28 April 2016
EMA/CHMP/325573/2016
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Zinforo

International non-proprietary name: ceftaroline fosamil

Procedure No. EMEA/H/C/002252/II/0022

Note

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

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List of abbreviations

%*f*T>MIC	Percent time of free-drug concentration above the minimum inhibitory concentration (MIC) over the dose interval
AUC	Area under the plasma concentration versus time curve
AUC24SS	Area under the plasma concentration versus time curve over 24 hours at steady-state
AUC(0-t)	Area under the plasma concentration-time curve from zero to time of last quantifiable concentration
AUC(0-τ)	Area under the plasma concentration versus time curve from time 0 to the end of the dosing interval, τ
AUC0-∞	Area under the plasma concentration versus time curve from time 0 to infinity
BSA	Body surface area
CAP	Community-acquired pneumonia
CDS	Core data sheet
CE	Clinically evaluable
CLD	Haemodialysis clearance
Cmax	Maximum plasma drug concentration
CmaxSS	Maximum plasma drug concentration at steady state
CrCL	Creatinine clearance
CrCLN	Creatinine clearance normalized by body surface area
CSR	Clinical study report
cSSTI	Complicated skin and soft tissue infections
EOIV	End of IV study drug
EOT	End of treatment
IV	Intravenous
ME	Microbiologically evaluable
MIC	Minimum inhibitory concentration
MITT	Modified intent-to-treat
mMITT	Microbiological modified intent-to-treat
PIL	Patient information leaflet
PIP	Paediatric Investigation Plan

PK	Pharmacokinetic(s)
PMA	Post-menstrual age
PopPK	Population pharmacokinetic(s)
PTA	Probability of target attainment
q8h	Every 8 hours
q12h	Every 12 hours
SmPC	Summary of Product Characteristics
TEAE	Treatment emergent adverse event
t1/2λz	Terminal half-life
tmax	Time to maximum concentration
TOC	Test of cure

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, AstraZeneca AB submitted to the European Medicines Agency on 9 April 2015 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 new population, children over the age of 2 months and adolescents, for Zinforo; as a consequence, sections 4.1, 4.2, 5.2, 5.3 and 6.6 of the SmPC are updated with new information on dosing, pharmacokinetics and pre-clinical safety. The Package Leaflet is updated in accordance. In addition, the Marketing Authorisation Holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0074/2014 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0074/2014 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

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 and the evaluation teams were:

Rapporteur: Greg Markey Co-Rapporteur: N/A

Timetable	Actual dates
Submission date	9 April 2015
Start of procedure:	27 June 2015
CHMP Rapporteur Assessment Report	7 August 2015
CHMP members comments	14 September 2015
Updated CHMP Rapporteur(s) (Joint) Assessment Report	15 September 2015
Request for supplementary information (RSI)	24 September 2015
CHMP Rapporteur Assessment Report	19 November 2015
CHMP members comments	7 December 2015
Request for supplementary information (RSI)	17 December 2015
CHMP Rapporteur Assessment Report	21 March 2016
CHMP members comments	18 April 2016
Updated CHMP Rapporteur Assessment Report	21 April 2016
Opinion	28 April 2016

2. Scientific discussion

2.1. Introduction

Zinforo (ceftaroline fosamil) is an oxyimino cephalosporin antibacterial agent for intravenous administration, presented for clinical use as the more water soluble N-phosphono (fosamil), which is rapidly converted to ceftaroline by phosphatases in human plasma.

It was approved in the EU in August 2012 for treatment of adults with complicated skin and soft tissue infections (cSSTI) and community-acquired pneumonia (CAP). The recommended adult dosing regimen is 600 mg (reduced to 400 mg for patients with creatinine clearance [CrCL] >30 to ≤ 50 mL/min) administered as a 60-minute infusion every 12 hours (q12h) for 5 to 14 days for cSSTI and 5 to 7 days for CAP. In 2014 a Type II variation added dosage adjustment recommendations for adults with severe renal impairment (CrCL ≤ 30 mL/min) and end-stage renal disease (ESRD; CrCL <15 mL/min), including patients undergoing haemodialysis.

The main purpose of this extension of indication application is to extend the use of Zinforo to children aged from 2 months to 17 years based on submission of the CSRs for the following studies, which were conducted in children (aged from 2 months to less than 18 years), in accordance with the agreed PIP:

- **D3720c00004 (P903-23)** A multicentre, randomized, observer-blinded, active-controlled study to evaluate the safety, tolerability, efficacy, and pharmacokinetics of ceftaroline versus comparator in paediatric subjects with acute bacterial skin and skin structure infections
- **D3720c00007 (P903-31)** A multicentre, randomized, observer blinded, active-controlled study evaluating the safety, tolerability, pharmacokinetics, and efficacy of ceftaroline versus ceftriaxone in paediatric subjects with community-acquired bacterial pneumonia requiring hospitalization
- **D3720c00013 (P903-24)** A multicentre, randomized, observer-blinded, active-controlled study evaluating the safety, tolerability, pharmacokinetics, and efficacy of ceftaroline versus ceftriaxone plus vancomycin in paediatric subjects with complicated community-acquired bacterial pneumonia

The **initial proposals** for doses in children ages > 2 months and adolescents < 18 years were as follows:

Infection	Age/weight range	Dose	Frequency	Infusion time (minutes)	Recommended duration of antimicrobial treatment
cSSTI	2 months to < 24 months	8 mg/kg	every 8 hours	60	5-14 days
	≥ 24 months (≤ 33 kg)	12mg/kg	every 8 hours	60	5-14 days
	≥ 24 months (> 33 kg)	400 mg	every 8 hours	60	5-14 days
CAP	> 2 to < 24 months	8 mg/kg	every 8 hours	60	5-7 days
	≥ 24 months (≤ 33 kg)	12 mg/kg	every 8 hours	60	5-7 days
	≥ 24 months (> 33 kg)	400 mg	every 8 hours	60	5-7 days

2.2. Non-clinical aspects

2.2.1. Introduction

Additional toxicity studies using ceftaroline fosamil were conducted in juvenile rats to support this submission as follows:

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

The MAH also updated the in-vitro susceptibility data.

2.2.2. Pharmacology

The *in vitro* activity of ceftaroline 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 activity was assessed against Gram-positive and Gram-negative bacteria isolated from adult and paediatric infected patients. Overall, susceptibility to ceftaroline 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 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 when assessed using established interpretative criteria on susceptibility.

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

The MAH concluded that ceftaroline is equally active against adult and paediatric isolates that are clinically important in the two indicated infection types. CHMP agreed to this conclusion.

2.2.3. Pharmacokinetics

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 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 (based on simulations) in patients with mild renal impairment.

The maximum plasma levels of ceftaroline tested in the juvenile rat at 270 mg/kg/day were approximately 20 to 28-fold higher than the predicted median steady state Cmax values of ceftaroline (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 1 Summary of ceftaroline fosamil and M1 TK 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 2 Summary of TK 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 (bolus) injection (lateral tail vein) 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 (toxicokinetic [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 desheathing 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, because of its focal nature, was considered not to be of toxicological concern.

Table 3 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 4 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).

The MAH stated that as microscopic assessment is considered to provide a more accurate assessment of cyst incidence and relationship to test article administration, the microscopic findings more accurately reflected the true incidence of this finding.

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. The MAH explained that 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 No Observed Adverse Effect Level (NOAEL) was considered to be 270 mg/kg in juvenile, suckling rats.

Table 5 Summary of ceftaroline fosamil and M1 TK 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 updated data submitted in this application do not lead to a significant increase in environmental exposure further to the use of Zinforo.

Considering the above data, CHMP agreed that Zinforo is not expected to pose a risk to the environment.

2.2.6. Discussion on non-clinical aspects

Assessment of paediatric data on non-clinical aspects

Exposure levels (AUC(0-t)) of ceftaroline 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 (based on

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

Table 6: Median (90% PI) ceftaroline steady-state CmaxSS and AUC24SS, by age following the proposed dose for subjects aged from 6 to <24 months in paediatric patients with either normal renal function, or mild renal impairment based on simulations.

AGE	Weight (kg)	CmaxSS (mg/L)	AUC24SS (mg*hr/L)	Dose*
Adults 600 mg q12h 1 hr	77.6 (52.5,105)	21.0 (11.9,36.5)	97.3 (59.1,164)	600 mg
Normal renal function (CrCL >80ml/min)				
12-<18 years	52.9 (36.8,75.3)	19.7 (11.0,34.2)	122 (72.7,201)	12 mg/kg (max of 400 mg)
6-<12 years	28.5 (19.3,46.5)	27.6 (16.4,43.3)	157 (99.7,245)	12 mg/kg (max of 400 mg)
2-<6 years	15.8 (11.8,22.2)	27.1 (16.8,41.8)	144 (92.6,225)	12 mg/kg (max of 400 mg)
18-<24 months	11.7 (9.8,14.1)	18.8 (11.8,29.1)	107 (69.0,165)	8 mg/kg (max of 400 mg)
12-<18 months	10.4 (8.6,12.7)	19.1 (11.9,29.4)	113 (71.8,174)	8 mg/kg (max of 400 mg)
6-<12 months	8.43 (6.55,10.7)	19.6 (12.2,30.0)	120 (78.3,188)	8 mg/kg (max of 400 mg)
2-<6 months	5.75 (4.12,7.66)	19.2 (12.1,29.7)	134 (86.6,208)	8 mg/kg (max of 400 mg)
Mild renal impairment (>50ml/min CrCL < 80ml/min				
Adults 600 mg q12h 1 hr	77.6 (52.2,105)	20.9 (11.7,36.6)	97.1 (58.8,164)	600 mg
12-<18 years	52.7 (36.7,74.7)	20.7 (11.5,35.6)	136 (80.9,227)	12 mg/kg (max of 400 mg)
6-<12 years	28.6 (19.2,46.8)	28.8 (17.0,45.4)	175 (110,276)	12 mg/kg (max of 400 mg)
2-<6 years	15.8 (11.8,22.4)	28.3 (17.5,44.0)	160 (102,252)	12 mg/kg (max of 400 mg)
18-<24 months	11.7 (9.8,14.1)	20.6 (12.8,32.3)	133 (82.7,219)	8 mg/kg (max of 400 mg)

12-<18 months	10.4 (8.6,12.7)	20.9 (13.0,32.6)	140 (86.0,227)	8 mg/kg (max of 400 mg)
6-<12 months	8.43 (6.55,10.7)	21.4 (13.3,33.3)	152 (92.6,247)	8 mg/kg (max of 400 mg)
2-<6 months	5.75 (4.11,7.67)	21.2 (13.2,33.3)	168 (103,275)	8 mg/kg (max of 400 mg)

Median (5th, 95th percentile) based on summary of 100 trials and corresponds to median (90% PI). Adult dose and regimen is listed in first row of column 1. *Paediatric dose administered q8h as 1 hour infusion. Abbreviations: AUC24SS area under the concentration-time curve over 24 hours at steady-state; CmaxSS maximum concentration for a dosing interval at steady-state; PI prediction interval; q12h every 12 hours.

To describe the juvenile toxicity data, CHMP asked the MAH to include the following wording in section 5.3 of the Zinforo SmPC:

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.

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 <18 years with CAP or cSSTI. 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 (bolus) injection (lateral tail vein) 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 finding 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 (bolus) injection (lateral tail vein) 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 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 (based on simulations) in paediatric patients with mild renal impairment. The maximum plasma levels of ceftaroline tested in the juvenile rat at 270 mg/kg/day were approximately 20 to 28-fold higher than the predicted median steady state Cmax values of ceftaroline (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, 270 mg/kg is considered 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). This could indicate a progression of these effects, which were not present in the controls and therefore cannot be attributed to procedural factors. 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 2 months of age), the MAH was asked to provide a more extensive discussion concerning the renal findings in juvenile rats, to justify the conclusion that these findings are not adverse.

The MAH responded to this issue and clarified that overall, as the cysts involved only a small area of the kidney and the fibrosis was focal and minimal in nature and both occurred in the absence of significant changes in renal function or urinary parameters, did not appear to have any significant implications for the animals (no adverse clinical signs, only transient effects on body weight gain and no significant changes in clinical pathology or organ weights) they are considered not to be adverse. Based on the above analysis the MAH's proposal for the additional text in Section 5.3 of the SmPC was accepted by CHMP.

The updated data submitted in this application do not lead to a significant increase in environmental exposure further to the use of 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.

2.3.2. Pharmacokinetics

Special populations

The details of the two prior PK studies in patients aged < 18 years are provided, so that all the relevant data are made available for review.

Previously reported studies:

P903-15 was included in the initial application dossier for ceftaroline even though use below 18 years of age was not sought at that time. This study planned to evaluate safety and PK in patients aged from 12 to 17 years who were to receive a single dose of 8 mg/kg if < 75 kg or 600 mg if ≥75 kg while being hospitalised and treated with licensed antibacterial agents for infections of any type.

P903-21 was submitted and assessed as part of variation II/08 in 2013, which did not lead to any changes in the Zinforo SmPC. The study evaluated the pharmacokinetics and safety of a single dose of ceftaroline in children from birth to < 12 years of age. This was an open-label, sequential, single dose study in children while being hospitalised and treated with licensed antibacterial agents for infections of any type. The study enrolled 5 cohorts who were dosed as follows:

- Cohort 1 - 6 to <12 years (n=10); 10 mg/kg (max 600 mg) as a 1 hour infusion
- Cohort 2 - 2 to <6 years (n=8); 15 mg/kg as a 1.5 hour infusion
- Cohort 3 - 28 days to <2 years with equal numbers < or > 12 months (n=12); 12 mg/kg as a 1 hour infusion if ≥5 months and 8 mg/kg as a 1 hour infusion if ≥28 days to <5 months
- Cohort 4 - full-term neonates aged <28 days with equal numbers < or > 14 days (n=12); 8 mg/kg as a 1 hour infusion
- Cohort 5 - preterm neonates (gestational age 32 to 37 weeks) aged <28 days with 5 older than 14 days and 6 younger than 14 days (n=11); 8 mg/kg as a 1 hour infusion

Plasma concentrations of ceftaroline, ceftaroline fosamil (prodrug) and ceftaroline M-1 (inactive metabolite) were determined in samples obtained at end of infusion and then at 15 to 45 minutes, 3 to 4 h and 5 to 7 h from the end of infusion.

New studies:

The study designs for studies P903-23, P903-24 and P903-31 are described in the clinical efficacy section. In each CSR there is a bioanalytical report on the assay performance and the individual concentration

data are listed for ceftaroline, ceftaroline fosamil and the open ring form (M-1). Due to sparse sampling, the data were included in the POPPK and PK-PD analyses and not analysed separately.

D3720c00004 (P903-23) acute bacterial skin and skin structure infections

Sparse PK blood sampling (2 samples of no more than 2 mL/kg per patient) was performed only at selected study centres, and for only those patients that consented to PK evaluation and were randomized to ceftaroline fosamil. A total of 198 plasma samples from 99 patients in the ceftaroline treatment group were analysed.

D3720c00007 (P903-31) community-acquired bacterial pneumonia requiring hospitalization

Sparse PK blood sampling was conducted as above.

D3720c00013 (P903-24) complicated community-acquired bacterial pneumonia

Sparse PK blood sampling was conducted as above.

Dose selection for P903-23, P903-31 and P903-24:

The POPPK models for ceftaroline fosamil and ceftaroline from the original MAA were updated to incorporate data in adolescents (12 to <18 years) from P903-15 and to include allometric scaling of PK parameters by weight for children. Data from several additional studies in adults were added to the model and the dose range was limited to 250 mg to 1000 mg.

The initial POPPK model comprised 11 Phase 1 studies in healthy volunteers, 4 Phase 2/3 studies in patients with cSSTI and 2 Phase 3 studies in patients with CAP. Interim PK data from P903-21 were then added and the final POPPK model consisted of a simultaneous two-compartment disposition model for the prodrug ceftaroline fosamil and a two-compartment disposition model for ceftaroline.

As in the previous model the variability in clearance was primarily predicted by creatinine clearance (normalized by BSA). The relationship between age and clearance was estimated and kept constant for children 2 to <18 years of age. For children aged < 2 years a published sigmoid hyperbolic model based on post-menstrual age was used to account for maturation of renal function. The model adequately predicted observed data in paediatric patients and adults.

The model was then used to simulate a range of dose regimens to assess steady-state exposure measures (Cmax, AUC and %*f*T>MIC) and make dose recommendations for the three new studies.

Three thousand patients (1000 per cohort) aged 2 to <18 years and 3000 aged 28 days to <24 months were simulated with a uniform distribution for each year of age for those 2 years and older or each month for those aged <24 months. An equal number of males and females were simulated. Body weights for each simulated patient were predicted based on age in accordance with CDC growth charts. For children <24 months, dosing scenarios with various infusion lengths (1, 1.5 and 2 h) and dose amounts (4, 6, 8, 10 and 12 mg/kg) were simulated. In all simulated scenarios, the dose was capped based on weight so that paediatric patients would not receive more than the currently approved adult dose per day (1200 mg/day).

For P903-23 and P903-31, the goal was to select doses to match or exceed the %*f*T>MIC in adults dosed with ceftaroline fosamil 600 mg q12h without appreciably exceeding the Cmax and AUC in adults at this dose. For P903-24, which enrolled subjects with complicated CAP, the goal was to select doses to match or exceed the %*f*T>MIC in adults dosed with ceftaroline fosamil 600 mg q8h. Based on the simulations, the following dose regimens were selected:

P903-23 and P903-31:

- 6 months to <18 years: 12 mg/kg q8h as a 1 h infusion up to a maximum of 400 mg q8h for subjects weighing >33 kg
- 2 months to <6 months: 8 mg/kg q8h as a 1 h infusion

P903-24:

- 6 months to <18 years: 15 mg/kg q8h as a 2 h infusion up to a maximum of 600 mg q8h for subjects weighing >40 kg
- 2 months to <6 months: 10 mg/kg q8h as a 2 h infusion

Results

P903-15

The nine adolescents dosed in this study had a mean age of 13.7 years (range 12-16 years) and included 5 male and 4 female subjects. Mean BMI was 21.51 kg/m2 and mean CrCl was 156.84 mL/minute. The actual amount of ceftaroline administered ranged from 320 to 600 mg based on a weight range of 40.6 to 79.1 kg. Eight subjects received a complete single dose of ceftaroline fosamil while one refused further infusion after receiving about 80% (199 ml and 406 mg) of the planned dose of 510 mg based on a weight of 64 kg) because of extravasation at the infusion site. The PK data are summarised in the table below:

Table 7: PK parameters (mean±SD) for ceftaroline, ceftaroline fosamil and ceftaroline M1 following a single intravenous dose of ceftaroline fosamil-PK population

PK Parameter	*Ceftaroline (N = 8)[a]*	*Ceftaroline M-1 (N = 8)[a]*	*Ceftaroline Fosamil (N = 8)[a]*
AUC_{0-t}, ng•h/mL	38391.81 ± 16063.63	10355.04 ± 7799.51	2293.90 ± 2476.80
$AUC_{0-\infty}$, ng•h/mL	38876.55 ± 16240.87	11186.77 ± 7830.76	NC
C_{max}, ng/mL	15276.14 ± 5996.84	2130.92 ± 2536.78	3272.51 ± 3378.25
T_{max}, h[b]	0.95 (0.48-1.00)	1.15 (0.92-3.00)	0.50 (0.48-0.92)
$T_{½}$, h	1.94 ± 0.27	3.26 ± 0.55	NC
CL, mL/h	14045.58 ± 13409.84	44194.74 ± 16849.96	NC
V_z, mL	35572.84 ± 45126.16	217519.74 ± 94399.62	NC
V_{ss}, mL	43091.61 ± 50837.89	214384.19 ± 89132.43	NC
Ae_{0-t}, mg	211.71 ± 72.38	18.82 ± 8.48	0
Percent recovered (% dose)	56.97 ± 18.23	5.00 ± 2.79	0
CL_r, mL/h	8762.12 ± 10882.35	2003.12 ± 969.70	0

One patient had unusually low plasma concentrations of ceftaroline and unusually high plasma concentrations of ceftaroline M-1.

For example, Cmax ceftaroline was only 18% and AUC0-∞ was only 14% compared to the mean values for the other subjects whereas AUC0-∞ ceftaroline M-1 was 3.5-times the mean for the others. Excluding data from this patient resulted in significantly lower standard deviations for mean PK parameters and gave higher mean Cmax and AUC0-∞ ceftaroline values (17031.49 ± 3632.80 ng/ml and 43569.02 ± 10110.04 ng•h/ml) compared to the table below. After exclusion of the data, the re-calculated mean T½ for ceftaroline was 1.86 ± 0.17 h and ~55% of the dose was excreted in urine.

The mean Cmax and AUC0-∞ for ceftaroline in these adolescents were about 10% and 23% less than the values observed in adult subjects following a 600 mg dose of ceftaroline fosamil in P903-01. After exclusion of the subject with unusual PK ceftaroline the mean Cmax for ceftaroline M-1 was 1250.07 ±

515.80 ng/ml (~ 7% Cmax ceftaroline) and the mean AUC0-∞ was 8466.58 ± 1574.58 ng•h/ml (~ 19% of the AUC0-∞ ceftaroline). The mean T½ for ceftaroline M-1 was 3.41 ± 0.39 h and approximately 4.4% of the dose was excreted in urine as ceftaroline M-1.

Ceftaroline fosamil was rapidly converted to ceftaroline and was generally only measurable in plasma for 0.25 to 1 h after the end of study drug infusion. The mean Cmax for ceftaroline fosamil was 3693.58 ± 3414.65 ng/ml (~ 22% of the Cmax for ceftaroline) and the mean AUC0-t was 2591.71 ± 2515.79 ng•h/ml (~ 6% of the AUC0-t for ceftaroline). Ceftaroline fosamil was not measurable in urine samples.

P903-21

Ceftaroline was measurable in all PK samples and all patients had ceftaroline plasma concentrations >1 µg/mL in samples collected 3 to 4 h after the end of the infusion. The majority (45/53) had >1 µg/mL in samples collected 5 to 7 h after the end of infusion.

The mean end of infusion (Cmax) concentrations of ceftaroline were lower in Cohorts 4 and 5 than in Cohorts 1, 2, or 3 but the lower dose may not fully explain the lower Cmax. In contrast, mean concentrations at 5 to 7 h post-infusion were higher for Cohorts 4 and 5 compared with Cohorts 1, 2, and 3, which suggested slower clearance in the youngest groups consistent with immature renal function. In keeping with the finding, ceftaroline plasma concentrations in samples collected during the last 2 PK collection intervals tended to be higher in patients aged from birth to 14 days compared to those aged >14 to <28 days.

Table 8 Mean ceftaroline plasma concentrations by cohort

Collection Times	*Mean (±SD) Ceftaroline Plasma Concentration (ng/mL)*				
	Cohort 1 (n = 10)	*Cohort 2 (n = 8)*	*Cohort 3 (n = 12)*	*Cohort 4 (n = 12)*	*Cohort 5 (n = 11)*
At end of infusion (± 5 minutes)	18325.08 ± 3563.06	23052.72 ± 5485.06	16938.90 ± 3693.24	10530.69 ± 2529.54	11091.64 ± 1505.90[a]
15 to 45 minutes from end of infusion	12114.21 ± 3157.54	14860.30 ± 3448.84	12549.92 ± 2861.96	9782.58 ± 2013.87[b]	10348.61 ± 1064.83[a]
3 to 4 hours from end of infusion	2769.49 ± 890.70	3626.51 ± 1663.57	3286.77 ± 1215.47	4600.61 ± 819.13	5061.97 ± 1668.45
5 to 7 hours from end of infusion.	1138.30 ± 489.43	1600.83 ± 641.75	1573.37 ± 688.59	2687.71 ± 623.84	3115.87 ± 1350.72

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.

Table 9 Mean ceftaroline plasma concentrations by age subgroup within cohorts 3,4 and 5

Collection Times	*Mean (±SD) Ceftaroline Plasma Concentration (ng/mL)*					
	Cohort 3A (n = 9)	*Cohort 3B (n = 3)*	*Cohort 4A (n = 6)*	*Cohort 4B (n = 6)*	*Cohort 5A (n = 5)*	*Cohort 5B (n = 6)*
At end of infusion (± 5 minutes)	17574.86 ± 4089.45	15031.02 ± 919.52	10808.87 ± 1995.66	10252.51 ± 3147.78	11168.62 ± 1599.43[a]	11030.05 ± 1614.37[b]
15 to 45 minutes from end of infusion	13183.51 ± 3045.91	10649.14 ± 844.47	9746.93 ± 1379.36	9825.35 ± 2785.08[b]	9848.78 ± 1535.71[a]	10748.48 ± 221.83[b]
3 to 4 hours from end of infusion	3440.01 ± 1360.72	2827.07 ± 544.61	4280.58 ± 870.61	4920.64 ± 687.30	3807.40 ± 1293.25	6107.45 ± 1159.26
5 to 7 hours from end of infusion.	1626.06 ± 786.01	1415.30 ± 294.35	2314.60 ± 381.99	3060.82 ± 613.34	2340.73 ± 1008.17	3761.81 ± 1316.91

Notes: Cohort substrata: 3A = 5 months to < 24 months, administered 12 mg/kg; 3B = 28 days to < 5 months, administered 8 mg/kg; 4A = term neonates > 14 days to < 28 days, administered 8 mg/kg; 4B = term neonates 0 to 14 days, administered 8 mg/kg; 5A = preterm neonates > 14 days to < 28 days, administered 8 mg/kg; 5B = preterm neonates 0 to 14 days, administered 8 mg/kg.

Ceftaroline fosamil plasma concentrations were variable and were typically only measurable at the end of the infusion or within 15-45 min post-infusion. Eight had no measurable ceftaroline fosamil in any samples but had ceftaroline and ceftaroline M-1 levels that were consistent with appropriate dosing.

The highest mean ceftaroline M-1 plasma concentration occurred in samples collected at 3 to 4 h post-infusion. At the end of infusion, mean ceftaroline M-1 plasma concentrations in each cohort were approximately 3% to 4% of mean ceftaroline plasma concentrations at the same time. For plasma samples collected 5 to 7 h after the end of infusion, mean ceftaroline M-1 levels were 53.3%, 50.3%, 51.1%, 26.0% and 25.7% of mean ceftaroline levels at the same time for Cohorts 1-5, respectively.

D3720c00004 (P903-23) acute bacterial skin and skin structure infections

A total of 198 plasma samples from 99 patients in the ceftaroline treatment group were analysed.

D3720c00007 (P903-31) community-acquired bacterial pneumonia requiring hospitalization

A total of 228 plasma samples from 116 patients in the ceftaroline treatment group were analysed. There were 22 patients with samples taken near the end of a ceftaroline fosamil infusion in which concentrations of ceftaroline were above 30 mg/L, including 12 with 30-40 mg/L and a maximum level of 68.9 mg/L. These levels exceeded the upper limit of the 90% prediction interval for the expected maximum plasma concentration in adults dosed with 600 mg q12h. However, concentrations had decreased by 4 to 50-fold by the time of the next PK sample from the same patient (typically 3-4 hours later). Safety data from these patients did not show trends in AEs or in laboratory abnormalities. The MAH concluded that the high concentrations may reflect sampling from sites near the site of infusion (e.g. the same arm).

D3720c00013 (P903-24) complicated community-acquired bacterial pneumonia

A total of 58 plasma samples from 29 patients in the ceftaroline treatment group were analysed.

The MAH compiled the paediatric PK data to support modelling and simulations.

The application contained a POPPK report dated 2011, which included P903-15 but not the data from the sequential studies in children, and a PK-PD report dated January 2015. The former report (**CPT-MS-14**) comprises the analyses reported above that were used to select the dose regimens for the three new paediatric studies. The latter report (**CPT-MS-08**) is the most relevant to this extension of indication and included all the available paediatric data.

Population PK modelling

After the completion of the three new studies the POPPK model for ceftaroline and ceftaroline fosamil was updated to include the new data and also the final data from P903-21.

- The resulting ceftaroline POPPK dataset comprised 525 patients and 195 healthy subjects or subjects with various degrees of renal impairment contributing a total of 6633 measurable concentrations (1799 ceftaroline fosamil and 4834 ceftaroline).
- Of the 525 patients 305 paediatric patients contributed a total of 974 measurable concentrations (234 ceftaroline fosamil and 740 ceftaroline).
- Of these 305 patients, 42 were ≥12 to <18 years of age, 74 were ≥6 to <12 years, 102 were ≥2 to <6 years, 64 were ≥24 days and <2 years, 12 were term neonates (gestational age ≥38 weeks, ages <28 days) and 11 were preterm neonates (gestational age 32-37 weeks, ages <28 days).
- The paediatric population consisted of 173 males and 132 females with ages ranging from 1 day to 18 years and weights ranging from 1.5 to 100 kg. All (with one exception) had either normal renal function or mild renal impairment.

Paediatric patients demonstrated similar PK for ceftaroline as adult patients after accounting for weight and maturational changes. The combined ceftaroline fosamil and ceftaroline population PK model provided a good description of the observed data. Diagnostic plots stratified by age group and study revealed that the model was consistent with the observed data and no systematic bias was evident. All paediatric age groups were adequately described by the model. This population PK model was used to generate individual predicted PK parameters for patients that had PK samples collected, as summarised in the tables below.

The final combined POPPK model for ceftaroline fosamil and ceftaroline was used to simulate plasma concentration-time data using the current ceftaroline dosing regimen for adults and various dosing regimens for paediatric patients (preterm neonates to <18 years old) with normal renal function, or mild renal impairment. Concentration data were simulated at steady-state. Weights for the paediatric age groups were based on CDC Growth Charts. Covariates for the adult simulations were generated from a multivariate normal distribution based on the covariances observed in the POPPK data in patients.

Table 10 **Median (90% confidence interval) ceftaroline PK parameters by cohort and dose based on individual population PK model-predicted parameters for study P903-23**

Cohort (Age Range)	Dose[a]	n[b]	CL, L/h	C_{max}, µg/mL	$AUC_{0\text{-}24h,SS}$, µg•h/mL	$T_{½}$, h
Cohort 1 (12 to < 18 years)	12 mg/kg q8h	1	2.47 (2.47-2.47)	32.6 (32.59-32.59)	292 (291.5-291.5)	2.16 (2.16-2.16)
Cohort 1 (12 to < 18 years)	400 mg q8h	21	9.33 (6.47,13.6)	16.3 (10.7,25.9)	129 (88.1,185)	2.00 (1.74,2.30)
Cohort 2 (6 to < 12 years)	12 mg/kg q8h	18	5.09 (4.14,7.02)	24.8 (22.1,28.8)	170 (127,211)	1.52 (1.34,1.81)
Cohort 2 (6 to < 12 years)	400 mg q8h	15	7.31 (5.88,10.5)	20.9 (14.6,28.3)	164 (114,204)	1.83 (1.59,2.03)
Cohort 3 (2 to < 6 years)	12 mg/kg q8h	21	3.68 (2.50,4.52)	24.6 (19.2,27.6)	175 (143,198)	1.55 (1.38,1.66)
Cohort 4 (2 months to < 2 years)	12 mg/kg q8h	21	2.18 (1.45,3.12)	23.5 (19.7,29.4)	182 (138,248)	1.64 (1.37,2.08)
Cohort 4 (2 to < 6 months)	8 mg/kg q8h	2	1.25 (0.99-1.5)	13.7 (11.89-15.49)	108 (100-115.15)	1.66 (1.44-1.89)

Table 11 **Median (90% confidence interval) ceftaroline PK parameters by cohort and dose based on individual population PK model-predicted parameters for study P903-31**

Cohort (Age Range)	Dose[a]	n[b]	CL, L/h	C_{max}, µg/mL	$AUC_{0-24h,ss}$, µg•h/mL	$T_{½}$, h
Cohort 1 (12 to < 18 years)	400 mg q8h	8	7.54 (5.49,13.4)	18.6 (9.88,25.7)	159 (92.6,219)	2.01 (1.79,2.45)
Cohort 2 (6 to < 12 years)	12 mg/kg q8h	17	4.61 (3.01,5.81)	23.4 (13.2,32.6)	189 (132,279)	1.65 (1.23,1.91)
Cohort 2 (6 to < 12 years)	400 mg q8h	6	6.14 (3.38,9.23)	22.7 (14.5,33.8)	196 (131,358)	1.89 (1.76,2.52)
Cohort 3 (2 to < 6 years)	12 mg/kg q8h	60	3.28 (2.01,4.83)	24.7 (11.8,30.8)	181 (135,252)	1.54 (1.28,2.03)
Cohort 3 (2 to < 6 years)	400 mg q8h	1	5.26 (5.26-5.26)	27. (27.9-27.9)	228(228.14-228.14)	1.96 (1.96-1.96)
Cohort 3 (2 to < 6 years)	4 mg/kg q8h	1	3.76 (3.76-3.76)	6.45 (6.45-6.45)	51.1 (51.06-51.06)	1.53 (1.53-1.53)
Cohort 4 (2 months to < 2 years)	12 mg/kg q8h	18	1.84 (1.22,3.03)	24.7 (18.6,31.8)	205 (154,285)	1.73 (1.36,2.24)
Cohort 4 (2 to < 6 months)	8 mg/kg q8h	5	1.17 (0.662,1.44)	17.8 (13.0,20.6)	139 (106,192)	1.90 (1.44,2.01)

Table 12 **Median (90% confidence interval) ceftaroline PK parameters by cohort and dose based on individual population PK model-predicted parameters for study P903-24**

Cohort (Age Range)	Dose[a]	n[b]	CL, L/h	C_{max}, µg/mL	$AUC_{0-24h,ss}$, µg•h/mL	$T_{½}$, h
Cohort 1 (12 to < 18 years)	600 mg q8h	5	12.6 (6.02,14.9)	12.7 (10.9,22.4)	143 (121,309)	2.09 (1.81,2.46)
Cohort 2 (6 to < 12 years)	600 mg q8h	1	8.66 (8.66-8.66)	20.2 (20.2-20.2)	208 (207.85-207.85)	1.61 (1.61-1.61)
Cohort 2 (6 to < 12 years)	15 mg/kg q8h	6	5.01 (4.56,7.34)	18.8 (16.0,24.6)	186 (176,256)	1.52 (1.34,1.82)
Cohort 3 (2 to < 6 years)	15 mg/kg q8h	11	3.60 (2.30,5.72)	21.4 (17.2,25.3)	224 (166,258)	1.53 (1.38,1.72)
Cohort 4 (2 months to < 2 years)	15 mg/kg q8h	4	1.42 (1.16-2.85)	25.9 (18.36-27.66)	287 (173.68-331.03)	1.82 (1.35-2.07)
Cohort 4 (2 to < 6 months)	10 mg/kg q8h	2	1.42 (1.28-1.55)	13.5 (13.28-13.78)	162 (145.16-178.12)	1.75 (1.73-1.77)

One hundred simulations were performed for each mg/kg dose, with 600 (300 male and 300 female) patients per 1 week age group from 28 to 40 post-menstrual weeks for each renal function category (normal renal function or mild, moderate, or severe renal impairment) and 600 (300 male and 300 female) patients from each 1 month age group from 0 to <18 years for each renal function category for each simulation. For adults, 300 patients were simulated for each dose and renal function category for each of the 100 simulated data sets. Results were summarized as the median (90% prediction interval),

calculated as median (of the 100 medians), median (of the 100 5th percentiles) and median (of the 100 95th percentiles) by age group.

From these simulations the area under the AUC_{24SS} and $Cmax_{SS}$ were compared to simulations for adult patients at steady-state. Paediatric simulations using 1 h infusions were compared to adults dosed with 600 mg q12h over 1 h and those using 2 h infusions were compared to adults dosed with 600 mg q8h with a 1 or 2 h infusion. Simulations are summarized by age group for normal renal function patients and those with mild impairment according to the regimens used in P903-23 and P903-31. It should be noted that the 600 mg q8h adult dose regimen is not currently approved in adults and the MAH does not propose to include equivalent dosing for children in this extension of indication application.

Table 13 **Median (90% PI) ceftaroline $C_{max,ss}$ and $AUC_{24,ss}$ by age following doses used in studies P903-23 and P903-31 to steady-state in paediatric patients with normal renal functions, based on simulations**

AGE	Weight (kg)	C_{maxSS} (mg/L)	AUC_{24SS} (mg*hr/L)	Dose*
Adults 600 mg q12h 1 hr	77.6 (52.5,105)	21.0 (11.9,36.5)	97.3 (59.1,164)	600 mg
12-<18 years	52.9 (36.8,75.3)	19.7 (11.0,34.2)	122 (72.7,201)	12 mg/kg (max of 400 mg)
6-<12 years	28.5 (19.3,46.5)	27.6 (16.4,43.3)	157 (99.7,245)	12 mg/kg (max of 400 mg)
2-<6 years	15.8 (11.8,22.2)	27.1 (16.8,41.8)	144 (92.6,225)	12 mg/kg (max of 400 mg)
18-<24 months	11.7 (9.81,14.1)	28.3 (17.6,43.4)	160 (104,247)	12 mg/kg (max of 400 mg)
12-<18 months	10.4 (8.60,12.7)	28.7 (17.9,44.0)	168 (109,260)	12 mg/kg (max of 400 mg)
6-<12 months	8.43 (6.55,10.7)	29.3 (18.2,45.1)	182 (116,282)	12 mg/kg (max of 400 mg)
2-<6 months	5.75 (4.12,7.66)	19.2 (12.1,29.7)	134 (86.6,208)	8 mg/kg (max of 400 mg)

Median (5th, 95th percentile) based on summary of 100 trials and corresponds to median (90% PI). Adult dose and regimen is listed in first row of column 1. *Paediatric dose administered q8h as 1 hour infusion.

Table 14 **Median (90% PI) ceftaroline $C_{max,ss}$ and $AUC_{24,ss}$ by age following doses used in studies P903-23 and P903-31 to steady-state in paediatric patients with mild renal impairment, based on simulations**

AGE	Weight (kg)	C_{maxSS} (mg/L)	AUC_{24SS} (mg*hr/L)	Dose*
Adults 600 mg q12h 1 hr	75.4 (51.9, 99.9)	22.5 (12.8,39.2)	113 (66.7,197)	600 mg
12-<18 years	52.7 (36.7,74.7)	20.7 (11.5,35.6)	136 (80.9,227)	12 mg/kg (max of 400 mg)
6-<12 years	28.6 (19.2,46.8)	28.8 (17.0,45.4)	175 (110,276)	12 mg/kg (max of 400 mg)
2-<6 years	15.8 (11.8,22.4)	28.3 (17.5,44.0)	160 (102,252)	12 mg/kg (max of 400 mg)
18-<24 months	11.7 (9.82,14.1)	31.0 (19.1,47.9)	201 (124,325)	12 mg/kg (max of 400 mg)
12-<18 months	10.4 (8.58,12.7)	31.5 (19.5,48.9)	210 (130,343)	12 mg/kg (max of 400 mg)
6-<12 months	8.43 (6.56,10.8)	32.2 (20.0,49.9)	227 (140,370)	12 mg/kg (max of 400 mg)
2-<6 months	5.75 (4.11,7.67)	21.2 (13.2,33.3)	168 (103,275)	8 mg/kg (max of 400 mg)

Median (5th, 95th percentile) based on summary of 100 trials and corresponds to median (90% PI). Adult dose and regimen is listed in first row of column 1. *Paediatric dose administered q8h as 1 hour infusion.

The median Cmax and AUC values in children aged 2 months to <18 years with normal renal function dosed with the regimens used in studies P903-23 and P903-31 were predicted to be up to 40% and 87% greater, respectively, than the median Cmax and AUC values in adults dosed with 600 mg q12h. The median Cmax and AUC values in children aged 2 months to <18 years with mild renal impairment dosed with the above regimen were predicted to be up to 43% and 100% greater, respectively, than the median Cmax and AUC values in adults dosed with 600 mg q12h.

Although no new safety issues were identified with the dose regimens used in P903-23, P903-31 and P903-24 the increased exposure in paediatric patients relative to the median exposure in adults

suggested that doses that are lower and more reflective of exposure in adults may be efficacious in the ≤24 months age group.

Proposed paediatric doses

The %*f*T>MIC for ceftaroline was previously identified as the PK/PD index and the PK/PD targets are shown below for *Staphylococcus aureus*, *Streptococcus pneumoniae* and *Enterobacteriaceae* based on a neutropenic murine thigh and lung infection model.

Table 15 Median (min-max range) of the PK/PD target (%fT>MIC) based on *in vivo* efficacy of ceftaroline in the neutropenic murine thigh infection model against various CAP pathogens

	Median % *f*T>MIC (range)		
Organism (N)	**Stasis**	**1 log_{10} kill**	**2 log_{10} kill**
Staphylococcus aureus (n=4)	26% (15-36%)	35% (18-44%)	51% (23-56%)
Streptococcus pneumoniae (n=5)	35% (29-52%)	44% (33-59%)	51% (36-64%)
Enterobacteriaceae (*E. coli* [n=2], *K. pneumoniae* [n=2])*	48.5% (30-59%)	73% (39-89%)	ND

Source: Report P0903-M-003 Addendum 1.

* *K. pneumoniae* 43816 (lung) data are included for stasis and 1 log_{10} kill but 2- log_{10} kill data are only available for the strains *E. coli* 25922 yielding a value of 47%T>MIC.

Paediatric dose selection was based on predictions of achieving 36%, 44% or 73% *f*T>MIC for *S. aureus, S. pneumoniae* and *Enterobacteriaceae*, respectively. The final dose selection was based on achieving >90% PTA against the current breakpoints of 1 mg/L for *S. aureus*, 0.25 mg/L for *S. pneumoniae* and 0.5 mg/L for *Enterobacteriaceae*.

Based on meeting the criteria described above the proposed doses for paediatric patients are not the same as the doses used in the clinical studies. As shown below, 12 mg/kg q8h as a 1 h infusion in children aged from ≥ 24 months to < 18 years and 8 mg/kg q8h as 1 h infusion in children aged from ≥ 2 months to < 24 months achieved good PTA in subsets with normal and mildly impaired renal function:

Table 16 Probability of target attainment by MIC and age group based on simulations for paediatric patients with normal renal function following proposed paediatric doses

MIC	Age Range, Dose[a]							
(mg/L)	12 to <18 years 12 mg/kg q8h	6 to <12 years 12 mg/kg q8h	2 to <6 years 12 mg/kg q8h	18 to <24 months 8 mg/kg q8h	12 to <18 months 8 mg/kg q8h	6 to <12 months 8 mg/k q8h	2 to <6 months 8 mg/kg q8h	Adults, 600 mg q12h
					36% *f*T>MIC			
0.125	100	100	100	100	100	100	100	100
0.25	100	100	100	100	100	100	100	100
0.5	100	100	100	100	100	100	100	100
1	100	100	100	100	100	100	100	99.7
2	97.0	99.4	98.2	94.0	95.9	98.5	99.8	81.0
4	44.7	71.6	56.8	28.3	36.0	48.4	68.5	16.3
8	1.33	5.00	2.25	0.167	0.250	0.833	2.75	0.333
					44% *f*T>MIC			
0.125	100	100	100	100	100	100	100	100
0.25	100	100	100	100	100	100	100	100
0.5	100	100	100	100	100	100	100	100
1	99.8	100	99.8	99.3	99.7	99.8	100	95.5
2	88.2	95.5	89.1	76.8	82.2	90.7	97.5	53.2
4	22.7	42.5	27.8	10.3	14.0	23.2	43.5	5.00
8	0.333	1.17	0.50	0.00	0.00	0.167	0.75	0.00

				73% *f*T>MIC				
0.125	100	100	100	100	100	100	100	99.7
0.25	100	100	99.0	98.8	99.3	99.7	100	95.7
0.5	97.7	97.5	90.4	87.4	91.2	95.7	99.0	73.0
1	73.7	77.3	55.8	46.2	54.3	68.1	87.6	29.0
2	18.8	25.8	11.8	5.83	8.83	15.6	37.0	3.33
4	0.667	1.50	0.500	0.00	0.00	0.333	2.25	0.00
8	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00

Table 17 Probability of target attainment by MIC and age group based on simulations for paediatric patients with mild renal impairment following proposed paediatric doses

MIC (mg/L)	Age Range, Dose[a]							
	12 to <18 years 12 mg/kg q8h	6 to <12 years 12 mg/kg q8h	2 to <6 years 12 mg/kg q8h	18 to <24 months 8 mg/kg q8h	12 to <18 months 8 mg/kg q8h	6 to <12 months 8 mg/k q8h	2 to <6 months 8 mg/kg q8h	Adults, 600 mg q12h
					36% *f*T>MIC			
0.125	100	100	100	100	100	100	100	100
0.25	100	100	100	100	100	100	100	100
0.5	100	100	100	100	100	100	100	100
1	100	100	100	100	100	100	100	99.7
2	98.8	99.8	99.2	98.8	99.3	99.8	100	81.0
4	60.0	83.8	72.6	61.8	68.5	78.4	89.5	16.7
8	3.50	11.6	6.25	3.50	5.00	9.17	16.8	0.00
					44% *f*T>MIC			
0.125	100	100	100	100	100	100	100	100
0.25	100	100	100	100	100	100	100	100
0.5	100	100	100	100	100	100	100	100
1	100	100	100	99.8	100	100	100	95.7
2	94.0	98.2	95.1	99.3	95.6	97.9	99.5	52.8
4	38.0	61.2	44.2	39.7	45.8	58.9	75.1	5.33
8	1.17	3.83	1.75	1.17	1.83	3.50	8.50	0.00
					73% *f*T>MIC			
0.125	100	100	100	100	100	100	100	99.7
0.25	100	100	99.5	99.8	99.8	100	100	95.8
0.5	99.2	99.0	95.5	97.0	98.2	99.2	99.8	72.7
1	85.8	88.2	71.9	78.8	83.7	90.4	97.0	27.7
2	34.8	43.4	25.0	32.5	39.5	52.7	72.9	3.00
4	2.33	4.67	1.75	2.75	4.25	7.83	18.2	0.00
8	0.00	0.00	0.00	0.00	0.00	0.00	0.250	0.00

Based on the PTA the proposed q8h dose for those aged 6 to <24 months has been lowered from that used in the clinical studies (see predicted exposures at the doses that were used in tables 5 and 6 above, which include the 2-<6 month group not shown again in Table 10) to 8 mg/kg q8h. This dose reduces the exposures in children aged 6-24 months and makes them more comparable with adults as shown below.

Table 18 **Median (90% PI) ceftaroline steady-state $C_{max, ss}$ and $AUC_{24,ss}$, by age following the proposed dose for subjects aged from 6 to <24 months in paediatric patients with either normal renal function, or mild renal impairment based on simulations**

AGE	Weight (kg)	C_{maxSS} (mg/L)	AUC_{24SS} (mg*hr/L)	Dose*
Adults 600 mg q12h 1 hr	77.6 (52.5,105)	21.0 (11.9,36.5)	97.3 (59.1,164)	600 mg
Normal renal function (CrCL >80ml/min)				
12-<18 years	52.9 (36.8,75.3)	19.7 (11.0,34.2)	122 (72.7,201)	12 mg/kg (max of 400 mg)
6-<12 years	28.5 (19.3,46.5)	27.6 (16.4,43.3)	157 (99.7,245)	12 mg/kg (max of 400 mg)
2-<6 years	15.8 (11.8,22.2)	27.1 (16.8,41.8)	144 (92.6,225)	12 mg/kg (max of 400 mg)
18-<24 months	11.7 (9.8,14.1)	18.8 (11.8,29.1)	107 (69.0,165)	8 mg/kg (max of 400 mg)
12-<18 months	10.4 (8.6,12.7)	19.1 (11.9,29.4)	113 (71.8,174)	8 mg/kg (max of 400 mg)
6-<12 months	8.43 (6.55,10.7)	19.6 (12.2,30.0)	120 (78.3,188)	8 mg/kg (max of 400 mg)
Mild renal impairment (>50ml/min CrCL < 80ml/min				
Adults 600 mg q12h 1 hr	77.6 (52.2,105)	20.9 (11.7,36.6)	97.1 (58.8,164)	600 mg
12-<18 years	52.7 (36.7,74.7)	20.7 (11.5,35.6)	136 (80.9,227)	12 mg/kg (max of 400 mg)
6-<12 years	28.6 (19.2,46.8)	28.8 (17.0,45.4)	175 (110,276)	12 mg/kg (max of 400 mg)
2-<6 years	15.8 (11.8,22.4)	28.3 (17.5,44.0)	160 (102,252)	12 mg/kg (max of 400 mg)
18-<24 months	11.7 (9.8,14.1)	20.6 (12.8,32.3)	133 (82.7,219)	8 mg/kg (max of 400 mg)
12-<18 months	10.4 (8.6,12.7)	20.9 (13.0,32.6)	140 (86.0,227)	8 mg/kg (max of 400 mg)
6-<12 months	8.43 (6.55,10.7)	21.4 (13.3,33.3)	152 (92.6,247)	8 mg/kg (max of 400 mg)

Additional analyses reported in CPT-MS-08

Infants < 2 months

CHMP noted that the MAH did not explain why dose recommendations are not made for infants < 2 months and that it did not discuss the additional analyses provided in CPT-MS-08.

The following tables present the target data as median (90% prediction interval) of the %fT>MIC predicted.

A dose of 4 mg/kg q8h as a 1 h infusion to preterm neonates (GA 28 to <40 weeks) and infants up to <2 months is predicted to provide median ceftaroline AUC_{24SS} that range from 59.5% to 77.8% and median ceftaroline $Cmax_{SS}$ that range from 35.3% to 44.7% of the respective adult median values using the approved adult dose. The report states that the median free percent time above MIC (*f*PTAM) for MICs of 1 and 2 mg/L were similar to or exceeded median *f*PTAM values in adults.

Table 19 Median (90% PI) ceftaroline state $C_{max, ss}$ $AUC_{24,ss}$ %T>MIC by age for normal renal function following doses used in studies P903-23 and P903-31 to steady-state for ceftaroline in paediatric patients based on simulations

AGE	Weight (kg)	CmaxSS (mg/L)	AUC24SS (mg*hr/L)	%T>MIC of 1 mg/L	%T>MIC of 2 mg/L	Dose*
Adults 600 mg q12h 1 hr	77.6 (52.5,105)	21.0 (11.9,36.5)	97.3 (59.1,164)	64.0 (44.6,93.4)	45.0 (29.8,68.6)	600 mg
12-<18 years	52.9 (36.8,75.3)	19.7 (11.0,34.2)	122 (72.7,201)	84.0 (59.3,100)	59.3 (38.9,88.9)	12 mg/kg (max of 400 mg)
6-<12 years	28.5 (19.3,46.5)	27.6 (16.4,43.3)	157 (99.7,245)	85.2 (61.7,100)	63.0 (44.4,91.4)	12 mg/kg (max of 400 mg)
2-<6 years	15.8 (11.8,22.2)	27.1 (16.8,41.8)	144 (92.6,225)	75.3 (54.3,98.8)	56.8 (40.7,81.5)	12 mg/kg (max of 400 mg)
18-<24 months	11.7 (9.81,14.1)	28.3 (17.6,43.4)	160 (104,247)	82.7 (60.5,100)	63.0 (45.6,88.9)	12 mg/kg (max of 400 mg)
12-<18 months	10.4 (8.60,12.7)	28.7 (17.9,44.0)	168 (109,260)	86.7 (63.0,100)	66.7 (47.5,92.7)	12 mg/kg (max of 400 mg)
6-<12 months	8.43 (6.55,10.7)	29.3 (18.2,45.1)	182 (116,282)	93.2 (67.9,100)	71.6 (50.6,97.5)	12 mg/kg (max of 400 mg)
2-<6 months	5.75 (4.12,7.66)	19.2 (12.1,29.7)	134 (86.6,208)	92.6 (66.7,100)	67.9 (46.9,96.3)	8 mg/kg (max of 400 mg)
1-<2 months	4.69 (3.63,5.77)	9.37 (5.87,14.4)	69.7 (45.4,108)	72.8 (50.6,97.5)	44.4 (27.2,69.1)	4 mg/kg (max of 400 mg)
0-<1 month	3.88 (2.91,4.75)	8.94 (5.58,14.0)	72.0 (46.8,111)	79.0 (54.3,100)	48.1 (28.3,75.3)	4 mg/kg (max of 400 mg)
GA 38-<40 weeks	3.40 (2.55,4.24)	8.45 (5.26,13.3)	75.8 (49.2,117)	88.9 (61.7,100)	53.1 (29.6,84.0)	4 mg/kg (max of 400 mg)
GA 36-<38 weeks	2.87 (2.07,3.75)	8.33 (5.14,13.0)	72.9 (47.4,113)	85.2 (58.0,100)	50.6 (28.4,80.9)	4 mg/kg (max of 400 mg)
GA 34-<36 weeks	2.32 (1.71,3.05)	8.09 (5.05,12.7)	69.2 (44.8,107)	80.2 (54.3,100)	46.9 (25.9,75.5)	4 mg/kg (max of 400 mg)
GA 32-<34 weeks	1.89 (1.38,2.44)	7.89 (4.88,12.2)	65.7 (42.7,101)	75.6 (51.9,98.8)	44.4 (24.7,70.4)	4 mg/kg (max of 400 mg)
GA 30-<32 weeks	1.50 (1.05,1.95)	7.68 (4.76,12.0)	61.9 (40.1,95.7)	71.6 (48.1,97.5)	40.7 (22.2,66.7)	4 mg/kg (max of 400 mg)
GA 28-<30 weeks	1.15 (0.779,1.52)	7.41 (4.58,11.6)	57.9 (37.3,89.8)	66.7 (45.7,95.1)	38.3 (19.8,61.7)	4 mg/kg (max of 400 mg)

***Paediatric dose administered q8h as 1 hour infusion.**

Corresponding predicted AUC and Cmax values (for 4 mg/kg q8h as a 1 h infusion to preterm neonates GA 28 to <40 weeks and infants up to <2 months) in the presence of mild renal impairment are higher (74.6% to 97.6% and 38.9% to 49.2%, respectively) than shown above. The report states that the median *f*PTAM for MICs of 1 and 2 mg/L exceeded median *f*PTAM values in adults.

Table 20 Median (90% PI) ceftaroline state $C_{max, ss}$ $AUC_{24,ss}$ %T>MIC by age for mild renal impairment following doses used in studies P903-23 and P903-31 to steady-state for ceftaroline in paediatric patients based on simulations

AGE	Weight (kg)	CmaxSS (mg/L)	AUC24SS (mg*hr/L)	%T>MIC of 1 mg/L	%T>MIC of 2 mg/L	Dose*
Adults 600 mg q12h 1 hr	77.6 (52.2,105)	20.9 (11.9,36.4)	97.3 (59.0,164)	64.5 (44.6,93.4)	44.6 (29.8,68.6)	600 mg**
Adults 600 mg q12h 1 hr	75.4 (51.9,99.9)	22.5 (12.8,39.2)	113 (66.7,197)	73.6 (49.6,100)	52.1 (33.8,84.4)	600 mg***
12-<18 years	52.7 (36.7,74.7)	20.7 (11.5,35.6)	136 (80.9,227)	92.6 (65.4,100)	66.7 (43.2,96.3)	12 mg/kg (max of 400 mg)
6-<12 years	28.6 (19.2,46.8)	28.8 (17.0,45.4)	175 (110,276)	93.8 (66.7,100)	70.4 (48.1,97.5)	12 mg/kg (max of 400 mg)
2-<6 years	15.8 (11.8,22.4)	28.3 (17.5,44.0)	160 (102,252)	82.7 (59.3,100)	63.0 (44.4,90.2)	12 mg/kg (max of 400 mg)
18-<24 months	11.7 (9.82,14.1)	31.0 (19.1,47.9)	201 (124,325)	98.8 (70.4,100)	79.0 (53.1,100)	12 mg/kg (max of 400 mg)
12-<18 months	10.4 (8.58,12.7)	31.5 (19.5,48.9)	210 (130,343)	98.8 (72.8,100)	82.7 (55.6,100)	12 mg/kg (max of 400 mg)
6-<12 months	8.43 (6.56,10.8)	32.2 (20.0,49.9)	227 (140,370)	100 (79.0,100)	90.1 (60.5,100)	12 mg/kg (max of 400 mg)
2-<6 months	5.75 (4.11,7.67)	21.2 (13.2,33.3)	168 (103,275)	100 (77.8,100)	86.4 (55.6,100)	8 mg/kg (max of 400 mg)
1-<2 months	4.69 (3.63,5.77)	10.3 (6.46,16.1)	87.6 (54.0,141)	91.4 (60.4,100)	59.3 (33.3,93.8)	4 mg/kg (max of 400 mg)
0-<1 month	3.86 (2.91,4.75)	9.88 (6.14,15.6)	90.0 (55.1,145)	96.3 (65.4,100)	63.3 (35.8,96.4)	4 mg/kg (max of 400 mg)
GA 38-<40 weeks	3.40 (2.56,4.26)	9.53 (5.87,15.1)	94.8 (58.8,152)	98.8 (74.0,100)	71.6 (39.4,98.8)	4 mg/kg (max of 400 mg)
GA 36-<38 weeks	2.86 (2.06,3.77)	9.31 (5.77,14.7)	90.9 (56.3,148)	98.8 (69.7,100)	67.9 (35.8,98.8)	4 mg/kg (max of 400 mg)
GA 34-<36 weeks	2.33 (1.73,3.06)	9.11 (5.58,14.2)	86.5 (53.3,141)	96.3 (66.6,100)	63.0 (34.6,97.5)	4 mg/kg (max of 400 mg)
GA 32-<34 weeks	1.89 (1.38,2.44)	8.76 (5.44,13.8)	82.2 (50.4,134)	93.8 (62.9,100)	59.3 (32.0,95.1)	4 mg/kg (max of 400 mg)
GA 30-<32 weeks	1.50 (1.06,1.95)	8.49 (5.27,13.4)	77.7 (47.4,126)	90.4 (58.0,100)	55.6 (29.0,91.4)	4 mg/kg (max of 400 mg)
GA 28-<30 weeks	1.16 (0.779,1.53)	8.19 (5.03,12.9)	72.5 (44.8,117)	84.0 (54.3,100)	50.6 (25.9,86.4)	4 mg/kg (max of 400 mg)

***Paediatric dose administered q8h as 1 hour infusion. **Results for adults with normal renal function. ***Results for adults with mild renal impairment.**

Additional tables were generated to compare PK in children dosed q8h using 2-h infusions with adults dosed q8h dosing using 1-h or 2-h infusions. The predicted exposures at these alternative paediatric doses using 2 h infusions are of some interest and can be compared to the results in adults using the approved regimen of q12h with 1 h infusions as shown in the tables above.

Compared to the approved adult dose in normal renal function (600 mg q12h using 1-h infusions) shown in the tables above, 5 mg/kg doses using 2-h infusions in the age groups shown in the tables below give similar or slightly lower AUCs.

Table 21 **Median (90% PI) ceftaroline $C_{max, ss}$ $AUC_{24,ss}$ %T>MIC by age for normal renal function following doses used in studies P903-24 to steady-state for ceftaroline in paediatric patients based on simulations**

AGE	Weight (kg)	CmaxSS (mg/L)	AUC24SS (mg*hr/L)	%T>MIC of 1 mg/L	%T>MIC of 2 mg/L	Dose*
Adults 600 mg q8h 1 hr	77.6 (52.5,105)	21.8 (12.5,38.0)	146 (87.8,249)	96.3 (67.9,100)	70.4 (45.7,98.8)	600 mg
Adults 600 mg q8h 2 hr	77.6 (52.5,105)	17.6 (10.5,29.3)	146 (88.6,246)	98.8 (75.3,100)	76.5 (51.8,100)	600 mg
12-<18 years	52.9 (36.8,75.3)	23.2 (13.7,37.3)	182 (110,293)	98.8 (77.8,100)	80.2 (56.8,100)	15 mg/kg (max of 600 mg)
6-<12 years	28.5 (19.3,46.5)	27.5 (17.5,41.4)	205 (131,316)	97.5 (74.1,100)	78.7 (56.8,100)	15 mg/kg (max of 600 mg)
2-<6 years	15.8 (11.8,22.2)	25.5 (16.6,38.2)	180 (116,279)	88.9 (66.6,100)	69.1 (50.6,95.1)	15 mg/kg (max of 600 mg)
18-<24 months	11.7 (9.81,14.1)	27.1 (17.5,40.6)	200 (130,310)	95.7 (72.8,100)	76.5 (56.8,98.8)	15 mg/kg (max of 600 mg)
12-<18 months	10.4 (8.60,12.7)	27.7 (18.0,41.6)	210 (135,324)	97.5 (75.3,100)	79.0 (59.2,100)	15 mg/kg (max of 600 mg)
6-<12 months	8.43 (6.55,10.7)	28.9 (18.7,43.2)	227 (147,350)	100 (80.2,100)	85.2 (63.0,100)	15 mg/kg (max of 600 mg)
2-<6 months	5.75 (4.12,7.66)	19.8 (12.8,29.7)	168 (109,260)	98.8 (79.0,100)	82.7 (59.3,100)	10 mg/kg (max of 600 mg)
1-<2 months	4.69 (3.63,5.77)	9.74 (6.24,14.7)	87.3 (56.5,134)	88.3 (63.0,100)	59.3 (38.2,86.5)	5 mg/kg (max of 600 mg)
0-<1 month	3.88 (2.91,4.75)	9.50 (6.15,14.5)	90.0 (58.6,138)	93.8 (67.9,100)	63.0 (40.7,91.4)	5 mg/kg (max of 600 mg)
GA 38-<40 weeks	3.40 (2.55,4.24)	9.29 (5.93,14.2)	94.9 (61.9,147)	98.8 (75.3,100)	70.4 (44.4,97.5)	5 mg/kg (max of 600 mg)
GA 36-<38 weeks	2.87 (2.07,3.75)	9.06 (5.81,13.9)	91.1 (59.3,141)	97.5 (72.8,100)	66.7 (41.9,95.1)	5 mg/kg (max of 600 mg)
GA 34-<36 weeks	2.32 (1.71,3.05)	8.76 (5.62,13.5)	86.8 (56.2,134)	95.1 (69.1,100)	63.0 (38.3,92.6)	5 mg/kg (max of 600 mg)
GA 32-<34 weeks	1.89 (1.38,2.44)	8.55 (5.45,13.1)	82.3 (53.6,127)	91.4 (65.4,100)	59.3 (35.8,87.7)	5 mg/kg (max of 600 mg)
GA 30-<32 weeks	1.50 (1.05,1.95)	8.17 (5.21,12.6)	77.5 (50.1,120)	87.7 (61.7,100)	55.2 (33.3,84.0)	5 mg/kg (max of 600 mg)
GA 28-<30 weeks	1.15 (0.779,1.52)	7.85 (4.99,12.2)	72.4 (46.4,113)	81.5 (58.0,100)	50.6 (29.6,77.8)	5 mg/kg (max of 600 mg)

***Paediatric dose administered q8h as 2 hour infusion.**

Table 22 **Median (90% PI) ceftaroline $C_{max, ss}$ $AUC_{24,ss}$ %T>MIC by age for mild renal impairment following doses used in studies P903-24 to steady-state for ceftaroline in paediatric patients based on simulations

AGE	Weight (kg)	CmaxSS (mg/L)	AUC24SS (mg*hr/L)	%T>MIC of 1 mg/L	%T>MIC of 2 mg/L	Dose*
Adults 600 mg q8h 1 hr	77.6 (52.2,105)	21.9 (12.4,38.3)	146 (87.8,249)	96.3 (67.9,100)	70.4 (45.7,98.8)	600 mg**
Adults 600 mg q8h 2 hr	77.6 (52.2,105)	17.5 (10.5,29.4)	146 (87.9,248)	98.8 (75.2,100)	76.5 (51.8,100)	600 mg**
Adults 600 mg q8h 1 hr	75.4 (51.9,99.9)	23.6 (13.5,41.3)	170 (100,296)	100 (76.4,100)	82.7 (51.9,100)	600 mg***
Adults 600 mg q8h 2 hr	75.4 (51.9,99.9)	19.4 (11.5,32.7)	169 (101,295)	100 (82.7,100)	88.6 (58.0,100)	600 mg***
12-<18 years	52.7 (36.7,74.7)	24.5 (14.5,40.0)	202 (121,329)	100 (84.0,100)	88.9 (61.7,100)	15 mg/kg (max of 600 mg)
6-<12 years	28.6 (19.2,46.8)	29.2 (18.5,44.3)	227 (144,358)	100 (80.2,100)	86.4 (61.7,100)	15 mg/kg (max of 600 mg)
2-<6 years	15.8 (11.8,22.4)	27.1 (17.5,40.8)	199 (127,313)	95.1 (70.4,100)	75.3 (55.5,98.8)	15 mg/kg (max of 600 mg)
18-<24 months	11.7 (9.82,14.1)	30.8 (19.6,47.1)	251 (154,409)	100 (82.7,100)	92.6 (65.4,100)	15 mg/kg (max of 600 mg)
12-<18 months	10.4 (8.58,12.7)	31.3 (20.0,48.1)	262 (163,428)	100 (85.2,100)	95.1 (67.9,100)	15 mg/kg (max of 600 mg)
6-<12 months	8.43 (6.56,10.8)	32.8 (21.0,49.8)	284 (176,459)	100 (92.5,100)	98.8 (72.8,100)	15 mg/kg (max of 600 mg)
2-<6 months	5.75 (4.11,7.67)	22.3 (14.2,34.3)	210 (130,343)	100 (91.3,100)	97.5 (69.1,100)	10 mg/kg (max of 600 mg)
1-<2 months	4.69 (3.63,5.77)	11.1 (6.99,17.1)	109 (67.6,177)	98.8 (74.1,100)	75.3 (46.9,100)	5 mg/kg (max of 600 mg)
0-<1 month	3.86 (2.91,4.75)	10.8 (6.88,16.7)	113 (69.7,181)	100 (80.2,100)	81.5 (49.4,100)	5 mg/kg (max of 600 mg)
GA 38-<40 weeks	3.40 (2.56,4.26)	10.7 (6.74,16.6)	119 (74.1,193)	100 (90.1,100)	90.1 (55.5,100)	5 mg/kg (max of 600 mg)
GA 36-<38 weeks	2.86 (2.06,3.77)	10.3 (6.55,16.3)	114 (70.1,186)	100 (85.2,100)	86.4 (51.8,100)	5 mg/kg (max of 600 mg)
GA 34-<36 weeks	2.33 (1.73,3.06)	10.0 (6.32,15.8)	109 (66.8,176)	100 (81.5,100)	82.7 (48.1,100)	5 mg/kg (max of 600 mg)
GA 32-<34 weeks	1.89 (1.38,2.44)	9.73 (6.12,15.1)	103 (63.4,166)	100 (77.8,100)	77.8 (45.6,100)	5 mg/kg (max of 600 mg)
GA 30-<32 weeks	1.50 (1.06,1.95)	9.32 (5.85,14.5)	97.0 (59.7,158)	98.8 (72.8,100)	71.6 (41.9,98.8)	5 mg/kg (max of 600 mg)
GA 28-<30 weeks	1.16 (0.779,1.53)	8.98 (5.60,14.1)	90.4 (55.6,148)	96.3 (67.9,100)	66.7 (38.3,97.5)	5 mg/kg (max of 600 mg)

***Paediatric dose administered q8h as 2 hour infusion. **Results for adults with normal renal function. ***Results for adults with mild renal impairment.**

It was clarified by the MAH during the procedure that dosing recommendations for children below 2 months of age will be the subject of a future application and that the suitability of the dose resulting from the above (5 mg/kg in a 2h infusion) will be considered, along with the suitability of any other proposed dose. This was agreed by CHMP.

Adolescents 12 - < 17 years

The initial dose recommendation proposed by the MAH for adolescents (400 mg q8h) differed from that in adults (600 mg q12h). Since it was unusual that adolescents are dosed differently to adults with antibacterial agents, especially for beta-lactam agents with relatively simple pharmacokinetics, CHMP asked the MAH to clarify this aspect.

The updated report presented results from Monte Carlo simulations that used the final population PK model, a measure of parameter uncertainty and appropriate covariate distributions for steady-state simulations of ceftaroline. Simulations were performed for the approved adult regimen and dosing regimens for patients aged 6 to <18 years with normal renal function or mild or moderate renal impairment. Covariates for the adult simulations were generated from a multivariate normal distribution based on the co-variances observed in the population PK data in patients. Weights for the paediatric age groups were based on CDC Growth Charts.

Simulations were performed for the following regimens:

- 600 mg every 12 hours as a 1 hour infusion (adult) - normal renal function
- 18 mg/kg (max 600 mg) every 12 hours as a 1 hour infusion - normal renal function
- 18 mg/kg (max 600 mg) every 12 hours as a 1 hour infusion - mild renal impairment
- 9 mg/kg (max 400 mg from 44.5 kg) every 12 hours as a 1 hour infusion - moderate renal impairment
- 12 mg/kg (max 400 mg from 33 kg) every 12 hours as a 1 hour infusion - moderate renal impairment

[of note, for adults with moderate renal impairment the recommended dose is 400 mg q12h]

The *f*PTAM and percentages of patients with a *f*PTAM 26%, 30%, 35%, 40%, 44%, 48.5%, 51%, 55%, 60% and 73% were presented in tabular format for MICs of 0.125 - 8 mg/L. Paediatric simulations of AUC_{24SS}, CmaxSS and *f*PTAM for various targets were compared to simulations for adult patients at steady state after administration of the approved dose. One hundred simulations were performed for each mg/kg dose, with 600 (300 male and 300 female) patients from each 1 month age group from 6–<18 years for normal renal function and mild or moderate renal impairment.

For adults, 300 patients were simulated for each dose for each of the 100 simulated data sets. Results were summarised as the median (90% prediction interval), calculated as median (of the 100 medians), median (of the 100 5*th* percentiles and 95*th* percentiles) by age group (6 to <12 and 12 to <18 years) and renal function category.

Normal Renal Function - 1 hr infusion - 18 mg/kg q12h

The 18 mg/kg dose (max 600 mg; which would be the dose used from 33 kg upwards) given every 12 h gave estimated PK parameters in adolescents that were very similar to those using the approved dose in adults as shown below.

Table 23 Median(90%PI), ceftaroline $C_{max, ss}$, $AUC_{24, ss}$, %T>MIC by age for normal renal function following 18 mg/kg (max of 600 mg) q12h dosing (1 hour infusion) to steady-state for ceftaroline in paediatric patients based on simulations

AGE	Weight (kg)	CmaxSS (mg/L)	AUC24SS (mg*hr/L)	%T>MIC of 1 mg/L	%T>MIC of 2 mg/L
Adults 600 mg q12h 1 hr	77.6 (52.5,105)	20.9 (11.9,36.8)	97.7 (58.9,165)	64.5 (44.6,93.4)	45.5 (29.8,68.7)
12-<18 years	52.8 (36.9,75.1)	28.6 (16.0,49.5)	122 (73.7,202)	64.5 (46.3,90.5)	47.9 (33.1,68.6)
6-<12 years	28.5 (19.3,46.6)	40.5 (23.7,64.0)	158 (99.8,246)	64.7 (47.1,89.3)	50.4 (36.4,70.3)

AGE	Weight (kg)	CmaxSS Ratios	AUC24SS Ratios	%T>MIC of 1 mg/L Ratios	%T>MIC of 2 mg/L Ratios
12-<18 years	52.8 (36.9,75.1)	1.37	1.25	1.00	1.05
6-<12 years	28.5 (19.3,46.6)	1.94	1.62	1.00	1.11

Ratios based on summary of 100 trials. Ratios are relative to adult dosing regimen and represent ratio of paediatric median to adult median for adult dose of 600 mg q12h 1 hr inf.

Mild Renal Impairment - 1 hr infusion

The 18 mg/kg q12h dose in adolescents with mild renal impairment gave slightly higher exposures compared to adolescents with normal renal function. The ratios for Cmax and AUC vs. adults were both 1.4-fold.

Table 24 Median(90%PI), ceftaroline $C_{max, ss}$, $AUC_{24, ss}$, %T>MIC by age for mild renal impairment following 18 mg/kg (max of 600 mg) q12h dosing (1 hour infusion) to steady-state for ceftaroline in paediatric patients based on simulations

AGE	Weight (kg)	CmaxSS (mg/L)	AUC24SS (mg*hr/L)	%T>MIC of 1 mg/L	%T>MIC of 2 mg/L
Adults 600 mg q12h 1 hr	77.6 (52.5,105)	20.9 (11.9,36.8)	97.7 (58.9,165)	64.5 (44.6,93.4)	45.5 (29.8,68.7)
12-<18 years	52.8 (36.9,75.1)	29.7 (16.6,51.6)	135 (81.4,226)	71.3 (50.8,97.5)	53.5 (36.4,77.7)
6-<12 years	28.5 (19.3,46.6)	42.1 (24.7,66.7)	175 (110,278)	71.1 (51.2,97.5)	55.4 (39.7,79.3)

AGE	Weight (kg)	CmaxSS Ratios	AUC24SS Ratios	%T>MIC of 1 mg/L Ratios	%T>MIC of 2 mg/L Ratios
12-<18 years	52.8 (36.9,75.1)	1.42	1.39	1.11	1.18
6-<12 years	28.5 (19.3,46.6)	2.02	1.80	1.10	1.22

Ratios based on summary of 100 trials. Ratios are relative to adult dosing regimen and represent ratio of paediatric median to adult median for adult dose of 600 mg q12h 1 hr inf.

Moderate Renal Impairment - 1 hr infusion

The reduction to 9 mg/kg (maximum 400 mg) q12h gave predicted exposures in adolescents with moderate renal impairment that were almost identical to those in adults using the approved regimen for normal renal function.

Table 25 Median(90%PI), ceftaroline $C_{max, ss}$, $AUC_{24, ss}$, %T>MIC by age for moderate renal impairment following 9 mg/kg (max of 400 mg) q12h dosing (1 hour infusion) to steady-state for ceftaroline in paediatric patients based on simulations

AGE	Weight (kg)	CmaxSS (mg/L)	AUC24SS (mg*hr/L)	%T>MIC of 1 mg/L	%T>MIC of 2 mg/L
Adults 600 mg q12h 1 hr	77.6 (52.5,105)	20.9 (11.9,36.8)	97.7 (58.9,165)	64.5 (44.6,93.4)	45.5 (29.8,68.7)
12-<18 years	52.8 (36.9,75.1)	20.9 (11.9,34.9)	111 (67.9,180)	76.0 (52.9,99.2)	53.7 (35.5,81.0)
6-<12 years	28.5 (19.3,46.6)	23.9 (14.4,37.4)	115 (73.2,183)	70.2 (49.6,98.3)	52.1 (35.5,76.5)

AGE	Weight (kg)	CmaxSS Ratios	AUC24SS Ratios	%T>MIC of 1 mg/L Ratios	%T>MIC of 2 mg/L Ratios
	52.8 (36.9,75.1)	1.00	1.13	1.18	1.18
	28.5 (19.3,46.6)	1.14	1.18	1.09	1.15

Ratios based on summary of 100 trials. Ratios are relative to adult dosing regimen and represent ratio of paediatric median to adult median for adult dose of 600 mg q12h 1 hr inf.

A 12 mg/kg q12h regimen in this subgroup (maintaining the maximum 400 mg) gave results that were very comparable to 9 mg/kg q12h so that estimates were again very similar to those in adults.

Table 26 Median(90%PI), ceftaroline $C_{max, ss}$, $AUC_{24, ss}$, %T>MIC by age for moderate renal impairment following 12 mg/kg (max of 400 mg) q12h dosing (1 hour infusion) to steady-state for ceftaroline in paediatric patients based on simulations

AGE	Weight (kg)	CmaxSS (mg/L)	AUC24SS (mg*hr/L)	%T>MIC of 1 mg/L	%T>MIC of 2 mg/L
Adults 600 mg q12h 1 hr	77.6 (52.5,105)	20.9 (11.9,36.8)	97.7 (58.9,165)	64.5 (44.6,93.4)	45.5 (29.8,68.7)
12-<18 years	52.8 (36.9,75.1)	21.3 (11.9,37.2)	113 (68.1,192)	76.9 (53.7,100)	54.5 (35.5,81.9)
6-<12 years	28.5 (19.3,46.6)	30.4 (17.8,48.0)	147 (91.8,234)	76.9 (54.5,100)	57.9 (40.5,85.1)

AGE	Weight (kg)	CmaxSS Ratios	AUC24SS Ratios	%T>MIC of 1 mg/L Ratios	%T>MIC of 2 mg/L Ratios
	52.8 (36.9,75.1)	1.02	1.16	1.19	1.20
	28.5 (19.3,46.6)	1.45	1.50	1.19	1.27

Ratios based on summary of 100 trials. Ratios are relative to adult dosing regimen and represent ratio of paediatric median to adult median for adult dose of 600 mg q12h 1 hr inf.

The MAH acknowledged that using the updated POPPK model, the predicted exposure estimates from q12h have changed such that Cmax was more aligned with the adult data. The basis for the MAH proposal of thrice daily dosing in adolescents relied on the fact that i) the predicted exposure in adolescents dosed was seen by the MAH to be more comparable than q12h dosing to the adult exposures using the approved regimen, that ii) thrice daily dosing was predicted to provide improved PTA over q12h dosing and that iii) the safety pool generated in paediatric clinical trials was considered reassuring and supportive than the evidence for the q12h dosing.

On the first point, CHMP analysed the comparisons between adolescents and adults with normal renal function or mild renal impairment using 600 mg q12h (or 18 mg/kg q12h up to 33 kg) and concluded that the claim that the predicted exposure in adolescents dosed q8h is more comparable than q12h dosing to the adult exposures using the approved regimen was not well justified. Taking also into account that safety issues for ceftaroline associated with a <1.5-fold increase in Cmax that would arise if adolescents of at least 33 kg were to be given 600 mg q12h were unlikely, CHMP was, based on the additional simulation data provided by the MAH, of the view that once adolescents (above 12 years of age) reach 33 kg they could be treated with 600 mg q12h.

At the same time it was considered that children aged 2-<18 years of < 33 kg could receive the proposed dose of 12 mg/kg q8h. All of the above were agreed upon by the MAH and the updated dose recommendation was implemented in the Zinforo PI.

Furthermore, the MAH proposed to also apply the adult dose adjustments for severe renal impairment to adolescents from 12 years and from 33 kg body weight. CHMP considered this proposal to be acceptable. The MAH presented the simulation for children aged from 12 years and with body weight from 33 kg with severe renal impairment if given the recommended adult dose adjustment (reduction to 300 mg q12h). Compared with adults with normal renal function dosed with 600 mg q12h the adjusted dose in this age and weight subset provides a similar Cmax and slightly higher AUC and hence higher *f*%T>MIC. The slightly higher predicted AUC falls between that observed in adults with normal renal function given 600 mg q12h and 600 mg q8h.

The results are based on simulating 9 mg/kg q12h with a cap at the adult dose for severe renal impairment (300 mg q12h), which is reached at 33 kg.

Table 27 **Median (90% PI) ceftaroline $C_{max, ss}$, $AUC_{24,ss}$, %T>MIC by age for severe renal impairment following 9 mg/kg (max of 300 mg) q12h dosing (1h infusion) to steady-state for ceftaroline in paediatric patients based on simulations**

AGE	Weight (kg)	CmaxSS (mg/L)	AUC24SS (mg*hr/L)	%T>MIC of 1 mg/L	%T>MIC of 2 mg/L	%T>MIC of 4 mg/L
Adults 600 mg q12h 1 hr	77.6 (52.2,105)	20.9 (11.7,36.2)	97.3 (58.8,165)	64.0 (44.6,93.4)	45.5 (29.8,68.6)	26.4 (15.7,44.6)
12-<18 years	52.7 (36.7,74.7)	18.3 (10.1,31.7)	122 (69.6,210)	94.2 (62.8,100)	66.9 (40.5,98.3)	37.2 (17.4,69.4)
6-<12 years	28.6 (19.2,40.8)	25.5 (15.0,40.7)	155 (93.9,250)	95.0 (65.2,100)	71.9 (46.3,99.2)	45.5 (27.3,78.1)
2-<6 years	15.8 (11.8,22.4)	25.2 (15.4,39.4)	140 (85.0,234)	84.3 (56.2,100)	62.8 (40.5,95.9)	40.5 (24.0,67.8)
18-<24 months	11.7 (9.82,14.1)	36.1 (21.5,60.0)	339 (185,676)	100 (100,100)	100 (89.3,100)	98.3 (59.5,100)
12-<18 months	10.4 (8.58,12.7)	36.8 (22.2,61.8)	353 (194,714)	100 (100,100)	100 (92.6,100)	99.2 (62.8,100)
6-<12 months	8.43 (6.56,10.8)	38.0 (22.8,64.5)	384 (208,770)	100 (100,100)	100 (96.7,100)	100 (69.0,100)
2-<6 months	5.75 (4.11,7.67)	38.7 (22.9,66.5)	425 (232,844)	100 (100,100)	100 (99.2,100)	100 (81.0,100)
1-<2 months	4.69 (3.63,5.77)	38.4 (22.7,66.2)	442 (239,866)	100 (100,100)	100 (100,100)	100 (87.6,100)
0-<1 month	3.86 (2.91,4.75)	37.9 (22.1,66.5)	454 (247,895)	100 (100,100)	100 (100,100)	100 (91.7,100)
GA 38-<40 weeks	3.40 (2.56,4.26)	37.4 (22.0,66.9)	479 (265,943)	100 (100,100)	100 (100,100)	100 (96.7,100)
GA 36-<38 weeks	2.86 (2.06,3.77)	36.5 (21.0,64.9)	457 (249,896)	100 (100,100)	100 (100,100)	100 (95.0,100)
GA 34-<36 weeks	2.33 (1.73,3.06)	35.1 (20.5,62.4)	432 (240,848)	100 (100,100)	100 (100,100)	100 (93.3,100)
GA 32-<34 weeks	1.89 (1.38,2.44)	33.8 (19.9,60.3)	414 (226,825)	100 (100,100)	100 (100,100)	100 (89.2,100)
GA 30-<32 weeks	1.50 (1.06,1.95)	32.5 (19.0,57.6)	392 (212,776)	100 (100,100)	100 (100,100)	100 (84.2,100)
GA 28-<30 weeks	1.16 (0.779,1.53)	31.1 (18.3,54.3)	366 (202,725)	100 (100,100)	100 (99.2,100)	100 (77.6,100)

median(5^{th}, 95^{th}) based on summary of 100 trials and corresponds to median(90% prediction interval).

The simulation for 6 mg/kg q12h in this subset also compared well with adult exposures (see table extract below) but the difference in AUC vs. 9 mg/kg q12h as shown above, which allows for a simple strategy of applying the adult dose adjustments to adolescents of at least 33 kg body weight, seems unlikely to be clinically important in terms of safety.

AGE	Weight (kg)	CmaxSS (mg/L)	AUC24SS (mg*hr/L)	%T>MIC of 1 mg/L	%T>MIC of 2 mg/L	%T>MIC of 4 mg/L
Adults 600 mg q12h 1 hr	77.6 (52.2,105)	20.9 (11.7,36.2)	97.3 (58.8,165)	64.0 (44.6,93.4)	45.5 (29.8,68.6)	26.4 (15.7,44.6)
12-<18 years	52.7 (36.7,74.7)	17.2 (9.97,28.0)	114 (68.1,189)	92.6 (61.2,100)	64.5 (38.8,97.5)	34.7 (16.5,64.5)

The applicant's additional proposal to apply the adult dose adjustments for severe renal impairment and ESRD to adolescents from 12 years and from 33 kg body weight was also considered to be acceptable by CHMP. This has not been simulated but there will be very few such patients and all other simulations do suggest that the adult regimens are suitable for this age and weight subset.

2.3.3. Discussion on clinical pharmacokinetics

The MAH's proposal for the Zinforo SmPC in the initial submission was as follows:

Age/weight range	Dose	Frequency	Infusion time (minutes)
2 months to < 24 months	8 mg/kg	every 8 hours	60
≥ 24 months (≤ 33 kg)	12mg/kg	every 8 hours	60
≥ 24 months (> 33 kg)	400 mg	every 8 hours	60

CHMP agreed that the MAH's approach to dose finding in paediatric patients has been broadly appropriate.

CHMP considered that the adjustment of the dose for the age range 6-< 24 months to reduce this to 8 mg/kg q8h rather than the 12 mg/kg q8h that was actually studied seemed appropriate, giving a standard dose across the age range 2-< 24 months. During the procedure, the MAH explained the lack of dose recommendations for patients < 2 months at this time point, but clarified that these will be proposed for regulatory review in the future. CHMP agreed to this proposal.

It was also agreed by CHMP that adolescents with a body weight of less than 33 kilograms would receive the same 12 mg/kg dose administered every eight hours, whereas adolescents with a body weight of more or equal than 33 kg would receive the adult dose (600 mg every 12 hours).

The final agreed posology in children with normal renal function is:

Age/weight range	Dose	Frequency	Infusion time (minutes)
≥2 months to < 2 years	8 mg/kg	every 8 hours	60
≥ 2 years to <12 years (< 33 kg)	12mg/kg*	every 8 hours	60
≥ 12 years to <18 years (< 33 kg)	12mg/kg*	every 8 hours	60
≥ 12 years to <18 years (≥33 kg)	600 mg	every 12 hours	60

*the dose administerd every 8 hours should not exceed 400 mg

The adequate posology for children above the age of 2 months depending of their renal function status was also agreed.

The POPPK model was considered very complex by CHMP, but was deemed comprehensive and the fact that the MAH report included extensive diagnostic plots was appreciated. It could be concluded that the model appeared to be appropriate for use in predicting doses for children.

2.3.4. Conclusions on clinical pharmacology

No outstanding issues remain. CHMP agreed that the PK evidence presented during this procedure is supportive for the agreed changes to the PI.

2.4. Clinical efficacy

2.4.1. Main studies

D3720c00004 (P903-23) acute bacterial skin and skin structure infections

This was a multicentre, randomized, observer-blinded, active-controlled, parallel-group study to evaluate the efficacy, safety, and PK of intravenous (IV) ceftaroline versus IV comparator (vancomycin or cefazolin with or without aztreonam) in children aged 2 months to < 18 years with ABSSSI.

Eligible patients were to have ABSSSI defined as:

- Abscess: presence of a loculated fluid collection with erythema, oedema or induration that extended from the abscess margin and onset within 7 days before randomisation. A "major abscess" either extended to deeper soft tissue or required significant surgical intervention. Incision and drainage was to be conducted within 24 h after first dose of IV study drug.
- Wound infection: presence of either purulent/seropurulent discharge from the surgical/traumatic wound with erythema, oedema or induration that surrounded the wound margin. Onset of infection must have occurred within 7 days before randomisation and within 30 days following the trauma or surgical procedure.
- Cellulitis/erysipelas: presence of advancing erythema, induration/oedema and heat with onset within 7 days before randomisation.

In addition at least 1 of the following local signs and symptoms of acute infection were to have been present for < 10 days:

- Purulent or seropurulent drainage or discharge
- Induration/oedema
- Fluctuance
- Heat or localized warmth

AND the presence of at least 1 of the following signs:

- Fever (> 38°C [100.4°F]) or hypothermia (< 35°C [95.0°F]); not axillary
- WBC count > 12,000/mm^3
    - 10% immature neutrophils (bands) regardless of total peripheral WBC
- Lymphangitic spread

Block 2:1 randomisation (IXRS) was used to assign patients to ceftaroline (min 180) or comparator (min 90). Stratification was by age cohort and region. Enrolment was in 4 cohorts as follows:

- Cohort 1: children from 12 years to < 18 years
- Cohort 2: children from 6 years to < 12 years
- Cohort 3: children from 24 months to < 6 years
- Cohort 4: young infants/toddlers from 2 months to < 24 months

Efforts were made to enrol at least 27 (10%) in each of the age cohorts. The IXRS was also used to assign patients at a 1:1 ratio to PK schedule 1 or 2 for the collection of blood samples for PK analysis.

Ceftaroline fosamil was dosed using 1-h infusions q8h as follows:

- ≥ 6 months: 12 mg/kg if ≤ 33 kg or 400 mg if > 33 kg
- < 6 months: 8 mg/kg

The comparator group received one of the following (dose adjustments were allowed):

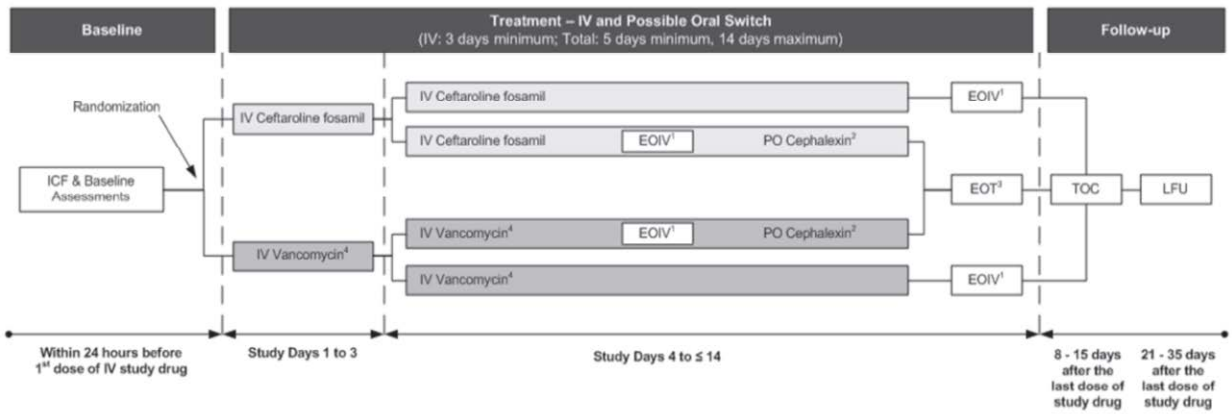
- IV vancomycin 15 mg/kg infused over 60 minutes every 6 hours
- IV cefazolin 75 mg/kg infused over 60 (± 10) minutes every 8 hours
- Optional aztreonam 30 mg/kg infused over 60 (± 10) minutes every 8 hours

Treatment was for a maximum of 14 days. A switch to an open-label oral drug on or after Day 4 was allowed if all of the protocol-specified criteria were met (cephalexin [preferred], clindamycin or linezolid).

A DSMB reviewed safety data from this study.

The overall study design and visits were as shown in the following figure:

Figure 1 D3720c00004 (P903-23) study design



Abbreviations: EOIV = End-of-Intravenous Study Drug Therapy; EOT = End-of-Therapy; ICF = informed consent form; IV = intravenous; LFU = Late Follow-up; PO = by mouth; TOC = Test-of-Cure.
[1] EOIV = within 24 hours after the last dose of IV study drug and before switch to PO study drug (if applicable).
[2] PO cephalexin, clindamycin, or linezolid; PO switch allowed on or after Study Day 4 per protocol.
[3] EOT = within 48 hours after the last dose of PO study drug.
[4] IV vancomycin or cefazolin; plus optional aztreonam.

The study was descriptive so there was no rationale for the study size.

Results

Of the 163 enrolled there were 159 treated patients, all of whom had a confirmed diagnosis of ABSSSI and were included in the MITT population while 74 (45%) were included in the mMITT population (had a

baseline pathogen). The majority (90.2% and 92.6% per treatment group) completed study drug therapy and the study.

Table 28 Subject disposition and reason for premature discontinuations-ITT population

Subject Status *Reason for Discontinuation/Withdrawal*	*Ceftaroline (N = 110)* *n (%)*	*Comparator (N = 53)* *n (%)*	*Total (N = 163)* *n (%)*
Completed study drug	**100 (90.9)**	**47 (88.7)**	**147 (90.2)**
Premature discontinuation of IV study drug	**7 (6.4)**	**4 (7.5)**	**11 (6.7)**
Subject randomized, but did not receive drug[a]	3 (2.7)	1 (1.9)	4 (2.5)
Adverse event	2 (1.8)	1 (1.9)	3 (1.8)
Withdrew consent	2 (1.8)	0	2 (1.2)
Other reasons	0	2 (3.8)	2 (1.2)
Premature discontinuation of oral study drug	**3 (2.7)**	**2 (3.8)**	**5 (3.1)**
Adverse event	0	1 (1.9)	1 (0.6)
Request of Sponsor or Investigator	2 (1.8)	0	2 (1.2)
Withdrew consent	1 (0.9)	0	1 (0.6)
Lost to follow-up	0	1 (1.9)	1 (0.6)
Premature discontinuation of any (IV or oral) study drug	**10 (9.1)**	**6 (11.3)**	**16 (9.8)**
Subject randomized, but did not receive drug[a]	3 (2.7)	1 (1.9)	4 (2.5)
Adverse event	2 (1.8)	2 (3.8)	4 (2.5)
Request of Sponsor or Investigator	2 (1.8)	0	2 (1.2)
Withdrew consent	3 (2.7)	0	3 (1.8)
Lost to follow-up	0	1 (1.9)	1 (0.6)
Other reasons	0	2 (3.8)	2 (1.2)
Completed study	**103 (93.6)**	**48 (90.6)**	**151 (92.6)**
Premature withdrawal from study	**7 (6.4)**	**5 (9.4)**	**12 (7.4)**
Subject did not meet inclusion/exclusion criteria	0	1 (1.9)	1 (0.6)
Withdrew consent	5 (4.5)	2 (3.8)	7 (4.3)
Lost to follow-up	0	2 (3.8)	2 (1.2)
Other reasons	2 (1.8)	0	2 (1.2)

The highest enrolment by age cohort was in Cohort 2 (6 to < 12 years).

Characteristic	*Ceftaroline (N = 107)*	*Comparator (N = 52)*	*Total (N = 159)*
Age, years			
Mean (SD)	6.99 (5.10)	6.94 (5.25)	6.97 (5.13)
Median (range)	7.00 (0.2, 17.0)	6.00 (0.6, 17.0)	7.00 (0.2, 17.0)
Age Cohort, n (%)			
12 years to < 18 years (Cohort 1)	23 (21.5)	13 (25.0)	36 (22.6)
6 years to < 12 years (Cohort 2)	36 (33.6)	15 (28.8)	51 (32.1)
24 months to < 6 years (Cohort 3)	23 (21.5)	12 (23.1)	35 (22.0)
2 months to < 24 months (Cohort 4)	25 (23.4)	12 (23.1)	37 (23.3)

The majority of patients had cellulitis or erysipelas (66%) followed by major abscesses (25%) and the most common body sites affected were similar between groups. Signs and symptoms of ABSSSI at baseline were also balanced between treatment groups and most were of moderate to severe intensity. Abscesses had been drained for ~20% per group. The primary infection site areas were similar between treatment groups with median (range) infection areas of 108 cm^2 (3.8, 742.5) and 112 cm^2 (19.3, 874.0) in the comparator group.

Overall 45.9% had Gram-positive pathogens and *Staphylococcus aureus* was the most common (40.2% and 42.3% per group), of which most were MSSA (18 ceftaroline and 6 comparator patients had MRSA). *S. pyogenes* was identified for 12.1% in the ceftaroline group and 1.9% in the comparator group. Most (87.8%) infections were monomicrobial. The highest ceftaroline MICs observed were 1 µg/mL for *S. aureus (including MRSA)* and 0.015 µg/mL for *S. pyogenes*.

Approximately 67% had received prior antibacterial therapy and 57% had been treated for at least 24 hours. Twelve of the 16 (10.1%) who had received > 24 hours of prior therapy were confirmed treatment failures.

At Study Day 3 in the MITT Population the response to treatment was similar between treatments according to the three parameters shown below.

Table 29 Clinical response at study day 3 by treatment group overall (MITT population)

Response	*Ceftaroline (N = 107) n (%)*	*Comparator (N = 52) n (%)*	*Difference*
Definition 1: ≥ 20% reduction from baseline infection area			
Responder	91 (85.0)	44 (84.6)	0.4%
95% CI	(76.9, 91.2)	(71.9, 93.1)	(–10.7, 13.9)
Non-responder	11 (10.3)	4 (7.7)	—
Incomplete data	5 (4.7)	4 (7.7)	—
Definition 2: Cessation of spread measured by total infection area			
Responder	98 (91.6)	47 (90.4)	1.2%
95% CI	(84.6, 96.1)	(79.0, 96.8)	(–7.7, 13.0)
Non-responder	4 (3.7)	1 (1.9)	—
Incomplete data	5 (4.7)	4 (7.7)	—
Definition 3: Cessation of spread measured by infection length and width separately, and temperature < 37.6°C			
Responder	86 (80.4)	39 (75.0)	5.4%
95% CI	(71.6, 87.4)	(61.1, 86.0)	(–7.8, 20.3)
Non-responder	16 (15.0)	9 (17.3)	—
Incomplete data	5 (4.7)	4 (7.7)	—

Clinical cure rates at TOC in the MITT population were 94.4% for the ceftaroline group and 86.5% for the comparator group, with a treatment difference of 7.9 (95% CI –1.2, 20.2). Clinical cure rates at TOC for the CE Population were 100.0% for the ceftaroline group and 97.8% for the comparator group with a treatment difference of 2.2% (95% CI –1.7, 11.6).

Table 30 Clinical outcomes at TOC by treatment group overall (MITT population)

Outcome	*Ceftaroline (N = 107) n (%)*	*Comparator (N = 52) n (%)*	*Difference*
Clinical cure	101 (94.4)	45 (86.5)	7.9%
95% CI	(88.2, 97.9)	(74.2, 94.4)	(–1.2, 20.2)
Clinical failure	0	1 (1.9)	—
Observed failure at EOIV	0	1 (1.9)	—
Observed failure at EOT	0	0	—
Observed failure at TOC	0	0	—
Indeterminate	6 (5.6)	6 (11.5)	—

The most common reasons for an indeterminate outcome were extenuating circumstances and lost to follow-up. Cure rates by age cohort are shown in the following table.

Table 31 Clinical outcome at the test of cure visit by cohort (MITT population)

	Cohort 1				Cohort 2				Cohort 3				Cohort 4			
	Ceftaroline (N=23) n (%)		Comparator (N=13) n (%)		Ceftaroline (N=36) n (%)		Comparator (N=15) n (%)		Ceftaroline (N=23) n (%)		Comparator (N=12) n (%)		Ceftaroline (N=25) n (%)		Comparator (N=12) n (%)	
Clinical cure	22	(95.7)	10	(76.9)	35	(97.2)	14	(93.3)	22	(95.7)	11	(91.7)	22	(88.0)	10	(83.3)
Clinical failure	0		0		0		1	(6.7)	0		0		0		0	
Observed failure at EOIV	0		0		0		1	(6.7)	0		0		0		0	
Observed failure at EOT	0		0		0		0		0		0		0		0	
Observed failure at TOC	0		0		0		0		0		0		0		0	
Indeterminate	1	(4.3)	3	(23.1)	1	(2.8)	0		1	(4.3)	1	(8.3)	3	(12.0)	2	(16.7)

In the mMITT population the cure rates at TOC were 94.2% for ceftaroline and 81.8% for comparator. The clinical cure rates for the two major pathogens are shown in the following table. Microbiological responses followed the clinical responses.

Table 32 Clinical outcome at the test of cure visit by baseline pathogen (mMITT population)

		Ceftaroline (N=52)			Comparator (N=22)		
Baseline Pathogen	Clinical Outcome	Tissue or Blood n (%)	Tissue n (%)	Blood n (%)	Tissue or Blood n (%)	Tissue n (%)	Blood n (%)
Gram-positive organisms							
Staphylococcus aureus	N1	43	42	1	22	22	0
	Clinical cure	40 (93.0)	39 (92.9)	1 (100.0)	18 (81.8)	18 (81.8)	
	Clinical failure	0	0	0	0	0	
	Indeterminate	3 (7.0)	3 (7.1)	0	4 (18.2)	4 (18.2)	
MRSA	N1	18	18	0	7	7	0
	Clinical cure	16 (88.9)	16 (88.9)		4 (57.1)	4 (57.1)	
	Clinical failure	0	0		0	0	
	Indeterminate	2 (11.1)	2 (11.1)		3 (42.9)	3 (42.9)	
MSSA	N1	25	24	1	15	15	0
	Clinical cure	24 (96.0)	23 (95.8)	1 (100.0)	14 (93.3)	14 (93.3)	
	Clinical failure	0	0	0	0	0	
	Indeterminate	1 (4.0)	1 (4.2)	0	1 (6.7)	1 (6.7)	
Streptococcus pyogenes	N1	13	13	0	1	1	0
	Clinical cure	13 (100.0)	13 (100.0)		1 (100.0)	1 (100.0)	
	Clinical failure	0	0		0	0	
	Indeterminate	0	0		0	0	

The same percentages had a favourable microbiological response (i.e. eradication presumed). Colonisation occurred in 2 (3.8%) ceftaroline and 3 (13.6%) comparator patients. No new infections or superinfections occurred during the study. There were no documented relapses and the sustained cure rates at LFU were 99/101 and 45/45.

Outcomes by gender, region, baseline CrCL and type of baseline infection showed comparable or slightly higher cure rates for ceftaroline vs. comparator.

D3720c00007 (P903-31) community-acquired bacterial pneumonia requiring hospitalization

This was a Phase 2/3 multicentre, randomized, observer-blinded, active-controlled study to evaluate the safety, tolerability, PK, and efficacy of ceftaroline versus ceftriaxone in paediatric patients aged 2 months to < 18 years with CABP requiring hospitalization.

Eligible patients were to have CABP that required hospitalization and IV antibacterial therapy and which met each of the following criteria:

I. Fever (temperature > 38.0°C) or hypothermia (temperature < 35.0°C) (not axillary)

II. New infiltrate(s) compatible with bacterial pneumonia, including a new alveolar/lobar infiltrate or consolidation (based on imaging results or diagnostic testing)

III. Acute onset or worsening within the previous 5 days before randomisation of at least 2 of the following clinical signs or symptoms:

- ○ Cough
- ○ Tachypnoea, defined as:
  - 2 months to < 12 months: ≥ 50 breaths/min
  - 12 months to < 5 years: ≥ 40 breaths/min
  - ≥ 5 years: ≥ 20 breaths/min
- ○ Dyspnoea
- ○ Grunting
- ○ Sputum production
- ○ Chest pain
- ○ Cyanosis
- ○ Evidence of pneumonia with parenchymal consolidation
- ○ Increased work of breathing (e.g. nasal flaring, chest wall retractions)

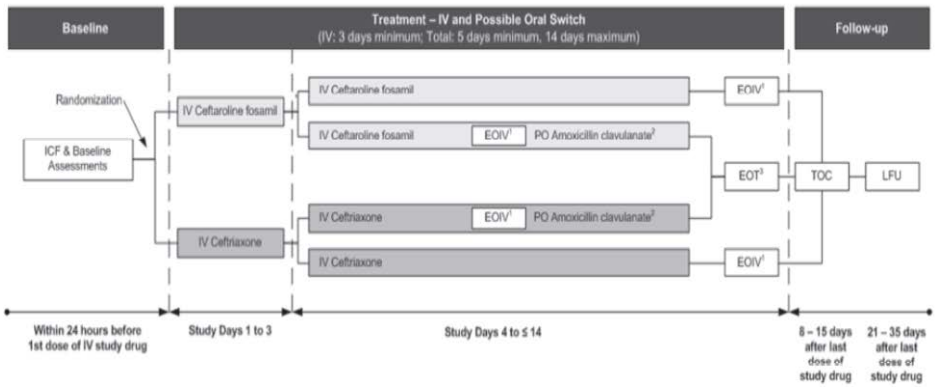
IV. At least 1 of the following:

- ○ Typical respiratory pathogen identified or isolated from a respiratory or blood culture
- ○ Leukocytosis (> 15,000 white blood cells [WBC]/mm3)
- ○ > 15% immature neutrophils (bands) regardless of total peripheral WBC
- ○ Leukopenia (< 4500 WBC/mm3) likely due to the bacterial infection
- ○ Hypoxaemia (oxygen saturation < 92% on room air)

Block randomization (3:1) using an IXRS was used to assign patients to ceftaroline (120) or ceftriaxone (40) with stratification by age cohort and region and using the same PK schema as above. Patients were enrolled in 4 cohorts of descending age as described above with a plan to enrol at least 16 (10%) per cohort.

Ceftaroline was dosed as described above. Ceftriaxone was dosed at 75 mg/kg/day up to a maximum of 4 g/day. Dosing was q12h using equally divided doses infused over 30. A switched to oral amoxicillin clavulanate up to 90 mg/kg/day in two divided doses (q12h) was allowed on or after Day 4 if protocol-specified criteria were met. The total duration of treatment was to be 5 to 14 days including at least 3 days (7 infusions for ceftaroline) of IV study drug. A DSMB reviewed safety data from this study. The overall study design and visits were as shown in the following figure:

Figure 2 Study diagram for study D3720c00007 (P903-31)



The study was descriptive so there was no rationale for the study size.

Results

Of the 160 patients treated ~10% had a sole atypical pathogen (note this based only on a baseline IgM assay) and were excluded from the MITT Population (88.8%). The mMITT Population comprised only 20.5% (33) with an identified typical baseline pathogen. Most (90.7%) patients completed study drug and 95.7% completed the study.

Table 33 Subject completion and reasons for premature discontinuations / withdrawals (ITT population)

Subject Status Reason for Discontinuation/Withdrawal	*Ceftaroline (N = 122) n (%)*	*Ceftriaxone (N = 39) n (%)*	*Total (N = 161) n (%)*
Completed study drug	**111 (91.0)**	**35 (89.7)**	**146 (90.7)**
Premature discontinuation of any IV study drug	**9 (7.4)**	**4 (10.3)**	**13 (8.1)**
Subject randomized, but did not receive drug[a]	1 (0.8)	0	1 (0.6)
Adverse event	1 (0.8)	0	1 (0.6)
Pregnancy/nursing during the study	0	0	0
Request of Sponsor or Investigator	0	0	0
Insufficient therapeutic effect	5 (4.1)	3 (7.7)	8 (5.0)
Withdrew consent	1 (0.8)	0	1 (0.6)
Lost to follow-up	0	0	0
Other reasons	1 (0.8)	1 (2.6)	2 (1.2)
Premature discontinuation of any (IV or oral) study drug	**11 (9.0)**	**4 (10.3)**	**15 (9.3)**
Subject randomized, but did not receive drug[a]	1 (0.8)	0	1 (0.6)
Adverse event	2 (1.6)	0	2 (1.2)
Pregnancy/nursing during the study	0	0	0
Request of Sponsor or Investigator	0	0	0
Insufficient therapeutic effect	5 (4.1)	3 (7.7)	8 (5.0)
Withdrew consent	1 (0.8)	0	1 (0.6)
Lost to follow-up	0	0	0
Other reasons	2 (1.6)	1 (2.6)	3 (1.9)
Premature discontinuation of oral study drug	**2 (1.6)**	**0**	**2 (1.2)**
Adverse event	1 (0.8)	0	1 (0.6)
Pregnancy/nursing during the study	0	0	0
Request of Sponsor or Investigator	0	0	0
Insufficient therapeutic effect	0	0	0
Withdrew consent	0	0	0
Lost to follow-up	0	0	0
Other reasons	1 (0.8)	0	1 (0.6)

Completed study	**116 (95.1)**	**38 (97.4)**	**154 (95.7)**
Premature withdrawal from study	**6 (4.9)**	**1 (2.6)**	**7 (4.3)**
Subject did not meet inclusion/exclusion criteria	0	0	0
Withdrew consent	2 (1.6)	0	2 (1.2)
Lost to follow-up	1 (0.8)	1 (2.6)	2 (1.2)
Withdrawn by Investigator	0	0	0
Lack of compliance	0	0	0
Death	0	0	0
Other reasons	3 (2.5)	0	3 (1.9)

The highest enrolment was in Cohort 3 (24 months to < 6 years) and the lowest was in Cohort 1 (12 to < 18 years). Hence the mean age was 4.19 years with a range 10 weeks through 17 years.

Characteristic	*Ceftaroline (N = 107)*	*Ceftriaxone (N = 36)*	*Total (N = 143)*
Age, years			
Mean ± SD	4.26 ± 3.45	3.98 ± 3.47	4.19 ± 3.44
Median (range)	3.00 (0.2, 17.0)	3.00 (0.4, 16.0)	3.00 (0.2, 17.0)
Age Cohort, n (%)			
12 years to < 18 years	7 (6.5)	2 (5.6)	9 (6.3)
6 years to < 12 years	19 (17.8)	7 (19.4)	26 (18.2)
24 months to < 6 years	58 (54.2)	21 (58.3)	79 (55.2)
2 months to < 24 months	23 (21.5)	6 (16.7)	29 (20.3)

Demographics and baseline characteristics were balanced between treatment groups. Nasopharyngeal swabs for viral PCR were collected. The CSR states that the majority had 1 or more positive findings but no details are given. Approximately one half of patients had prior pneumococcal vaccination.

Baseline pneumonia and disease characteristics were generally similar between treatment groups. The median CRP was elevated at baseline and higher in the ceftriaxone vs. ceftaroline group. All patients had a baseline chest X-ray, and the majority had involvement of 1 lobe. A higher percentage in the ceftriaxone group had an effusion. Most pathogens were identified only by pneumococcal urinary antigen and few respiratory specimens were obtained (11 patients). Two were considered to have *M. pneumoniae* with a typical pathogen. Blood cultures were obtained from 97.2% but only 4.2% were positive (1 MRSA and 2 per group with *S. pneumoniae*).

Nearly half (44.8%) in the MITT population had received systemic antibacterial treatment within 96 hours. Most (30.8%) had received ≤ 24 hours and all of the 14% who had received > 24 hours were confirmed treatment failures.

The clinical response rates on Day 4 (improvement in ≥ 2/7 symptoms and no worsening) were similar between treatments (69.2% ceftaroline vs. 66.7% ceftriaxone; difference 2.5% [95%CI -13.9, 20.9]). The clinical cure rates at TOC were also similar between groups in the MITT (87.9% and 88.9%, respectively), CE (91.8 and 88.9%) and mMITT populations (79.2% and 77.8%; all derived from clinical outcomes.). Rates were comparable in the age cohorts with the largest numbers in the MITT population.

Table 34 Clinical outcome at the TOC visit (MITT population)

Outcome	*Ceftaroline (N = 107) n (%)*	*Ceftriaxone (N = 36) n (%)*	*Difference (%)*
Clinical cure	94 (87.9)	32 (88.9)	-1.0
95% CI	(80.1, 93.4)	(73.9, 96.9)	(-11.5, 14.1)
Clinical failure	8 (7.5)	4 (11.1)	
At EOIV	7 (7.5)	3 (8.3)	
At EOT	0	1 (2.8)	
At TOC	1 (0.9)	0	
Indeterminate	5 (4.7)	0	

	Cohort 1		Cohort 2		Cohort 3		Cohort 4	
	Ceftaroline (N=7) n (%)	Ceftriaxone (N=2) n (%)	Ceftaroline (N=19) n (%)	Ceftriaxone (N=7) n (%)	Ceftaroline (N=58) n (%)	Ceftriaxone (N=21) n (%)	Ceftaroline (N=23) n (%)	Ceftriaxone (N=6) n (%)
Clinical cure	6 (85.7)	2 (100.0)	15 (78.9)	6 (85.7)	50 (86.2)	18 (85.7)	23 (100.0)	6 (100.0)
Clinical failure	1 (14.3)	0	2 (10.5)	1 (14.3)	5 (8.6)	3 (14.3)	0	0
Observed failure at EOIV	1 (14.3)	0	2 (10.5)	1 (14.3)	4 (6.9)	2 (9.5)	0	0
Observed failure at EOT	0	0	0	0	0	1 (4.8)	0	0
Observed failure at TOC	0	0	0	0	1 (1.7)	0	0	0
Indeterminate	0	0	2 (10.5)	0	3 (5.2)	0	0	0

No subject had a clinical relapse at the LFU visit. One patient in the ceftaroline group with *S. pneumoniae* had a new infection (*Haemophilus parainfluenzae*) at TOC visit (Day 25) and was assessed as a clinical failure since this required further antimicrobial therapy.

D3720c00013 (P903-24) complicated community-acquired bacterial pneumonia

This was a multicentre, randomised, observer-blinded, active-controlled study to evaluate the safety, tolerability, PK, and efficacy of IV ceftaroline fosamil versus IV ceftriaxone plus IV vancomycin in paediatric patients aged 2 months to < 18 years with complicated CABP. It was designed to enrich for patients at risk for infection due to MRSA.

Eligible patients were to have CABP that met criteria I-IV as in study P903-31 above PLUS confirmed presence of at least one indicator of complicated CABP or staphylococcal pneumonia as follows:

- Empyema defined as the presence of pus and fluid from infected tissue collected in the pleural space as confirmed via thoracentesis
- Pulmonary abscess defined as a collection of pus in the lung
- Necrotizing pneumonia defined as a consolidative pneumonia that has areas of non-enhancement on contrast-enhanced CT but no air-fluid level or rim enhancement or development of a pneumatocele after the pneumonia
- Pneumatocele defined as a thin-walled, air-containing cyst of the lungs
- Pleural effusion needing chest tube drainage, but not considered an empyema
- Gram-positive cocci in clusters on Gram stain from a respiratory specimen (sputum, pleural fluid, bronchoalveolar lavage, deep tracheal)
- Requirement for positive pressure assisted ventilation
- Previous influenza-like illness (defined as temperature > 38.0°C plus cough or sore throat in the absence of a known cause other than influenza) or documented influenza infection (e.g. by culture or molecular testing) within 28 days of enrolment
- Severe CABP, defined as requirement for treatment in an intensive care unit

Block randomization, using an IXRS, stratified by age cohort, was used to assign patients (3:1) to the ceftaroline or comparator group (IV ceftriaxone plus IV vancomycin). Patients were to be enrolled in 4 cohorts of descending age as described above.

Ceftaroline fosamil was dosed using 2-h infusions q8h as follows:

≥ 6 months: 15 mg/kg if ≤ 40 kg or 600 mg if > 40 kg

< 6 months: 10 mg/kg

Ceftriaxone was dosed at 75 mg/kg/day up to a maximum of 4 g/day. Dosing was q12h using equally divided doses infused over 30 min. Vancomycin was dosed at 15 mg/kg q6h infused over at least 60 minutes or at a maximum of 10 mg/min and could be discontinued after 72 hours of IV study drug if MRSA, PRSP or PISP was not confirmed or suspected. At study centres where trough levels were measured as standard of care the values were recorded in the eCRF.

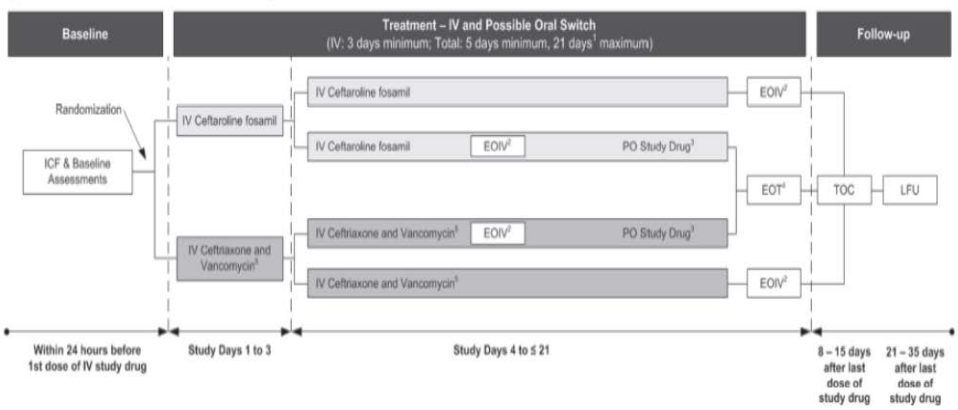
A switch to open-label oral study drug (amoxicillin clavulanate, clindamycin, or linezolid; selected according to known or documented organisms and susceptibility) could occur after 72 hours of IV study drug if the criteria for oral switch were met.

- Amoxicillin clavulanate was dosed at 45 to 90 mg/kg/day divided q12h
- Clindamycin was dosed at 13 mg/kg q8h
- Linezolid was dosed at 600 mg q12h (Cohort 1) or 10 mg/kg q8h (Cohorts 2, 3 and 4)

The total duration of study drug therapy was 5 to 21 days. A DSMB reviewed safety data from this study.

The overall study design and visits were as shown in the following figure:

Figure 3 D3720c00013 (P903-24) study design



The study was descriptive so there was no rationale for the study size.

Results

Of 40 patients enrolled (30 ceftaroline) two (one per treatment group) were excluded from the MITT population due to having a sole atypical pathogen. There were 18 (45%) with at least one typical pathogen (mMITT population). The mean age was 5.4 years (range 16 weeks through 17 years). None had CrCL < 50 ml/min but one had CrCL of 355.2 mL/min/1.73m² with serum creatinine of 8.8 µmol/L. Seven had a history of pneumococcal vaccination. Baseline pneumonia disease characteristics were similar between treatment groups. Approximately 40% had pleural effusion and 60% had multi-lobar involvement.

Table 35 Demographic and baseline characteristics (MITT population)

Characteristic	*Ceftaroline (N = 29)*	*Comparator (N = 9)*	*Total (N = 38)*
Age, years			
Mean (SD)	5.31 (4.65)	5.74 (5.18)	5.4 (4.71)
Median (range)	4.00 (0.3, 17.0)	4.00 (0.3, 16.0)	4.00 (0.3, 17.0)
Age Cohort, n (%)			
12 years to <18 years	4 (13.8)	2 (22.2)	6 (15.8)
6 years to <12 years	7 (24.1)	1 (11.1)	8 (21.1)
24 months to <6 years	12 (41.4)	4 (44.4)	16 (42.1)
2 months to <24 months	6 (20.7)	2 (22.2)	8 (21.1)

Nasopharyngeal swabs were collected from the majority and most had one or more findings positive for viral testing by PCR but details are not provided. Respiratory samples were obtained from 17 patients (11 ceftaroline). *Staphylococcus aureus* was cultured from 4 ceftaroline and 1 comparator patients. Two in the ceftaroline group had positive blood cultures. A third had a urinary antigen test that was positive for *S. pneumoniae*.

More than half (62.1% ceftaroline and 55.6% comparator) had received prior systemic antibacterial medications within 96 hours. All patients who had > 24 hours prior (20.7% in the ceftaroline group and 11.1% in the comparator group) were confirmed treatment failures.

On Day 4 the clinical response (defined as above) rates were 51.7% in the ceftaroline group and 66.7% in the comparator group.

Clinical cure rates at TOC were 89.7% ceftaroline vs. 100% comparator in the MITT population, 88.5% vs. 100%, respectively, in the CE population and 86.7% vs. 100%, respectively, in the mMITT population. Three MITT patients in the ceftaroline group were clinical failures but only one was due to insufficient therapeutic effect (the other two discontinued due to AEs). All but 2 in the ceftaroline group and all in the comparator group had a favourable microbiological outcome at TOC in the mMITT Population.

2.4.2. Discussion on clinical efficacy

CHMP agreed that overall the efficacy findings are very supportive of the likely adequacy of the regimens tested in the various age groups, despite several limitations (e.g. the allowance for oral switch to other agents). As discussed in the clinical pharmacology section, the final dose recommendations in the SmPC are not identical to those studied clinically. Nevertheless, CHMP agreed that the amended doses are predicted to be adequate.

2.4.3. Conclusions on the clinical efficacy

No outstanding issues could be identified. CHMP agreed that the available efficacy data are broadly supportive.

2.5. Clinical safety

Safety in special populations

D3720c00004 (P903-23) acute bacterial skin and skin structure infections

The median duration of IV treatment was 5.0 days in each treatment group and most received 3 - 8 days. No comparator group patients received aztreonam. The median duration of total (IV + PO) therapy was

10 days. A switch to oral occurred in 59% after a median time of 4 days and with a median duration of 8.0 days in each treatment group. The most commonly used oral treatment was cephalexin.

The following table summarises the AE rates:

Table 36 Summary of Adverse Events by treatment group overall (safety population)

Adverse Event Category	*Ceftaroline (N = 106) n (%)*	*Comparator (N = 53) n (%)*	*Total (N = 159) n (%)*
Number of subjects with:			
Any TEAE	51 (48.1)	23 (43.4)	74 (46.5)
Any study drug-related TEAEs	23 (21.7)	12 (22.6)	35 (22.0)
Any SAEs	4 (3.8)	1 (1.9)	5 (3.1)
Any study drug-related SAEs	2 (1.9)	0	2 (1.3)
Discontinuations of any study drug (IV or oral) due to AE	4 (3.8)	2 (3.8)	6 (3.8)
Discontinuations of any IV study drug due to AE	2 (1.9)	1 (1.9)	3 (1.9)
Deaths	0	0	0

Treatment-emergent AEs were more common in Cohort 4 (the youngest) than in other Cohorts (70.8% ceftaroline and 61.5% comparator vs. <50% in all other cohorts). The most frequently occurring TEAEs in the ceftaroline group were diarrhoea, rash (8 [7.5%] each) and vomiting (7 [6.6%]). Diarrhoea and vomiting were also the most frequently reported TEAEs in the comparator group.

Table 37 Treatment-emergent adverse events reported by at least 2% of patients by treatment group overall (safety population)

System Organ Class Preferred Term[a]	*Ceftaroline (N = 106) n (%)*	*Comparator (N = 53) n (%)*
Subjects with ≥ 1 TEAE	**51(48.1)**	**23(43.4)**
Blood and lymphatic system disorders		
Eosinophilia	5 (4.7)	1 (1.9)
Gastrointestinal disorders		
Diarrhea	8 (7.5)	8 (15.1)
Vomiting	7 (6.6)	8 (15.1)
Nausea	5 (4.7)	0
Abdominal pain	3 (2.8)	1 (1.9)
General disorders and administration site conditions		
Pyrexia	4 (3.8)	0
Infections and infestations		
Upper respiratory tract infection	5 (4.7)	1 (1.9)
Injury, poisoning and procedural complications		
Arthropod bite	0	2 (3.8)
Nervous system disorders		
Headache	3 (2.8)	1 (1.9)
Respiratory, thoracic and mediastinal disorders		
Cough	4 (3.8)	2 (3.8)
Skin and subcutaneous tissue disorders		
Rash	8 (7.5)	2 (3.8)
Pruritus	1 (0.9)	3 (5.7)

Most TEAEs were of mild intensity. Severe TEAEs were reported for three patients per group (2.8% ceftaroline vs. 5.7% comparator). Treatment-related TEAEs were reported for 21.7% vs. 22.6%; the most common in the ceftaroline group were rash and eosinophilia (5 patients; 4.7% each vs. 1 patient each in the comparator group).

Six SAEs were reported from 5 patients including 4 [3.8%] in the ceftaroline group and 1 [1.9%] in the comparator group. Two SAEs in different patients in the ceftaroline group (*Clostridium difficile* colitis and hypersensitivity) were considered drug-related. Also, two in the ceftaroline group were discontinued from treatment due to SAEs (hypersensitivity and osteomyelitis).

Table 38 List of serious adverse events (safety population)

Treatment Group Subject ID/Cohort	*Age (y)/ Sex/ Race*	*Date of First/ Last Dose of Study Drug*	*Days of IV/Oral Therapy*	*Preferred Term[a]/ Investigator Term[b]*	*SAE Start Date (Day)/ Stop Date (Day)*	*Severity/ Relationship to Study Drug*	*Action Taken*	*Outcome*
Ceftaroline								
001523001/ Cohort 4	1.2/F/W	07 Mar 13/ 20 Mar 13	4/11	Pneumonia viral	25 Mar 13 (19)/ 02 Apr 13 (27)	Moderate/No	None	Recovered/ resolved
006323001/ Cohort 1	15/F/W	12 Sep 12/ 30 Sep 12	3/17	*Clostridium difficile* colitis/*Clostridium difficile* enterocolitis	25 Oct 12 (44)/ 20 Nov 12 (70)	Severe/Yes	None	Recovered/ resolved
021923002/ Cohort 1	12/F/W	24 Jul 13/ 01 Aug 13	9/-	Hypersensitivity/allergic reaction	01 Aug 13 (9)/ 04 Aug 13 (12)	Moderate/Yes	Study drug discontinued/ subject continued in study	Recovered/ resolved
170123003/ Cohort 2	11/M/W	22 Mar 13/ 26 Mar 13	5/-	Osteomyelitis	26 Mar 13 (5)/ Ongoing	Severe/No	Study drug discontinued/ subject continued in study	Recovered/ resolving
Comparator								
180223007/ Cohort 3	3/F/W	08 Mar 14/ 13 Mar 14	6/-	Tonsillitis/purulent tonsillitis, hospital treatment	28 Mar 14 (21)/ 01 Apr 14(25)	Severe/No	None	Recovered/ resolved
				Lymphadenitis/acute inflammation of mesenteric lymph nodes	06 Apr 14 (30)/ 10 Apr 14 (34)	Moderate/No	None	Recovered/ resolved

TEAEs leading to discontinuation of study drug therapy were reported for 3.8% per treatment group (4 and 2 patients) and 2 vs. 1 discontinued IV therapy. These included the two discontinuations of ceftaroline that resulted from SAEs and a comparator group patient who discontinued IV due to non-serious hypersensitivity.

The rate of occurrence of PCS haematology and chemistry values was low, with little difference observed between treatment groups. In light of the reported AEs of eosinophilia, PCS values occurred in two ceftaroline and no comparator group patients.

Table 39 Overall potentially clinically significant postbaseline haematology values based on both normal ranges and percent change from baseline (safety population)

Clinical Laboratory Parameter (Unit)	*PCS Criterion*	*Ceftaroline (N = 106) n/N1 (%)*	*Comparator (N = 53) n/N1 (%)*
Eosinophils (%)	> 4.00 × ULN and > 400% increase from Baseline	2/100 (2.0)	0/46
Neutrophils absolute cell count (10^9/L)	< 0.50 × LLN and > 70% decrease from Baseline	1/93 (1.1)	2/46 (4.3)
Neutrophils (%)	< 0.50 × LLN and > 70% decrease from Baseline	2/99 (2.0)	2/47 (4.3)

Direct Coombs test seroconversion occurred in 17.2 % in the ceftaroline group and 4.2% in the comparator group but no patient had any evidence of haemolytic anaemia or haemolysis.

D3720c00007 (P903-31) community-acquired bacterial pneumonia requiring hospitalization

Median exposure to IV study drug was 5 days in the ceftaroline group and 6 days in the ceftriaxone group. There was a switch to oral study drug in 65% of patients after a median of 6 days IV. The median duration of oral treatment was 6 days. The overall safety data are summarised in the following table:

Table 40 Summary of subjects with treatment-emergent adverse events (safety population)

Adverse Event Category	*Ceftaroline (N = 121) n (%)*	*Ceftriaxone (N = 39) n (%)*	*Total (N = 160) n (%)*
Number of subjects with:			
Any TEAE	55 (45.5)	18 (46.2)	73 (45.6)
Any study drug-related TEAEs	12 (9.9)	3 (7.7)	15 (9.4)
Any SAEs	6 (5.0)	1 (2.6)	7 (4.4)
Any (IV or oral) study drug-related SAEs	0	0	0
Discontinuations due to any (IV or oral) study drug due to AE	3 (2.5)	0	3 (1.9)
Discontinuations of IV study drug due to AE	2 (1.7)	0	2 (1.3)
Deaths	0	0	0

The most commonly reported events in each treatment group were gastrointestinal events (diarrhoea and vomiting).

Table 41 Treatment-emergent adverse events reported by at least 3% of subjects (safety population)

System Organ Class / Preferred Term	*Ceftaroline (N = 121) n (%)*	*Ceftriaxone (N = 39) n (%)*
Blood and lymphatic system disorders		
Thrombocytosis	2 (1.7)	3 (7.7)
Gastrointestinal disorders		
Diarrhoea	10 (8.3)	2 (5.1)
Vomiting	4 (3.3)	2 (5.1)
General disorders and administration site conditions		
Pyrexia	3 (2.5)	2 (5.1)
Infections and infestations		
Otitis media	1 (0.8)	3 (7.7)

Most TEAEs were assessed by the Investigators as mild or moderate in severity. Severe TEAEs were reported for 3 (2.5%) in the ceftaroline group (thrombocytosis, infectious plural effusion and Kawasaki's disease) and for one (2.6%) in the ceftriaxone group (2 TEAEs: thrombocytosis and pulmonary thrombosis). TEAEs considered to be related to study drug occurred in 9.9% in the ceftaroline group and 7.7% in the ceftriaxone group. The most common in the ceftaroline group were diarrhoea (4), urticaria (2) and elevated transaminases (AST 2 and ALT 1). In the ceftriaxone group the TEAEs considered related were vulvovaginal erythema and dermatitis (1 each) and elevated AST/ALT in one patient.

There were 8 SAEs reported from 7 patients (6 in the ceftaroline group reporting 7 SAEs), most of which were infections and infestations and none was considered related to study drug treatment or led to discontinuation of assigned treatment (see following table).

Three (2.5%) in the ceftaroline group and none in the ceftriaxone group prematurely discontinued study drug due to AEs. Two discontinued from IV treatment because of headache and one because of the change in diagnosis of Kawasaki's disease. The other discontinued oral therapy.

Table 42 List of serious adverse events (safety population)

Treatment Group Subject ID/Cohort	Age (y)/ Sex/ Race	Date of First/ Last Dose of Study Drug	Days of IV/Oral Therapy	Preferred Term[a]/ Investigator Term[b]	SAE Start Date (Day)/ Stop Date (Day)	Severity/ Relationship to Study Drug	Action Taken
Ceftaroline							
002331001/ Cohort 3	2/M/W	14 Jan 13/ 25 Jan 13	4/9	Pneumonia respiratory syncytial viral / RSV pneumonia	25 Jan 13 (12)/ 08 Feb 13 (26)	Moderate/No	None
021931013/ Cohort 3	3/F/W	20 Oct 13/ 02 Nov 13	14/-	Infectious pleural effusion / Phyothorax	04 Nov 13 (16)/ 22 Nov 13 (34)	Severe/No	None
140931001/ Cohort 3	5/M/W	16 May 13/ 22 May 13	4/4	Dehydration / dehydration	23 May 13 (8)/ 26 May 13 (11)	Moderate/No	None
				Gastroenteritis / gastroenteritis	23 May 13 (8)/ 27 May 13 (12)	Moderate/No	None
141331004/ Cohort 3	4/F/W	09 Jan 14/ 16 Jan 14	8/-	Gastroenteritis / gastroenteritis	20 Jan 14 (12)/ 24 Jan 14 (16)	Moderate/No	None
141731006/ Cohort 4	1.2/M/W	12 Sep 13/ 18 Sep 13	4/4	Bronchitis / Obstructive bronchitis	10 Oct 13 (29)/ 14 Oct 13 (33)	Mild/No	None
141731008/ Cohort 2	6/F/W	24 Sep 13/ 27 Sep 13		Pneumonia / Long-lasting left side pneumonia	14 Oct 13 (21)/ 22 Oct 13 (29)	Mild/No	None
Ceftriaxone							
202931001/ Cohort 3	4/M/W	10 Dec 13/ 23 Dec 13	12/3	Pulmonary thrombosis / Left lower lobe (lung) thrombus	07 Jan 14 (29)/ 11 Jan 14 (33)	Severe/No	None

The rate of occurrence of PCS haematology values was low with little differences observed between treatment groups.

Table 43 Potentially clinically significant postbaseline haematology values (safety population)

Clinical Laboratory Parameter (Unit)[a]	PCS Criterion	Ceftaroline (N = 121) n/N1 (%)	Ceftriaxone (N = 39) n/N1 (%)
Neutrophils absolute cell count (10^9/L)	< 0.5 x LLN and > 70% decrease	1/111 (0.9)	0/34
	> 2.20 x ULN and > 100% increase	0/111	0/34
Neutrophils (%)	< 0.5 x LLN and > 70% decrease	1/118 (0.8)	1/39 (2.6)
	> 2.20 x ULN and > 100% increase	0/118	0/39
Platelet count (thrombocytes) (10^9/L)	< 0.4 x LLN and > 40% decrease	0/119	0/39
	> 2.0 x ULN and > 100% increase	3/119 (2.5)	5/39 (12.8)
Red blood cell count (10^{12}/L)	< 0.8 x LLN and > 20% decrease	0/119	2/39 (5.1)
	> 1.3 x ULN and > 30% increase	0/119	0/39

Three patients had elevated liver chemistry values but none met Hy's Law.

Table 44 Potentially clinically significant postbaseline chemistry values (safety population)

Clinical Laboratory Parameter (Unit) / PCS Criterion	Ceftaroline (N = 121) n/N1 (%)	Ceftriaxone (N = 39) n/N1 (%)
Alanine aminotransferase U/L		
> 3.0 x ULN and > 300% increase	1/115 (0.9)	1/35 (2.9)
Aspartate aminotransferase U/L		
> 3.0 x ULN and > 300% increase	1/115 (0.9)	1/35 (2.9)
Potassium (mmol/L)		
< 0.8 x LLN and > 15% decrease	0/114	2/36 (5.6)
> 1.2 x ULN and > 20% increase	2/114 (1.8)	0/36

A shift from negative at baseline to a positive Coomb's test was found in 17% in the ceftaroline group and 2.7% in the ceftriaxone group. No evidence of haemolytic anaemia or haemolysis was identified in the study.

D3720c00013 (P903-24) complicated community-acquired bacterial pneumonia

The median duration of treatment with IV study drug was 9 days in the ceftaroline group and 7.5 days in the comparator group. In both treatment groups most switched to oral study drug (73.3% ceftaroline and

100% comparator) with a median time to switch on Day 8 in both groups. In those who switched the median exposure to oral study drug was 7.5 days in each group. The overall safety profile is summarised in the following table:

Table 45 Summary of adverse events (safety population)

Adverse Event Category	*Ceftaroline (N = 30) n (%)*	*Comparator (N = 10) n (%)*	*Total (N = 40) n (%)*
Number of subjects with:			
Any TEAE	12 (40.0)	8 (80.0)	20 (50.0)
Any (IV or oral) study drug-related TEAEs	7 (23.3)	3 (30.0)	10 (25.0)
Any SAEs	0	1 (10.0)	1 (2.5)
Any (IV or oral) study drug-related SAEs	0	0	0
Discontinuations of any (IV or oral) study drug due to AE	3 (10.0)	0	3 (7.5)
Discontinuations of IV study drug due to AE	2 (6.7)	0	2 (5.0)
Deaths	0	0	0

TEAEs reported by at least 3 ceftaroline or 2 comparator group patients are shown below.

Table 46 Treatment emergent adverse events reported by at least 3 subjects in the ceftaroline group or 2 subjects in the comparator group (safety population)

System Organ Class Preferred Term[a]	*Ceftaroline (N = 30) n (%)*	*Comparator (N = 10) n (%)*
Subjects with ≥ 1 TEAE	12 (40.0)	8 (80.0)
Blood and lymphatic system disorders		
Anemia	3 (10.0)	0
Gastrointestinal disorders		
Vomiting	2 (6.7)	2 (20.0)
Infections and infestations		
Viral upper respiratory tract infection	0	2 (20.0)
Skin and subcutaneous tissue disorders		
Pruritus	3 (10.0)	0

One patient in the ceftaroline group had TEAEs assessed as severe (AST increase and ALT increase). Drug-related TEAEs were reported for 23.3% ceftaroline and 30% comparator patients.

Table 47 Incidence of treatment emergent adverse events related to study drug (safety population)

System Organ Class Preferred Term[a]	*Ceftaroline (N = 30) n (%)*	*Comparator (N = 10) n (%)*
Subjects with ≥ 1 related TEAE	7 (23.3)	3 (30.0)
Blood and lymphatic system disorders		
Eosinophilia	1 (3.3)	0
Gastrointestinal disorders		
Vomiting	1 (3.3)	0
Diarrhea	1 (3.3)	0
General disorders and administration site conditions		
Infusion site extravasation	1 (3.3)	0
Investigations[b]		
ALT increased	1 (3.3)	1 (10.0)
AST increased	1 (3.3)	0
Transaminases increased	1 (3.3)	1 (10.0)
Skin and subcutaneous tissue disorders		
Pruritus	1 (3.3)	0
Dermatitis diaper	1 (3.3)	0
Rash	1 (3.3)	0
Rash erythematous	0	1 (10.0)
Rash macular	1 (3.3)	0
Red man syndrome	0	1 (10.0)

There were two SAEs (lower respiratory tract viral infection and upper respiratory tract viral infection), which were both reported for the same patient in the comparator group.

Two (10.0%) in the ceftaroline group discontinued IV study drug due to AEs of ALT increased and AST increased (see above under severe TEAEs) in one and rash and pruritus of moderate intensity in the other. These were considered to be drug-related. A third ceftaroline patient discontinued oral therapy.

Table 48 List of adverse events leading to discontinuation of study drug by individual subject (safety population)

Table 12.3.1.3-2. List of Adverse Events Leading to Discontinuation of Study Drug by Individual Subject—Safety Population

Treatment Group Subject ID/ Cohort	*Age (y)/ Sex/Race*	*Date of First/Last Dose of Study Drug*	*Preferred Term[a]/ Investigator Term[b]*	*AE Start/ Stop Date*	*Day of AE Start/Stop*	*SAE?/Caused Death?/On Therapy?*	*Severity/ Relationship to Study Drug*	*Action Taken*
Ceftaroline								
001124001/ Cohort 3	4/M/W	27 Feb 2013/ 07 Mar 2013	Aspartate aminotransferase increased/elevated AST	06 Mar 2013/ 13 Mar 2013	8/15	N/-/Y	Severe/Y	Study drug discontinued, subject continued in study
			Alanine aminotransferase increased/elevated ALT	06 Mar 2013/ 18 Mar 2013	8/20	N/-/Y	Severe/Y	Study drug discontinued, subject continued in study
001124002/ Cohort 1	17/M/W	25 Apr 2013/ 13 May 2013	Rash macular/erythematous macular rash on face, trunk, and extremities	02 May 2013/ 04 May 2013	8/10	N/-/Y	Moderate/Y	Study drug discontinued, subject continued in study
002324001/ Cohort 3	5/M/W	23 Jan 2013/ 30 Jan 2013	Pruritus/itching	30 Jan 2013/ 05 Feb 2013	8/14	N/-/Y	Moderate/Y	Study drug discontinued, subject continued in study
			Rash/rash	30 Jan 2013/ 05 Feb 2013	8/14	N/-/Y	Moderate/Y	Study drug discontinued, subject continued in study

The rates of PCS haematology and chemistry values were low. No patient met the criteria for Hy's Law.

Table 49 Overall potentially clinically significant postbaseline haematology values based on both normal ranges and percent change from baseline (safety population)

Clinical Laboratory Parameter (Unit)[a]	*PCS Criteria*	*Ceftaroline (N = 30) n/N1 (%)*	*Comparator (N = 10) n/N1 (%)*
Eosinophils percent (%)	> 4.0 × ULN and > 400% increase	1/30 (3.3)	0/10
Lymphocytes absolute count (10^9/L)	< 0.2 × LLN and > 70% decrease	0/29	0/9
	> 2.2 × ULN and > 100% increase	1/29 (3.4)	0/9
Lymphocytes percent (%)	< 0.2 × LLN and > 70% decrease	1/30 (3.3)	0/10
	> 2.2 × ULN and > 100% increase	0/30	0/10
Platelet count (thrombocytes) (10^9/L)	< 0.4 × LLN and > 40% decrease	0/30	0/10
	> 2.0 × ULN and > 100% increase	1/30 (3.3)	2/10 (20.0)
Red blood cell count (10^{12}/L)	< 0.8 × LLN and > 20% decrease	1/30 (3.3)	0/10
	> 1.3 × ULN and > 30% increase	0/30	0/10
White blood cell count (10^9/L)	< 0.5 × LLN and > 60% decrease	0/30	0/10
	> 2.0 × ULN and > 100% increase	0/30	1/10 (10.0)

Table 50 Overall potentially clinically significant postbaseline chemistry values based on both normal ranges and percent change from baseline (safety population)

Clinical Laboratory Parameter (Unit)[a]	*PCS Criteria*[a]	*Ceftaroline (N = 30) n /N1 (%)*	*Comparator (N = 10) n/N1 (%)*
ALT (SGPT) (U/L)	> 3.0 × ULN and > 300% increase	1/30 (3.3)	0/10
AST (SGOT) (U/L)	> 3.0 × ULN and > 300% increase	1/30 (3.3)	0/10
Bicarbonate	< 0.7 × LLN and > 50% decrease	0/28	0/10
	> 1.3 × ULN and > 30% increase	1/28 (3.6)	0/10
Potassium	< 0.8 × LLN and > 15% decrease	0/30	0/10
	> 1.2 × ULN and > 20% increase	1/30 (3.3)	0/10

Direct Coombs test seroconversion occurred in 26.1% in the ceftaroline group and none in the comparator group. No evidence of haemolytic anaemia or haemolysis was identified.

2.5.1. Discussion on clinical safety

The additional safety data do not raise any new concerns compared to the existing adult data. The rate of Coombs test positivity was already noted in adults to be considerably higher than for comparators but thus far has not been linked to haemolytic anaemia. A statement on the safety experience in children has been added to section 4.8 of the Zinforo SmPC.

2.5.2. Conclusions on clinical safety

CHMP agreed that the additional safety data assessed in this application do not change the known safety profile for Zinforo.

2.5.3. PSUR cycle

The PSUR cycle remains unchanged.

2.6. Risk management plan

N/A

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.8, 5.2, 5.3 and 6.6 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

Changes were also made to the PI to bring it in line with the current Agency/QRD template which were accepted by the CHMP.

In addition, the list of local representatives in the PL has been revised to amend contact details for the representative of Bulgaria.

Please refer to Attachment 1 which includes all agreed changes to the Product Information.

2.7.1. User consultation

A full user consultation with target patient groups on the package leaflet was not performed and it has

been found acceptable for the following reasons: changes made to the package leaflet were not considered significant and were not affecting its readability.

3. Benefit-Risk Balance

CHMP agreed that the nonclinical data provided by the MAH to support the extension of use of ceftaroline to children aged from 2 months onwards were adequate.

The MAH has completed a series of studies, in accordance with the agreed PIP and has used the PK data from treated children to derive dose recommendations that are intended to provide plasma exposures comparable with those in adults. Simulations have shown that the final proposed posology by age and weight is likely to achieve the target exposures. In addition, CHMP and the MAH agreed during the procedure to the posology which will be recommended for children above the age of 2 months, depending on their age, body weight and renal function status.

Ceftaroline was previously shown to be efficacious in the indications granted for adults (complicated skin and soft tissue infections and community-acquired pneumonia) with an acceptable safety profile typical of that of the cephalosporins. The additional safety and efficacy data in children suggest high efficacy at the doses tested with a similar safety profile as that observed in adults.

Overall, CHMP considered that the extension of use of ceftaroline to children from the age of 2 months for the treatment of complicated skin and soft tissue infections (cSSTI) and community-acquired pneumonia (CAP) is acceptable and agreed that the benefit-risk ratio for Zinforo in this population is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends by consensus 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, IIIA and IIIB

Extension of indication for Zinforo to include a new population, children from the age of 2 months; as a consequence, sections 4.1, 4.2, 4.8, 5.1, 5.2, 5.3 and 6.6 of the SmPC have been updated with new information on dosing, PK and safety. The Package Leaflet is updated in accordance. In addition, the Marketing Authorisation Holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet and to align the PI with the latest QRD template 10.0.

The requested variation leads to amendments to the Summary of Product Characteristics, Labelling and Package Leaflet.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric

Investigation Plan P/0074/2014 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 for Zinforo to include a new population, children from the age of 2 months; as a consequence, sections 4.1, 4.2, 4.8, 5.1, 5.2, 5.3 and 6.6 of the SmPC have been updated with new information on dosing, PK and safety. The Package Leaflet is updated in accordance. In addition, the Marketing Authorisation Holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet and to align the PI with the latest QRD template 10.0.

Summary

Please refer to the scientific discussion for Zinforo EMEA/H/C/002252/II/0022.