients with late onset neonatal sepsis (LOS). In total 11 term and preterm neonates were included. The study population was heterogeneous and only 2 patients were born prematurely. The study was planned to enrol 24 patients (aged 28 to <60 days, term neonates with GA >37 weeks and PNA <28 days, and preterm neonates with GA 32-37 weeks and PNA <28 days). The study was stopped prematurely after it had recruited 11 subjects- 4, 5 and 2, respectively. 3 patients received ceftaroline fosamil at doses of 4 mg/kg q8h and remaining 8 patients received doses of 6 mg/kg q8h. The final dataset included 7 patients as 4 patients discontinued treatment prematurely. This very small dataset does not allow drawing any meaningful conclusion on efficacy of ceftaroline fosamil in neonates and young infants with LOS. It should be noted that LOS is not an indication proposed for this application, in which the MAH is not seeking an approval of a new indication.

Noting that there were no efficacy data generated in patients aged from birth to less than two months of age with cSSTI or CAP, CHMP agreed that, based on the similar exposure achieved, efficacy of ceftaroline in the proposed indications can be extrapolated from adults and from older paediatric age groups.

2.4.3. Conclusions on the clinical efficacy

CHMP agreed that, based on the similar exposure achieved, efficacy of ceftaroline in the proposed indications can be extrapolated from adults and from older paediatric age groups.

2.5. Clinical safety

Introduction

Ceftaroline fosamil is a cephalosporin, which has antibacterial activity against aerobic and anaerobic Gram-positive (including MRSA, VISA, methicillin resistant *coagulase negative staphylococci*, and drug resistant *Streptococcus pneumoniae*) and common Gram-negative organisms (such as *Escherichia coli* and *Klebsiella pneumoniae*, although its activity is restricted to strains that do not produce ESBL). Ceftaroline fosamil is not active against *Pseudomonas aeruginosa* and other non-fermenters. Similar to other β-lactam antibiotics, ceftaroline fosamil's bactericidal mode of action involves targeting penicillin-binding proteins to inhibit biosynthesis of the bacterial cell wall.

Important identified risks, as per Summary of safety concerns in the RMP, for ceftaroline fosamil are *Clostridium difficile*-associated diarrhoea (CDAD) and hypersensitivity/ anaphylaxis; important potential risks are bacterial resistance development, convulsions/ seizures, drug-induced liver injury (DILI), haemolytic anaemia, renal impairment (including potential drug interactions with nephrotoxic agents), and potential for off-label use.

Coombs seroconversion is a well-characterized side effect of the cephalosporin class and has been observed in higher frequency in adults and children after ceftaroline fosamil administration. The incidence was higher in adult patients who received 600 mg q8h as compared to those receiving 600 mg q12h. However, haemolytic anaemia was not observed.

Missing information, as per Summary of safety concerns in the RMP, includes immunocompromised population, lactation, paediatric population exposure, pre-existing seizure disorder, pre-existing significant hepatic disease, pregnancy exposure and efficacy in MRSA community acquired pneumonia (CAP).

Patient exposure

The summary of safety data for ceftaroline fosamil includes data from 2 studies: Study D3720C00006 (P903-21, single-dose study to evaluate the pharmacokinetic profile, safety and tolerability IV ceftaroline fosamil) and Study D3720C00009 (C2661002, multiple-dose study to assess the safety and tolerability, PK and efficacy of ceftaroline fosamil and ampicillin, plus an optional aminoglycoside in neonates and young infants with LOS).

Table 31 Duration of Ceftaroline fosamil Exposure [Safety Analysis Set, Study D3720C00009 (C2661002)

Variable	Summary Statistic	Cohort 1 (N = 4)	Cohort 2 (N = 5)	Cohort 3 (N = 2)	Total (N = 11)
Duration of exposure (days)	n	4	5	2	11
	Mean	7.8	9.0	8.5	8.5
	SD	2.87	4.90	0.71	3.53
	Minimum	6	3	8	3
	Median	6.5	11.0	8.5	8.0
	Maximum	12	15	9	15

Duration of exposure is the number of days of treatment received (end date – start date +1).
Three patients were treated with 4 mg/kg prior to protocol amendment 2 which changed the dose to 6 mg/kg.
Cohort 1 = Young infants, Cohort 2 = Term neonates, Cohort 3 = Preterm neonates.
n = number of patients included in analysis; N = number of patients in the cohort; SD = standard deviation.

Study D3720C00006 (P903-21): 53 subjects were enrolled, completed treatment, and were evaluable for PK analysis.

Table 32 Cohorts in Study P903-21

Cohort	Age group	Patients number
1	≥6 years to <12 years	10
2	≥24 months to <6 years	8
3	≥28 days to <24 months	12
4	term (gestational age ≥38 weeks) neonates <28 days	12
5	preterm (gestational age 32-37 weeks) neonates <28 days	11

Ceftaroline fosamil was to be given as a single IV infusion at the following doses:

- Cohort 1: 10 mg/kg (up to 600 mg for subjects ≥ 60 kg) as a 1-hour infusion
- Cohort 2: 15 mg/kg as a 1.5-hour infusion
- Cohort 3: ≥ 5 months: 12 mg/kg as a 1-hour infusion; < 5 months: 8 mg/kg as a 1-hour infusion
- Cohort 4 and Cohort 5: 8 mg/kg as a 1-hour infusion

Patients were administered study drug on Day 1, the EOT Visit was on Day 2, and the F/U Evaluation visit was on Day 4 (±1 day).

Fifty-two (52) subjects completed the study and 1 subject was lost to follow-up, which was considered a premature discontinuation from the study.

ITT population consisted of all enrolled subjects. Summaries of subject disposition were conducted using the ITT Population.

The Safety Population consisted of all subjects who received any amount of ceftaroline fosamil. All demographic and safety summaries were conducted using the Safety Population.

The PK Population consisted of subjects who received the entire 60-minute ceftaroline fosamil infusion on Study Day 1 and from whom any scheduled PK samples were obtained.

All 53 subjects were included in each population.

The main objective of this study was to evaluate the single-dose PK profile, safety, and tolerability of ceftaroline fosamil administered by IV infusion in children ages ranging from birth to younger than 12 years who were receiving systemic antibiotic therapy for suspected or confirmed infection. Plasma concentrations of ceftaroline fosamil, ceftaroline fosamil (prodrug), and ceftaroline fosamil M-1 (inactive metabolite) were reported. Safety outcome measures included AEs, serious adverse events (SAEs), deaths, clinical laboratory parameters (e.g., complete blood count [CBC] with differential, chemistry panel), vital signs, and pain scale parameters).

Table 33 Summary of Demographic and Baseline Characteristics by Cohort—Safety Population

Demographic Variable		Cohort 1 (N = 10)	Cohort 2 (N = 8)	Cohort 3 (N = 12)	Cohort 4 (N = 12)	Cohort 5 (N = 11)	All Subjects (N = 53)
Race, n(%)	White	5 (50.0)	4 (50.0)	7 (58.3)	5 (41.7)	8 (72.7)	29 (54.7)
	Black or African American	4 (40.0)	4 (50.0)	4 (33.3)	6 (50.0)	3 (27.3)	21 (39.6)
	American Indian or Alaska Native	0	0	1 (8.3)	0	0	1 (1.9)
	Other	1 (10.0)	0	0	1 (8.3)	0	2 (3.8)
Sex, n (%)	Male	5 (50.0)	4 (50.0)	10 (83.3)	6 (50.0)	9 (81.8)	34 (64.2)
	Female	5 (50.0)	4 (50.0)	2 (16.7)	6 (50.0)	2 (18.2)	19 (35.8)
Ethnicity, n (%)	Non-Hispanic	10 (100)	7 (87.5)	11 (91.7)	11 (91.7)	9 (81.8)	48 (90.6)
	Hispanic	0	1 (12.5)	1 (8.3)	1 (8.3)	2 (18.2)	5 (9.4)
Mean age, years[a]		8.4	3.4	-	-	-	6.2
SD (range)		2.0 (6, 11)	1.3 (2, 5)	-	-	-	3.1 (2, 11)
Mean age, days[b]		-	-	371.3	12.1	13.0	135.5
SD (range)		-	-	232.5 (72, 698)	8.5 (0, 22)	10.6 (1, 27)	217.7 (0, 698)
Mean gestational age, weeks[c]		-	-	37.8	39.2	35.2	37.4
SD (range)		-	-	4.2 (25, 40)	0.7 (38, 40)	1.8 (32, 37)	3.1 (25, 40)

Notes: Cohort 1: ≥ 6 years to < 12 years; Cohort 2: ≥ 24 months to < 6 years; Cohort 3: 28 days to < 24 months; Cohort 4: term (gestational age ≥ 38 weeks) neonates < 28 days; Cohort 5: preterm (gestational age 32 - 37 weeks) neonates < 28 days.
Abbreviations: N = number of subjects in Safety Population; n = number of subjects in specific category.
a Age in years was derived for subjects in Cohorts 1 and 2 only (n = 18).
b Age in days was derived for subjects in Cohorts 3, 4, and 5 only (n = 35).
c Gestational age was collected for subjects in Cohorts 3, 4, and 5 only (n = 35).

Thirty four male (n = 34) and nineteen female (n = 19) subjects between ages of 0 and 11 years with confirmed or suspected infections were enrolled in the study.

Table 34 Summary of Demographics and Baseline Characteristics by Cohort Substrata (Cohorts 3, 4, and 5 only)—Safety Population

Demographic Variable		Cohort 3A (N = 6)	Cohort 3B (N = 6)	Cohort 4A (N = 6)	Cohort 4B (N = 6)	Cohort 5A (N = 5)	Cohort 5B (N = 6)
Race, n(%)	White	3 (50.0)	4 (66.7)	2 (33.3)	3 (50.0)	4 (80.0)	4 (66.7)
	Black or African American	2 (33.3)	2 (33.3)	4 (66.7)	2 (33.3)	1 (20.0)	2 (33.3)
	American Indian or Alaska Native	1 (16.7)	0	0	0	0	0
	Other	0	0	0	1 (16.7)	0	0
Sex, n (%)	Male	4 (66.7)	6 (100.0)	2 (33.3)	4 (66.7)	5 (100)	4 (66.7)
	Female	2 (33.3)	0	4 (66.7)	2 (33.3)	0	2 (33.3)
Ethnicity, n (%)	Non-Hispanic	6 (100.0)	5 (83.3)	5 (83.3)	6 (100.0)	4 (80.0)	5 (83.3)
	Hispanic	0	1 (16.7)	1 (16.7)	0	1 (20.0)	1 (16.7)
Mean age, days[b]		574.0	168.5	19.7	4.5	23.2	4.5
SD (range)		99.8	101.3	1.5	4.5	4.9	3.9
		(426, 698)	(72, 337)	(18, 22)	(0, 11)	(15, 27)	(1, 9)
Mean gestational age, weeks[c]		36.7	38.8	39.2	39.2	36.4	34.2
SD (range)		5.9	1.2	0.8	0.8	0.5	1.9
		(25, 40)	(37, 40)	(38, 40)	(38, 40)	(36, 37)	(32, 37)

Notes: Cohort substrata: 3A = 12 months to < 24 months; 3B = 28 days to < 12 months; 4A = term neonates > 14 days to < 28 days; 4B = term neonates 0 to 14 days; 5A = preterm neonates > 14 days to < 28 days; -5B = preterm neonates 0 to 14 days. Percentages calculated as 100 × (n/N). Age = date of informed consent - date of birth, and reported in years or days, dependent on cohort.
Abbreviations: N = number of subjects in Safety Population; n = number of subjects in specific category.
a Age in years was derived for subjects in Cohorts 1 and 2 only (n = 18).
b Age in days was derived for subjects in Cohorts 3, 4, and 5 only (n = 35).
c Gestational age was collected for subjects in Cohorts 3, 4, and 5 only (n = 35).

CHMP noted that study D3720C00006 (P903-21) was a single dose PK study that also included patients appropriate for this application. From the data initially presented by the MAH it was unclear how many patients were at age 0 to <2 months and CHMP asked for a clarification during the assessment. The MAH clarified that a total of 34 infants aged <60 days received ceftaroline fosamil as study treatment and were evaluated for safety (4 infants aged >28 to<60, 17 infants term, aged <28, 13 infants preterm, aged <28 days). Of 34 infnants, 11 received multiple doses of ceftaroline fosamil and 23 received a single dose.

Though the number of patients aged <60 days was small, the incidence of TEAE in SOC Blood and lymphatic systems disorders, Hepatobiliary disorders and Investigations was numerically higher in infants <60 days compared to older age groups. 6 patients (5 [9.4%] in P903-21 and 1 [9.1%] in D3720C00009) had 8 PCS laboratory abnormalities which were all assessed by the Investigator as unrelated to study treatment.

In multidose study D3720C00009 with 11 patients there was only 1 serious AE (Salmonellosis), which started 21 days after last dose of ceftaroline and was assessed as unrelated to study treatment by the Investigator.

CHMP agreed that based on the additional information, there were no additional specific safety concerns.

Study D3720C00009 (C2661002): The study was to be conducted in approximately 30 centres worldwide. At least 24 patients with late-onset sepsis (LOS) were to be enrolled and treated within 3 age cohorts of 8 patients each. 11 patients were enrolled in the study and received study treatment with ceftaroline fosamil.

Cohort 1: young infants aged >28 days to <60 days (4 patients)

Cohort 2: term neonates (defined as gestational age ≥37 weeks) aged 7 to ≤28 days (5 patients)

Cohort 3: preterm neonates (defined as gestational age ≥34 to <37 weeks) aged 7 to ≤28 days (2 patients)

Patients received a combination of IV ceftaroline fosamil and ampicillin, plus an optional aminoglycoside of choice as empiric therapy for LOS. The total duration of ceftaroline fosamil treatment was 48 hours (minimum) to 14 days (maximum). Hospitalization was required during IV study treatment. Patients

received ceftaroline fosamil 6 mg/kg as a 60-minute (±10 min) infusion q8h (±1 hour). Patients treated prior to protocol amendment 2 were dosed with ceftaroline fosamil 4 mg/kg as a 60 minute (±10 min) infusion every 8 hours (q8h) (±1 hour).

If the presence of an organism that required treatment with ampicillin could not be excluded, the use of IV ampicillin for the first 48 hours was mandatory. If the results of additional microbiology, PCR or other investigations indicated that ampicillin during the first 48 hours of treatment was not required, then its use was at the discretion of the Investigator. The use of an aminoglycoside was considered optional from Baseline through the entire study and could be started and stopped at the discretion of the Investigator.

Patients participated in the study for up to 49 days. The Safety Follow up (**SFU**) visit occurred 21 to 35 days after the last dose of study treatment.

All enrolled patients completed the study. The 4 (36.4%) patients who were discontinued from study treatment had improved to the extent that a switch to other standard of care oral/IV antibacterial therapy was made so that discharge from the hospital was possible.

Evaluating the safety and tolerability of ceftaroline fosamil for the treatment of LOS in neonates and young infants aged 7 to <60 days was a primary objective, and all safety analyses were performed on the Safety Analysis Set. Outcome measures included AEs, serious adverse events (SAEs), deaths, clinical laboratory parameters (eg, complete blood count [CBC] with differential, chemistry panel), and vital signs.

An external Data and Safety Monitoring Board (DSMB) was used in this study to monitor the safety of the study at periodic intervals. DSMB members were familiar with AEs and SAEs likely to occur in this patient population, based on experience in adults and children older than 2 months of age, as well as with this class of drugs (cephalosporins). During the study, the DSMB conducted pre-planned reviews of accumulated data. Over the course of the study, the only recommendation from the DSMB was to continue the study without modification.

As per the protocol, the duration of ceftaroline fosamil therapy was 48 hours (minimum) up to 14 days (maximum). Across all patients in the Safety Analysis Set, the mean duration of ceftaroline fosamil exposure was 8.5 ±3.53 days (median 8.0 days, range 3-15 days). Mean duration of exposure in the individual cohorts was similar.

Nine (9) of the 11 patients in the study received ampicillin and the mean duration of exposure was 4.8 ±2.86 days (median 3.0, range 2-11 days). Patients in Cohort 1 had the shortest mean exposure (3.0 ±0.0 days), while mean exposure in Cohorts 2 (6.0 ±3.74 days) and 3 (5.0 ±2.83 days) was similar.

The use of an aminoglycoside was optional from Baseline through the entire study. Six (6) patients received aminoglycoside and the mean duration of exposure was 7.7 ±3.78 days (median 7.5, range 3-12 days). Brulamycin, gentamicin, and tobramycin were the aminoglycosides administered to 2 patients each.

Please refer to the Table 4.4.2-10 (p 48) for demographic characteristics of ITT analysis set.

Across all patients, the mean age was 30.3 ±14.8 days (median 24.0, range 12-53 days).

Gender across all cohorts was nearly evenly divided, with 5 (45.5%) females and 6 (54.5%) males, although the distribution varied by cohort. Ten (10, 90.9%) patients were White (1 [9.1%] Hispanic or Latino), and 1 (9.1%) patient was Asian.

The length and weight of the patients in the ITT Analysis Set were as expected for infants in these age groups.

Baseline Medical and Surgical History

The most frequently reported medical history terms were anaemia and pyrexia, both reported for 3 (27.3%) patients, followed by pyelonephritis, irritability, respiratory distress, and caesarean section, all reported for

2 (18.2%) patients.

Relevant surgical history was only recorded for 1 patient (Cohort 1) who had a thoracostomy prior to study entry.

Serious adverse event / deaths / other significant events

Study D3720C00006 (P903-21)

AEs that occurred from the signing of the informed consent form through the F/U Evaluation were collected. All unresolved AEs and SAEs, and any spontaneously reported up through 14 days (Study Day 15) after ceftaroline fosamil administration, were followed by the study staff for resolution or stabilization.

Safety evaluations were conducted in the Safety Population (all patients who received any amount of ceftaroline fosamil). The incidence of treatment-emergent AEs (TEAEs) was presented by system organ class (SOC) and preferred term (PT) according to the MedDRA®, version 15.1, relationship to ceftaroline fosamil, and severity. Descriptive statistics of clinical laboratory results and the change from baseline were presented as well as a summary of potentially clinically significant (PCS) laboratory abnormalities.

This was an exploratory study and was therefore not powered for inferential statistical analyses.

Common AEs

Table 35 Incidence of Treatment-Emergent AEs by Cohort, System Organ Class, and Preferred Term—Safety Population

System Organ Class Preferred Term	Number (%) of Patients Cohort 1 (N = 10)	Cohort 2 (N = 8)	Cohort 3 (N = 12)	Cohort 4 (N = 12)	Cohort 5 (N = 11)	All Subjects[a] (N = 53)
Subject with at least 1 TEAE, n (%)	**3 (30)**	**0**	**7 (58.3)**	**7 (58.3)**	**6 (54.5)**	**23 (43.4)**
Investigations	**0**	**0**	**1 (8.3)**	**4 (33.3)**	**1 (9.1)**	**6 (11.3)**
ALT increased	0	0	0	2 (16.7)	0	2 (3.8)
AST increased	0	0	0	2 (16.7)	0	2 (3.8)
Blood CPK increased	0	0	0	2 (16.7)	0	2 (3.8)
Blood LDH increased	0	0	0	2 (16.7)	0	2 (3.8)
PT prolonged	0	0	0	2 (16.7)	0	2 (3.8)
aPTT prolonged	0	0	0	1 (8.3)	0	1 (1.9)
Blood phosphorus increased	0	0	0	0	1 (9.1)	1 (1.9)
GGT increased	0	0	1 (8.3)	0	0	1 (1.9)
INR increased	0	0	0	1 (8.3)	0	1 (1.9)
Neutrophil count decreased	0	0	0	0	1 (9.1)	1 (1.9)
General disorders and administration site conditions	**2 (20.0)**	**0**	**2 (16.7)**	**0**	**0**	**4 (7.5)**
Device occlusion	0	0	1 (8.3)	0	0	1 (1.9)
Infusion site pain	1 (10.0)	0	0	0	0	1 (1.9)
Pain	1 (10.0)	0	0	0	0	1 (1.9)
Pyrexia	0	0	1 (8.3)	0	0	1 (1.9)
Blood and lymphatic system disorders	**0**	**0**	**0**	**2 (16.7)**	**1 (9.1)**	**3 (5.7)**
Anemia	0	0	0	1 (8.3)	0	1 (1.9)
Anemia neonatal	0	0	0	0	1 (9.1)	1 (1.9)
Coagulopathy	0	0	0	1 (8.3)	0	1 (1.9)
Injury, poisoning and procedural complications	**0**	**0**	**2 (16.7)**	**1 (8.3)**	**0**	**3 (5.7)**
Excoriation	0	0	0	1 (8.3)	0	1 (1.9)
Overdose	0	0	1 (8.3)	0	0	1 (1.9)
Procedural pain	0	0	1 (8.3)	0	0	1 (1.9)
Respiratory, thoracic and mediastinal disorders	**0**	**0**	**1 (8.3)**	**0**	**2 (18.2)**	**3 (5.7)**
Atelectasis	0	0	0	0	1 (9.1)	1 (1.9)
Respiratory acidosis	0	0	0	0	1 (9.1)	1 (1.9)
Tachypnea	0	0	1 (8.3)	0	0	1 (1.9)
Gastrointestinal system disorders	**1 (10.0)**	**0**	**1 (8.3)**	**0**	**0**	**2 (3.8)**
Abdominal pain	1 (10.0)	0	0	0	0	1 (1.9)
Diarrhea	0	0	1 (8.3)	0	0	1 (1.9)
Nausea	1 (10.0)	0	0	0	0	1 (1.9)
Perianal erythema	0	0	1 (8.3)	0	0	1 (1.9)
Hepatobiliary disorders	**0**	**0**	**0**	**1 (8.3)**	**1 (9.1)**	**2 (3.8)**
Hyperbilirubinemia	0	0	0	1 (8.3)	1 (9.1)	2 (3.8)
Infections and infestations	**0**	**0**	**1 (8.3)**	**0**	**1 (9.1)**	**2 (3.8)**
Bronchiolitis	0	0	1 (8.3)	0	0	1 (1.9)
Candidiasis	0	0	0	0	1 (9.1)	1 (1.9)
Metabolism and nutrition disorders	**0**	**0**	**1 (8.3)**	**1 (8.3)**	**0**	**2 (3.8)**
Alkalosis hypochloremic	0	0	1 (8.3)	0	0	1 (1.9)
Hypoalbuminemia	0	0	0	1 (8.3)	0	1 (1.9)
Skin and subcutaneous tissue disorders	**1 (10.0)**	**0**	**0**	**1 (8.3)**	**0**	**2 (3.8)**
Dry Skin	0	0	0	1 (8.3)	0	1 (1.9)
Rash	1 (10.0)	0	0	0	0	1 (1.9)
Congenital, familial and genetic disorders	**0**	**0**	**1 (8.3)**	**0**	**0**	**1 (1.9)**
Coarctation of the aorta	0	0	1 (8.3)	0	0	1 (1.9)
Nervous system disorders	**0**	**0**	**1 (8.3)**	**0**	**0**	**1 (1.9)**
Tremor	0	0	1 (8.3)	0	0	1 (1.9)

Notes: MedDRA version 15.1 was used to code adverse events. Cohorts: 1 = children ages ≥ 6 years to < 12 years; 2 = children ages ≥ 24 months to < 6 years; 3 = infants and toddlers ages ≥ 28 days to < 24 months; 4 = term neonates ages < 28 days; 5 = preterm (defined as gestational age 32 - 37 weeks) neonates ages < 28 days. Subjects reporting a particular adverse event (preferred term) more than once were counted only once by preferred term and System Organ Class. Percentages were calculated as 100 × (n/N).
Abbreviations: ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; CPK = creatine phosphokinase; GGT = gamma-glutamyltransferase; INR = international normalized ratio; LDH = lactate dehydrogenase; N = number of subjects in the Safety Population; n = number of subjects in the specific category; PT = prothrombin time.
[a] All Subjects = subjects pooled across all age cohorts.

A total of 44 AEs were reported in 23 (43.4%) patients. The most common TEAEs overall were ALT increased, AST increased, blood creatine phosphokinase (CPK) increased, blood lactate dehydrogenase (LDH) increased, and prothrombin time prolonged (2 subjects each).

Most TEAEs were mild (56.8%) or moderate (31.8%) in severity, and only 5 (11.4%) TEAEs were

determined to be severe in intensity by the Investigator. Out of the 44 AEs, 4 (9.1%) events were considered to be related to treatment by the Investigator.

There were no deaths among patients who participated in this study.

Other Serious Adverse Events

Three (3) SAEs were reported in 3 (5.7%) subjects in the study (Subject 01121005, Cohort 1: rash; Subject 02021003, Cohort 3: tremor; Subject 01021004, Cohort 5: anaemia neonatal). All SAEs were resolved and did not result in discontinuation from the study. Subject 02021003 (Cohort 3) was a 20-month-old white male, out of the range of age of interest for the current procedure.

Subject 01021004 (Cohort 5) was a 9-day-old white Hispanic female of a gestational age of 36 weeks who experienced a mild SAE of anaemia neonatal (ie, anaemia of prematurity) on Study Day 2 (1 day after study infusion). Medical history included anaemia, bilateral Grade 1 hydronephrosis, hypoalbuminemia, hypovolemia, and status post gastroschisis closure. She was treated with ampicillin and gentamicin for suspected neonatal sepsis. She was treated with packed RBCs for the anaemia. On Study Day 2, her haematocrit and haemoglobin levels dropped and she received another treatment with packed RBCs. This was considered clinically significant, and per the Investigator, the study required blood draws that may have contributed to the decrease. The event was not considered study drug related. To prevent additional blood loss, no additional haematology testing was ordered at that time; however, on Study Day 13, her haemoglobin and haematocrit levels decreased again. The subject continued to receive additional packed RBCs during the following month. The subject recovered from the SAE of anaemia neonatal on Study Day 47.

Adverse Events Related to Study Drug

Out of the 44 AEs, 4 (9.1%) events were considered to be related to treatment by the Investigator (Subject 01121005, Cohort 1: infusion site pain; Subject 01521001, Cohort 1: abdominal pain, nausea; Subject 01721003, Cohort 5: neutrophil count decreased).

Neutrophil count decrease in Subject 01721003 in Cohort 5 (preterm (gestational age 32-37 weeks) neonates <28 days)) was considered treatment related by the Investigator. The patient was 7 days old male, Neutrophils Absolute Cell Count 2.83x109/L (25%). Subject 01721003 in Cohort 5 had an unusually high ceftaroline fosamil concentration in the plasma sample taken 3 to 4 hours after the end of infusion.

There were no AEs leading to discontinuation of study treatment.

Study D3720C00006 (P903-21) was a single dose study – no dose reductions due to AEs.

CHMP noted that all the reported AEs related to study drug are listed ADRs: Infusion site pain, abdominal pain and nausea are common ADRs and Neutropenia is uncommon ADR. The data from Study D3720C00006 (P903-21) correspond to the known safety profile of ceftaroline fosamil.

Study D3720C00009 (C2661002)

AEs were reviewed at Baseline, throughout the treatment period, and at EOT, TOC, and SFU.

Safety evaluations were conducted in the Safety Analysis Set (patients who received any amount of ceftaroline fosamil). The number and percentage of patients with AEs occurring after the start of administration of the first dose of study therapy, including AEs that started prior to treatment and worsened on treatment, up to the SFU visit are summarized for the Safety Analysis Set. Descriptive statistics (including n, mean, SD, minimum, median, and maximum) of observed results (eg, laboratory data and vital signs) and change from baseline were presented for continuous results by age cohort and overall for the Safety Analysis Set. The study was not powered for inferential statistical analysis and was intended to provide descriptive statistics only.

Common AEs

Table 36 Treatment-Emergent AEs, by System Organ Class and Preferred Term (Safety Analysis Set)

System Organ Class Preferred Term	Number (%) of Patients[a] Cohort 1 (N = 4)	Cohort 2 (N = 5)	Cohort 3 (N = 2)	Total (N = 11)
Patients with any AE	**1 (25.0)**	**3 (60.0)**	**1 (50.0)**	**5 (45.5)**
Infections and infestations	**0**	**1 (20.0)**	**1 (50.0)**	**2 (18.2)**
Oral candidiasis	0	1 (20.0)	0	1 (9.1)
Otitis externa	0	0	1 (50.0)	1 (9.1)
Rhinitis	0	0	1 (50.0)	1 (9.1)
Salmonellosis	0	0	1 (50.0)	1 (9.1)
Blood and lymphatic system disorders	**0**	**0**	**1 (50.0)**	**1 (9.1)**
Anaemia	0	0	1 (50.0)	1 (9.1)
Nervous system disorders	**0**	**1 (20.0)**	**0**	**1 (9.1)**
Cerebral cyst	0	1 (20.0)	0	1 (9.1)
Gastrointestinal disorders	**1 (25.0)**	**1 (20.0)**	**0**	**2 (18.2)**
Diarrhoea	1 (25.0)	1 (20.0)	0	2 (18.2)
Skin and subcutaneous tissue disorders	**0**	**1 (20.0)**	**0**	**1 (9.1)**
Dermatitis	0	1 (20.0)	0	1 (9.1)
Renal and urinary disorders	**1 (25.0)**	**0**	**0**	**1 (9.1)**
Pyelocaliectasis	1 (25.0)	0	0	1 (9.1)

A patient can have 1 or more PTs reported under a given SOC. Includes AEs with an onset date between the date of first dose and Safety Follow-up assessment.
MedDRA version 20.0 applied.
Percentages are based on the total number of patients in the cohort (N).
Cohort 1 = Young infants, Cohort 2 = Term neonates, Cohort 3 = Preterm neonates.
AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients in each age cohort and overall; PT = preferred term; SAE = serious adverse event; SOC = system organ class.
a. Number (%) of patients with AEs, sorted by SOC in international order and by PT in decreasing order of frequency in the total column.

A total of 10 AEs were reported in 5 (45.5%) patients. Diarrhoea was reported for 2 patients, while all other reported AEs were reported for 1 patient each. Of the 10 AEs reported, all except 1 were mild in severity. One severe AE, salmonellosis, was experienced by a patient in Cohort 3; this was an SAE.

Out of the 10 AEs, only 1 event, diarrhoea, was assessed by the Investigator as related to study treatment. This event of diarrhoea was mild in severity and was resolved. No action was taken in regards to the study treatment.

There were no deaths among patients who participated in this study.

CHMP noted that diarrhoea is one of the most common ADR of ceftaroline fosamil. Out of the 10 AEs, only 1 event, diarrhoea, was assessed by the Investigator as related to study treatment. The numbers are very small and thus not conclusive.

Still TEAE were more common in cohort 4 and cohort 5 as compared to cohort 1 and cohort 2 in study P903-21. The reasons for that were not entirely elucidated.

In a multiple dose study almost a half of patients (45.5%) had TEAE; the rate is very similar with older children who received ceftaroline fosamil for treatment of cSSTI (48%) (The Pediatric Infectious Disease Journal: August 2016 - Volume 35 - Issue 8 - p e239–e247).

Other Serious Adverse Events

One SAE, salmonellosis, was reported for 1 (9.1%) patient in Cohort 3.

The SAE started on Day 29 (21 days after last dose of ceftaroline fosamil), was severe, resolved and was considered unrelated to study treatment. This AE does not raise any additional safety issues related to ceftaroline fosamil treatment.

Adverse Events Related to Study Drug

The single AE deemed related to study drug, diarrhoea, is a recognized side-effect of ceftaroline fosamil treatment and is listed in the prescribing information as occurring in ≥3% of patients treated with ceftaroline fosamil. This AE does not raise any additional safety issues related to ceftaroline fosamil treatment.

There were no AEs leading to discontinuation of study treatment.

There were no AEs leading to dose reduction or temporary discontinuation of study treatment.

CHMP agreed that, according to the results of this very small study, the safety profile of ceftaroline fosamil remains unchanged.

Laboratory findings

As per the protocols for both Study D3720C00006 (P903-21) and Study D3720C00009 (C2661002), haematology, chemistry, and urinalysis were collected at Baseline and EOT; additional samples were collected as clinically indicated. Given the limited time points when laboratory assessments were required by the protocol, the ability to make conclusions related to laboratory results is limited.

Study D3720C00006 (P903-21)

For each of the clinical laboratory parameters, mean changes from Baseline were small and considered not clinically meaningful.

In amendment 2 (12 Jul 2011) of the study was removed references to Coombs tests (except from the Summary of Known and Potential Risks Section of the protocol), as these tests were not required; added the instruction to perform a workup for haemolytic anaemia per standard of care should a subject's haemoglobin or haematocrit decrease significantly (in the Investigator's judgment) after administration of ceftaroline fosamil; and added haemolytic anaemia to the nonexclusive list of categories of safety data to be monitored.

Cephalosporins are known to be associated with positive direct Coombs test results. Although rates of seroconversion from a negative to a positive direct Coombs test in the pooled data from Phase 3 cSSSI and CAP studies were higher in the ceftaroline fosamil group compared with the comparator groups (10.7% vs 4.4%, respectively) this was within the expected range of Coombs seroconversion associated with cephalosporins, and no subject was identified with clinical findings or laboratory results that were consistent with haemolytic anaemia.

For each of the clinical laboratory parameters shifts (from Baseline to EOT relative to individual normal ranges in haematology, blood chemistry, and coagulation parameters) were infrequent and consistent with the underlying infection of each subject.

Table 37 Number of Treatment-Emergent Adverse Events in ≥ 2 Subjects by Cohort, Frequency, and Severity—Safety Population

AE Preferred Term	Cohort 1 (N = 10)			Cohort 2 (N = 8)			Cohort 3 (N = 12)			Cohort 4 (N = 12)			Cohort 5 (N = 11)			All Subjects[b] (N = 53)		
	Mild	Mod	Sev	Mild	Mod	Sev	Mild	Mod	Sev	Mild	Mod	Sev	Mild	Mod	Sev	Mild	Mod	Sev
Overall n (%) (subjects with at least 1 TEAE)	3 (30)			0			7 (58.3)			7 (58.3)			6 (54.5)			23 (43.4)		
	1 (10.0)	2 (20.0)	0	0	0	0	5 (41.7)	2 (16.7)	0	4 (33.3)	1 (8.3)	2 (16.7)	5 (45.5)	1 (9.1)	0	15 (28.3)	6 (11.3)	2 (3.8)
Total Number of TEAEs	6			0			12			18			8			44		
	4 (66.7)	2 (33.3)	0	0	0	0	9 (75)	3 (25)	0	5 (27.8)	8 (44.4)	5 (27.8)	7 (87.5)	1 (12.5)	0	25 (56.8)	14 (31.8)	5 (11.4)
ALT increased	0			0			0			2 (16.7)			0			2 (3.8)		
	0	0	0	0	0	0	0	0	0	0	1 (8.3)	1 (8.3)	0	0	0	0	1 (1.9)	1 (1.9)
AST increased	0			0			0			2 (16.7)			0			2 (3.8)		
	0	0	0	0	0	0	0	0	0	0	1 (8.3)	1 (8.3)	0	0	0	0	1 (1.9)	1 (1.9)
Blood CPK increased	0			0			0			2 (16.7)			0			2 (3.8)		
	0	0	0	0	0	0	0	0	0	1 (8.3)	0	1 (8.3)	0	0	0	1 (1.9)	0	1 (1.9)
Blood LDH increased	0			0			0			2 (16.7)			0			2 (3.8)		
	0	0	0	0	0	0	0	0	0	0	0	2 (16.7)	0	0	0	0	0	2 (3.8)
Hyperbilirubinemia	0			0			0			1 (8.3)			1 (9.1)			2 (3.8)		
	0	0	0	0	0	0	0	0	0	0	1 (8.3)	0	0	1 (9.1)	0	0	2 (3.8)	0
Prothrombin time prolonged	0			0			0			2 (16.7)			0			2 (3.8)		
	0	0	0	0	0	0	0	0	0	0	2 (16.7)	0	0	0	0	0	2 (3.8)	0

Notes: MedDRA version 15.1 was used to code adverse events. Cohort 1: ≥ 6 years to < 12 years; Cohort 2: ≥ 24 months to < 6 years; Cohort 3: 28 days to < 24 months; Cohort 4: term (gestational age ≥ 38 weeks) neonates < 28 days; Cohort 5: preterm (gestational age 32 - 37 weeks) neonates < 28 days. Subjects reporting a particular adverse event (preferred term) more than once were counted only once by preferred term and System Organ Class, and at the highest severity. Percentages were calculated as 100 × (n/N).

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CPK = creatine phosphokinase; LDH = lactate dehydrogenase; Mod = moderate; N = number of subjects in the Safety Population; n = number of subjects in the specific category; Sev = severe; TEAE = treatment-emergent adverse event.

a Overall TEAE values are provided but only TEAEs occurring in > 1 subject are listed.

b All Subjects = subjects pooled across all age cohorts.

Individual Clinically Significant Laboratory Abnormalities

The incidence of potentially clinically significant (PCS) laboratory abnormalities was generally low. Five (9.4%) subjects (Cohorts 4 and 5) had 7 PCS laboratory abnormalities. All PCS laboratory abnormalities that were reported as AEs were considered not related to study drug by the Investigator.

Subject 01121013 (Cohort 4) had ALT and AST elevations at EOT/Study Day 2 that met PCS criteria. The subject's baseline AST value was high, but did not meet PCS criteria. In addition, the subject had AEs of severe blood LDH increased, moderate coagulopathy (elevated INR), and moderate prothrombin time prolonged, all at EOT/Study Day 2. All AEs were considered not related to study drug by the Investigator and with the exception of blood LDH increased, all were resolved.

Subject 01121015 (Cohort 4) had AST and CPK elevations at EOT/Study Day 2 that met PCS criteria. These abnormalities were reported as severe AEs on Study Day 2. In addition, the subject had severe AEs of ALT increased and blood LDH increased, both reported on Study Day 2. All AEs were considered not related to study drug by the Investigator and were ongoing at the time of study completion.

Subject 02221006 (Cohort 4) had a high absolute neutrophil count at baseline, he had decrease in absolute neutrophil count at EOT/Study Day 2 that met PCS criteria. Other laboratory abnormalities included high absolute basophil count at Baseline, high absolute eosinophil count at EOT, low absolute lymphocyte count at EOT, high absolute monocyte count at Baseline and EOT, low blood LDH at Baseline and EOT, high phosphorus at EOT, and high total bilirubin at Baseline and EOT. Medical history included ongoing meningitis, sepsis, neutrophilia, and hyperbilirubinemia; and resolved respiratory distress. He was treated with ampicillin, gentamicin, and penicillin for the infections. No AEs were reported for this subject.

Subject 01021003 (Cohort 5) had decreased haematocrit at Baseline/Study Day 1 and EOT/Study Day 2. The subject also had 2 separate AEs of respiratory acidosis, both at EOT/Study Day 2, which were considered to be mild and not related to the study drug by the Investigator and were resolved. A decrease in RBC count from Baseline met PCS criteria at EOT. Because the child was anaemic prior to study entry, this was not reported as an AE by the Investigator.

Subject 01521006 (Cohort 5) had a decrease in percent neutrophils at EOT/Study Day 2 that met PCS

criteria. However, the subject was neutropenic at Baseline. A mild AE of candidiasis was also reported at EOT. The AE was considered not related to the study drug by the Investigator and was ongoing at the time of study completion.

Elevated post-baseline chemistry values for ALT, AST, total bilirubin, and laboratory criteria for potential Hy's law were assessed by cohort. Elevated liver chemistry values were reported in 3 subjects (ALT, 1 subject; AST, 2 subjects; total bilirubin, 1 subject) were reported in Cohort 4. After clinical review, no subjects met potential Hy's law criteria.

CHMP noted that increased transaminases are known ADRs in Hepatobiliary disorders SOC with frequency of common for ceftaroline fosamil. This study was SD study and included patients of age up to 12 years. During the assessment the MAH also provided some data for the age group of interest (less than 60 days), which did not lead to additional safety concerns. CHMP also noted that, similar to other TEAE they were more common in cohort 4 and 5 as compared to cohort 1 and cohort 2 – 60% of TEAE occurred in 2 former cohort while only 43% of patients were included to those two cohorts.

Study D3720C00009 (C2661002)

There were 5 patients with changes in chemistry values and 7 patients with changes in hematology values. None of these changes were considered by the Investigator to be clinically significant and no AE was reported. There were no changes in laboratory values for any patient between Baseline and the laboratory tests done at SFU.

Individual Clinically Significant Laboratory Abnormalities

A single laboratory value considered to be potentially clinically significant was reported during the study. The hematocrit (ratio) value for 1 patient in Cohort 3 (Male, aged 19 days) at TOC (Day 19) had dropped to 0.237 from a Baseline (Day -2) value of 0.360.

An AE of anaemia was reported, mild in severity, and considered unrelated to study treatment. On Day 47, hematocrit (ratio) had increased to 0.271. The outcome of the AE was reported as recovering/resolving. The anaemia was mild in severity, but there is no information available about the Coombs test. Generally anaemia is a listed ADR for Ceftaroline fosamil, but in this case it was considered unrelated to the study drug.

Vital Signs, Physical Findings, and Other Observations Related to Safety

Study D3720C00006 (P903-21)

Patients' vital signs were monitored throughout the study.

Vital signs and pain scale assessments were similar at end of therapy (EOT) in comparison to baseline.

Table 38. Mean Vital Sign Values at Baseline and EOT and Change at EOT from Baseline—Safety Population

Parameter	*Time Point*	*Cohort 1*	*Cohort 2*	*Cohort 3*	*Cohort 4*	*Cohort 5*
Systolic BP, mmHg	BL	106.0	105.3	105.9	84.17	73.73
	EOT	108.1	102.9	102.3	82.0	74.18
	Change	2.1	-2.38	-3.67	-2.17	0.45
Diastolic BP, mmHg	BL	63.1	55.88	58.08	49.92	42.18
	EOT	58.8	58.88	59.08	49.17	44.27
	Change	-4.3	3.0	1.0	-0.75	2.09
Pulse rate, bpm	BL	95.3	112.1	128.9	154.4	153.0
	EOT	86.6	106.5	121.2	147.2	152.0
	Change	-8.7	-5.63	-7.75	-7.25	-1.0
Temperature, °C	BL	36.62	37.15	36.74	37.06	36.65
	EOT	36.80	36.59	37.15	37.35	36.75
	Change	0.18	-0.56	0.41	0.29	0.11
Respiratory rate, breaths per minute	BL	22.80	31.50	32.08	43.58	56.00
	EOT	20.80	29.50	35.92	41.33	49.45
	Change	-2.0	-2.0	3.83	-2.25	-6.55

Notes: Cohort 1: ≥ 6 years to < 12 years; Cohort 2: ≥ 24 months to < 6 years; Cohort 3: 28 days to < 24 months; Cohort 4: term (gestational age ≥ 38 weeks) neonates < 28 days; Cohort 5: preterm (gestational age 32 - 37 weeks) neonates < 28 days.

Abbreviations: BL = baseline; BP = blood pressure; bpm = beats per minute; EOT = end of therapy.

Slight improvements in pain scale evaluations at EOT were noted in all cohorts. These improvements were most likely related to the overall improvement of the underlying infection.

No other clinically significant safety observations were noted.

Study D3720C00009 (C2661002)

Patients' vital signs were monitored throughout the study.

In regards to physical exam, only a single clinically significant change from Baseline was noted: dermatitis was reported as an AE, mild in severity, onset Day 5, resolved.

No other clinically significant safety observations were noted.

CHMP agreed that the safety profile of ceftaroline fosamil remained unchanged based on the data from studies D3720C00009 (C2661002) and D3720C00006 (P903-21). It was noted that the use of ceftaroline fosamil in paediatric population aged <2 mo is very limited, but the safety profile in children was similar to that observed in the adult population.

Discontinuation due to adverse events

In the study D3720C00006 (P903-21) 52 subjects completed the study and 1 subject was lost to follow-up and considered as a premature discontinuation from the study. There were no premature discontinuations due to an AE.

There were neither deaths nor AEs leading to discontinuation of study treatment in the study D3720C00009 (C2661002). The 4 (36.4%) patients who were discontinued from study treatment had improved to the extent that discharge from the hospital was desired.

Post marketing experience

Forest Laboratories received US NDA approval from the FDA on 29 October 2010 under the brand name TEFLARO, which was the first approval worldwide. TEFLARO was launched in the US on 03 January 2011.

The exposure tables are based on the number of vials sold available from January 2011 to June 2018.

The European Commission granted marketing approval (Centralised Procedure) for ceftaroline fosamil on 23 August 2012 under the brand name ZINFORO. Ceftaroline fosamil has been approved in 69 countries worldwide under the brand name ZINFORO.

The exposure tables are based on the number of vials sold from post-approval date 23 August 2012 to June 2018.

It is estimated that approximately 615,450 patients, equivalent to 12,260 patient-years, were exposed to ceftaroline fosamil worldwide since the product was first approved. The estimated patient exposure is based on worldwide sales of 8,616,304 vials containing 600 mg of ceftaroline fosamil and on the assumption that the average dose and duration of ceftaroline fosamil treatment is 600 mg every 12 hours for 7 days (equals fourteen 600 mg vials) in adults with normal renal function across all approved indications.

Table 39. Cumulative Estimated Exposure by Region

	US[a b]	EU	Latin America	ROW
Vials sold	7,697,884	267,800	223,410	427,210
Estimated exposure (patient-years)	11,002[b]	249[c]	192[c]	538[c]

a. Exposure (person-years) - Calculated for number of vials sold: Number of vials sold/1.917/365 person-years
b. US calculation: a factor of 1.917 for patient - years was used
c. EU, Latin America and ROW calculation: (Number of vials sold/14 vials)/52.14 weeks in a year.

Table 40. Cumulative Estimated Exposure by Indication, Gender and Age Group

	Indication		Sex		Age (years)			
	CAP	cSSTI	M	F	≤17	18-64	65-74	≥75
Vials sold	1,580,222	6,117,662	4,428,146	3,269,732	18,824	4,635,856	1,759,779	1,283,421
Estimated exposure (patient-years)[b c]	2,258	8,743	6,329	4,673	27	6,625	2,515	1,834

a. Information available from US data only. Source: Forest Laboratories (an Allergan affiliate) (licensing partner) – IQVIA (formerly IMS Health Incorporated).
b. Exposure (patient-years) - Calculated for number of vials sold: Number of vials sold/1.917/365 patient-years
c. US calculation: a factor of 1.917 for patient-years was used
CAP = community acquired pneumonia; cSSTI = complicated skin and soft tissue infection.

AEs in Post-Marketing Experience

A cumulative search of post marketing paediatric AE reports was conducted through 30 June 2018.

Thirty-six (36) events included in 19 individual case safety reports (ICSR) were identified, of which one (1) originated in a European Union Member state (France) and the remaining 18 concern patients in the US (11), Argentina (2), Australia (2), Malaysia, Mexico and South Africa (1 each).

The ICSRs concerned 2 children 4 to 9 years old and 15 paediatric patients 10 to 17 years old. Age was not provided in 2 ICSRs.

The most frequently reported PTs (≥2) were Off label use (5), Product use issue (3), Neutropenia (2), Drug ineffective (2), Drug administered to patient of inappropriate age (2), Product use in unapproved indication (2) and Rash (2).

Table 41. MedDRA Preferred Terms Reported in Cases Indicative of Use in Paediatric Patients

SOC and PT	Number of Events
Blood and lymphatic system disorders	**7**
Agranulotcytosis	1
Anaemia	1
Eosinophilia	1
Febrile neutropenia	1
Neutropenia	2
Pancytopenia	1
Gastrointestinal disorder	1
Nausea	1
General disorders and administration site conditions	**4**
Drug ineffective	2
Drug ineffective for unapproved indication	1
Drug resistance	1
Infections and infestations	**1**
Meningitis pneumococcal	1
Injury, poisoning and procedural complications	**13**
Drug administered to patient of inappropriate age	2
Off label use	5
Prescribed overdose	1
Product use in approved indication	2
Product use issue	3
Investigations	**1**
Hepatic enzyme increased	1
Nervous systems disorders	2
Headache	1
Seizure	1
Skin and subcutaneous tissue disorders	**6**
Pruritus	1
Rash	2
Rash erytemathosus	1
Rash papular	1

Urticaria	1
Product issues	**1**
Product odour abnormal	1
Total	**36**

Seven cases were reported as serious, 2012SE95404 reporting eosinophilia, 2014SE39478 reporting neutropenia, anaemia and off label use (CF exacerbation, MRSA and pneumonia), 2015SF05601 reporting seizure, 2017374644 reporting neutropenia, drug ineffective for unapproved indication (failure of treatment after 1 year/product was indicated for bone and joint infections) and product use issue (patient was administered with 600 mg three times a day), 2018079133 reporting febrile neutropenia, agranulocytosis, rash papular and rash erythematous, 2018111011 reporting pancytopenia and product use in unapproved indication (culture-negative osteomyelitis) and 2018263754 reporting meningitis pneumococcal.

The reported post marketing paediatric AEs are consistent with safety data and ADRs included in the ceftaroline fosamil SmPC. No new safety concerns with regard to the use of ceftaroline fosamil in this population have been identified from assessment of these cases. The MAH will continue to review the safety of ceftaroline fosamil, including all reports of adverse experiences and will revise the product documents if an evaluation of the safety data yields significant new information.

2.5.1. Discussion on clinical safety

The applicant has conducted two studies that included patients relevant for this application. Study P903-21 was a single dose PK study that recruited 11 preterm and 12 term neonates. There might have been more patients aged below 2 months in cohort 3 but this has not been reported separately. The other study was a single arm MD study in patients aged <2 months with LOS. Ceftaroline fosamil was given in 2 doses (4 mg/kg q8h for 3 patients and 6 mg/kg q8h for remaining 8 patients) in multiple dose study while a dose of 8 mg/kg was used in a SD study for term and preterm neonate cohorts. Most patients received ceftaroline fosamil in combination with other antibiotics in MD study. The latter study was planned to enrol 24 subjects equally distributed between premature, term babies aged <28 days and those aged between 28 and 60 days. The study, however, was prematurely discontinued due to MAH opinion that there was sufficient data available to provide ceftaroline fosamil dosing recommendations for neonates and that standard practice has changed to minimise intravenous antibiotics. Thus the study only recruited 11 patients. The small sample size, very low number of premature babies, heterogenous population in multiple dose study and use of concomitant antibiotics do not allow drawing firm conclusions. As much as one can observe from this limited dataset no new safety concerns were raised. In addition, in both studies the majority of AEs were mild to moderate and non-serious, there were no AEs that led to discontinuation of study drug, there were no death, for all laboratory parameters mean changes from screening were small and clinically not significant. Some of the class effects of cephalosporins (e.g. *Clostridium difficile* colitis, seizures) cannot be evaluated due either because of different pathomechanims (CID colitis) or small sample size (seizures).

2.5.2. Conclusions on clinical safety

CHMP agreed that the safety dataset was very limited (23 patients in a SD study and 11 patients in a MD study). In addition the population was heterogeneous. No new safety concerns were observed.

The majority of AEs were mild to moderate and non-serious, there were no AEs that led to discontinuation of study drug, there were no death, for all laboratory parameters mean changes from screening were small and clinically not significant.

Some of the class effects of cephalosporins (e.g. *Clostridium difficile* colitis, seizures) could not be evaluated

due either because of different pato-mechanims (CID colitis) or small sample size (seizures).

In addition, CHMP requests that the MAH should submit the following safety data in next PSUR: a detailed review of all neonatal cases.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 18.1 is acceptable.

The MAH is reminded that, within 30 calendar days of the receipt of the Opinion, an updated version of Annex I of the RMP template, reflecting the final RMP agreed at the time of the Opinion should be submitted to h-eurmp-evinterface@emea.europa.eu.

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 18.1 with the following content:

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Important identified risks		
None	Not applicable	Not applicable
Important potential risks		
Bacterial Resistance Development	RMMs: the risk is communicated through the label in SmPC Section 4.1 (Therapeutic indications) and Section 5.1 (Pharmacodynamic properties) No additional RMMs.	Routine PV activities beyond adverse reactions reporting and signal detection: targeted FU lack of effect questionnaire for post-marketing reports. Additional PV activities: None.
Convulsions/Seizures	RMMs: the risk is communicated through the label in SmPC Section 4.4 (Special warnings and precautions for use) No additional RMMs.	Routine PV activities beyond adverse reactions reporting and signal detection: targeted FU convulsions/seizure questionnaire/intake mechanism for clinical trial and post-marketing reports. Additional PV activities: None.
DILI	RMMs: the risk is communicated through the label in SmPC Section 4.8 (Undesirable effects) No additional RMMs.	Routine PV activities beyond adverse reactions reporting and signal detection: targeted FU DILI questionnaire/intake mechanism for post-marketing reports. Additional PV activities: None.
Haemolytic Anaemia	RMMs: SmPC Section 4.4 (Special warnings and precautions for use) and Section 4.8 (Undesirable effects) No additional RMMs.	Routine PV activities beyond adverse reactions reporting and signal detection: targeted FU haemolytic anaemia questionnaire/intake mechanism

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
		for post-marketing reports. Additional PV activities: None.
Renal Impairment (including Potential Drug Interactions with Nephrotoxic Agents)	RMMs: the risk is communicated through the label in SmPC Section 4.2 (Posology and method of administration), Section 4.8 (Undesirable effects), and Section 5.2 (Pharmacokinetic properties) No additional RMMs.	Routine PV activities beyond adverse reactions reporting and signal detection: targeted FU acute renal failure questionnaire/intake mechanism for post-marketing reports. Additional PV activities: None.
Potential for Off-Label Use	RMMs: the risk is communicated through the label in SmPC Section (4.1 Therapeutic indications) and Section 4.2 (Posology and method of administration) No additional RMMs.	Routine PV activities beyond adverse reactions reporting and signal detection: targeted FU lack of effect questionnaire inquiries about pathogen and susceptibility for healthcare professionals. Additional PV activities: None.
Missing information		
None	Not applicable	Not applicable

2.7. Update of the Product information

See full changes to the Product Information in the attached Appendix. As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons: there have been no significant changes to the package leaflet to warrant a readability test to be included with this submission. In accordance with *Articles 59(3) and 61(1) of Directive 2001/83/EC, as amended* a readability test is carried out at the next substantial change.

3. Benefit-Risk Balance

3.1. Therapeutic Context

Ceftaroline fosamil is a beta-lactam antibiotic that inhibits bacterial cell wall biosynthesis by binding to one or more penicillin-binding proteins (PBP). As a results built up of bacterial cell wall is disturbed and that lead to cell death. Ceftaroline fosamil exhibits unique properties that distinguish it from other β-lactams due to its high affinity for PBP2a in MRSA and PBP2x in PRSP that contribute to its potent antibacterial activity against these organisms.

3.1.1. Disease or condition

Ceftaroline fosamil is approved for adults and children above 2 months of age for treatment of cSSTI and community acquired bacterial pneumonia (CABP). This is an extension of indication application aiming to

include paediatric patients from birth to less than 2 months and also to include subsequent dosing recommendations for the proposed paediatric population for the treatment of cSSTI and CABP.

These indications, approved in adults and older children, are extremely rare in neonates and young infants (age ≤ 2 mo) as generalised rather than local disease is characteristic for this age group. The causative agents of cSSTI are likely to be similar in older children and neonates although well conducted studies are largely missing. With regards to community acquired pneumonia (CAP), the frequency of causative agents may differ in older children and adults vs neonates. While Group B streptococci (GBS) and *S.aureus* predominate and *S.pneumoniae* is very rare in neonates, the latter is the most common in older children and adults.

Late-onset sepsis (LOS) is still one of the leading causes of neonatal morbidity and mortality in developing but also in highly developed countries. The most affected populations are premature or extremely premature neonates. Mortality rate varies form 6-8% in highly developed countries up to 30% in developing world. Furthermore, even if the babies survive they may suffer from long-term side effects such as developmental delay, motor defects or seizures. LOS is predominantly caused by coagulase negative staphylococci (CoNS) (36-66% of cases), other organisms such as *S.aureus* and Gram-negative rods account for about 26-36% of cases (Hornick et al. 2012; Cohen-Wolkowiez et al. 2009). This indication is not applied for in this application.

3.1.2. Available therapies and unmet medical need

The early use of antibiotic regimens remains the cornerstone for the treatment of CAP and cSSTI. It is characteristic for neonatal population that systemic antibiotics will be used in hospitalised children even if they do not full-fill all the criteria of cSSTI used in adults and older children. There is no specific treatment guidelines for neonates with SSTI and thus those used for treatment of older children and adults will be followed. Antistaphylococcal beta-lactams are most commonly recommended and used in case of methicillin susceptible *S.aureus* (MSSA). Vancomycin or clindamycin or trimethoprim/sulfamethoxasol are recommended if MRSA is suspected or confirmed (Clinical Infectious Diseases 2014;59(2):e10–52; Arch Dis Child. 2016 Jan;101(1):72-6). Surgical treatment is employed similar to adults and older children.

For neonatal CAP, ampicillin plus an aminoglycoside or alternatively third generation cephalopsorins are recommended for treatment of CAP in neonates (The Pediatric Infectious Disease Journal. 2012; 00:e78–e85). In case of staphylococcal pneumonia antistaphylococcal penicillins are used.

For LOS which was the clinical condition studied in the very small clinical study supporting this application, most treatment guidelines recommend using combination of the penicillins (ampicillin or penicillin G) and aminoglycoside as a first choice. Broad spectrum antibiotics such as 3rd generation cephalosporins or beta-lactam lactamase inhibitors are used in some centres. Vancomycin is often given if CoNS are suspected or confirmed because most CoNS species are resistant to oxacillin worldwide. Vancomycin and aminoglycosides, however, have safety concerns and thus require therapeutic drug monitoring, especially if administered to vulnerable populations such as premature neonates.

New antibiotics effective against CoNS, *S.aureus* and non-ESBL producing *Enterobactriaceae* are especially needed for treatment of LOS but this is not the indication sought in this application. New antibiotics may have added value as alternative treatment of cSSTI and CAP but as mentioned above both diseases are rare in neonates and infants ages < 2 mo. Ceftaroline as an agent active against *S.aureus* and non-ESBL producing *Enterobactriaceae* is an appropriate candidate for treatment of CAP and cSSTI in this paediatric age group.

3.1.3. Main clinical studies

This application aims to extend dosing recommendation to neonates and young infants aged <2 months with cSSTI and CAP. The applicant presents 2 studies: one is a single-dose PK study that included 23 subjects (11 with GA of 32-37 weeks and 12 term babies aged <28 days). There might have been infants aged < 60 days recruited also into 3rd cohort (infants <2 years) but these are not specifically outlined in the application. The second study was a multiple dose safety/PK study that enrolled 11 patients aged <60 days with suspected or proven LOS. No patients with cSSTI or CAP were included in this study. Ceftaroline fosamil was given in different doses and often concomitantly with other antibiotics. There were 7 patients in total who completed the study.

Both studies used sparse sampling methodology to evaluate PK profile of ceftaroline fosamil. The dosing regimen for ceftaroline fosamil was chosen based on a population PK model updated with PK data from 3 multiple-dose safety and efficacy studies in children aged 2 months to <18 years. The studies were sufficient to define dosing recommendations for children aged <2 months by showing similar exposure to adults. However, in terms of efficacy in patients with LOS the study is too small to draw any meaningful conclusions; in addition, this indication was not applied for. The safety dataset did not reveal any new safety concerns but similar to efficacy results no firm conclusions can be drawn.

3.2. Favourable effects

The model predicted $C_{max24ss}$ and AUC_{24ss} in various age groups of neonates and infants after administration of ceftaroline fosamil 6 mg/kg q8h as 1h infusion were compared with the median adult $C_{max24ss}$ and AUC_{24ss} after administration of ceftaroline fosamil 600mg q12h as 1h infusion. The predicted AUC_{24ss} parameters in neonates and infants were within the range of 89% to 118% of the adult median values. Similarly, the median %fT>MIC for MICs of 1 mg/L and 2 mg/L that were similar to or exceeded median %fT>MIC values in adults. Similar predictions were simulated for various age groups of neonates and infants with mild renal impairment. The median AUC_{24SS} values in preterm neonates (GA 28 to <40 weeks) and infants up to <2 months with mild renal impairment given a dose of 6 mg/kg q8h were up to 48% higher than median AUC_{24SS} values in adults with normal renal function given a dose of 600 mg q12h. The proposed dosing of ceftaroline fosamil 6 mg/mg q8h as 1h infusion, was up to 25% higher in infants aged >2 months, but in infants younger than 2 months the current dosing may result in unnecessary overexposure.

Ceftaroline fosamil was in general well tolerated, the AEs were mostly mild to moderate, none of them resulted in discontinuation of study drug, there were no death and no unexpected AEs were identified.

3.3. Uncertainties and limitations about favourable effects

There are several uncertainties with in this application:

CoNS may cause cSSTI in neonates and young infants but no *in vitro* susceptibility data of CoNS are presented in this application. Based on the data presented in the application, ceftaroline fosamil seemed equally effective against various species of CoNS, including against strains of neonatal origin.

The PK/PD analysis considered the PK/PD target of 35% and 44% free percent of time above minimum inhibitory concentration (%f T>MIC) for *S. aureus* and *S. pneumonia.* These targets were identified in preclinical studies. To address some concerns expressed during the assessment with regard to the adequacy of these PD targets, the MAH performed simulations using MIC values of CoNS and ESBL negative *Enterobacteriaceae* by targeting greater T>MIC values (e.g. 60% fT>MIC and 100% fT>MIC).

The applicant conducted additional analyses as requested by CHMP and the required PTA was above 90% . for 60% fT>MIC, which was considered acceptable by CHMP. In addition, CHMP noted that in the additional simulations, the MAH did not consider GA adequately. The GA was entered into simulation but it only reflects

time at birth, the time period when ceftaroline is hardly needed or administered. It cannot be excluded that a higher dose might be needed to treat infections produced by pathogens with higher MICs, as is the case for adults and older children, but this is not subject to this application.

Despite the fact that the submitted studies did not generate conclusive efficacy data for treatment of cSSTI or CAP in neonates or young children, the efficacy of ceftaroline fosamil in this age group can be extrapolated from adults and older children, provided that similar exposure is achieved.

CHMP noted that this application did not seeking approval for treatment of LOS, a common neonatal infection for which new treatments are much needed.

The safety database is very limited and safety data were provided for children with LOS rather than for patients with cSSTI or CAP. Furthermore the study population was very heterogeneous. There were in total of 23 patients aged <2 months who received single dose and 11 who received multiple dose of ceftaroline fosamil. Different doses of ceftaroline fosamil were used, most patients received concomitant antibiotics and not all patients in MD study completed study treatment. Therefore less frequent AEs like seizures are likely missed and CID colitis can hardly be diagnosed in neonatal age. Still, no unexpected side effects were identified. Furthermore, cephalosporins have been used in clinical practice for several decades including in neonatology. In adults the safety profile of ceftaroline fosamil is similar to other cephalosporins therefore it is unlikely that unexpected side effects will emerge with the inclusion of the additional population. Hence CHMP agreed that a detailed review of all neonate cases should be provided in next PSUR, as it will allow a continued and thorough assessment.

As in adults, there is always a risk of out-selection of resistance, especially if cephalosporins are misused (wrong indication or wrong dosing regimen). Thus, development of emergent resistance should be monitored in post marketing studies.

3.4. Unfavourable effects

No new unfavourable effects were reported in the clinical studies presented in this application. The majority of AEs were mild to moderate and non-serious, there were no AEs that led to discontinuation of study drug, there were no deaths, for all laboratory parameters mean changes from screening were small and clinically not significant.

3.5. Benefit-risk assessment and discussion

3.5.1. Importance of favourable and unfavourable effects

Ceftaroline fosamil is an antibiotic that belongs to the cephalosporin class of antibacterial medicinal products. Cephalosporins have been in clinical use for several decades, including in the treatment of neonatal sepsis. They are effective against most microorganisms that cause cSSTI and CAP in neonates and young infants and are generally well tolerated.

During this application the MAH provided the data that underpin the fact that the chosen dosing regimen that achieves a similar exposure in term and preterm neonates with cSSTI and CAP to that observed in adults (and older children). CHMP therefore agreed that safety and efficacy can be extrapolated to children from birth to less than 2 months of age for the dosing regimen the 6 mg/kg q8h given via 1-h infusion.

Several uncertainties, mainly driven by relatively limited development programme, consist in the limited number of subjects in the safety dataset and the fact that no clinical data were generated from patients with cSSTI or CAP.

3.5.2. Balance of benefits and risks

There is a moderate need for the new effective and well tolerated antibiotic for neonates in treatment of cSSTI and CAP, as both diseases are relatively rare in this population and mostly covered by available antibiotics. Ceftaroline fosamil is a cephalosporin that has a good activity against most microorganisms causing cSSTI and CAP. Furthermore, ceftaroline fosamil belongs to well-known class of antibiotics (cephalosporins) that have been in clinical use for several decades and have demonstrated good safety profile. Cephalosporins are commonly used in neonatal units world-wide.

CHMP noted that the applicant is not seeking approval for LOS, the disease that is more common than cSSTI and CAP with poor outcome and limited treatment options in neonates and young children. As ceftaroline fosamil is theoretically a good candidate to improve treatment options for LOS there is a risk of off-label use.

Although cephalosporins are well tolerated there are some AEs related to their use as well. All beta-lactams have risk of seizures and can cause CID colitis. The latter is still very rare and difficult to diagnose in neonates and young infants. Coombs seropositivity is a well-known side effect of cephalosporins including ceftaroline fosamil that is sometimes accompanied by haemolytic anaemia that has not been observed with ceftaroline fosamil in adults or older children.

As with all antibiotics ceftaroline fosamil has potential to out-select resistant microorganisms especially in cases of inappropriate consumption.

3.6. Conclusions

The overall B/R of Zinforo is positive.

In addition the applicant should submit the following safety data in the next PSUR: a detailed review of all neonatal cases treated with ceftaroline fosamil.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include paediatric patients from birth to less than 2 months old for Zinforo; as a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated based on results from 2 new pharmacokinetic/clinical studies (studies D3720C00006 (P903-21) and D3720C00009 (C2661002)) and a population pharmacokinetic analysis (PMAR-EQDD-C266b-Other-809). The Package Leaflet is updated in accordance. The RMP version 18.1 has also been agreed upon.

The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list)) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk management plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

In addition, an updated RMP should be submitted:

At the request of the European Medicines Agency;

Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0176/2018–and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Extension of indication to include paediatric patients from birth to less than 2 months old for Zinforo; as a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated based on results from 2 new pharmacokinetic/clinical studies (studies D3720C00006 (P903-21) and D3720C00009 (C2661002)) and a population pharmacokinetic analysis (PMAR-EQDD-C266b-Other-809). The Package Leaflet is updated in accordance. The RMP version 18.1 has also been agreed upon.

Summary

Please refer to Scientific Discussion of Zinforo-H-C-2252-II-0041.