5 February 2015
EMA/85104/2015
Committee for Medicinal Products for Human Use (CHMP)

Zinforo

(ceftaroline fosamil)

EMEA/H/C/002252/P46 012

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

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

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Administrative information

Invented name of the medicinal product:	Zinforo
INN (or common name) of the active substance(s):	Ceftaroline fosamil
MAH:	AZ
Currently approved Indication(s)	cSSTI and CAP
Pharmaceutical form(s) and strength(s):	600 mg powder for concentrate for solution for infusion

1. Introduction

The present paediatric data is submitted by the MAH in accordance with article 46 of Regulation EC No 1901/2006.

This submission for Ceftaroline, in the treatment of cSSTI and CAP, relates to the submission of the results from the clinical study P903-31 / D3720C00007 (randomised, observer-blinded study to evaluate the safety and tolerability of ceftaroline versus ceftriaxone
in paediatric patients, ages 2 months to < 18 years, with CAP requiring hospitalization) which is a completed study from the EU Risk Management Plan and Paediatric Investigation Plan.

The full benefit and risk profile in the paediatric population will be evaluated when the additional studies in this plan have been completed. Paediatric patient exposure will continue to be specified as missing information in the EU Risk Management Plan until the completion of the paediatric studies. In view of this no changes to the SPC and proposed at this stage.

The overall benefit to risk balance for Zinforo is not affected by this new information and therefore does not require taking further regulatory action on the marketing authorization for Zinforo at this stage.

About the product

Ceftaroline fosamil is the prodrug of ceftaroline and is rapidly converted to microbiologically active drug after intravenous (iv) administration. Ceftaroline, inhibits bacterial cell growth by interfering with cell wall biosynthesis. Ceftaroline has high affinity for PBP2a and is highly potent against resistant staphylococci. Ceftaroline has also been shown to bind with high affinity to PBPs in S. pneumoniae including modified forms of PBP2x which are common in penicillin-resistant S. pneumoniae (PRSP).

Ceftaroline is approved for treatment of adult patients with cSSTI and CAP in the EU since August 2012. The recommended dosing regimen is 600 mg (reduced to 400 mg for patients with creatinine clearance <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.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that this study is a stand-alone study.

2. Scientific discussion

2.1 Clinical

As part of the EU-RMP and PIP, the MAH conducted the clinical study P903-31 / D3720C00007 (A randomised, observer-blinded study to evaluate the safety and tolerability of ceftaroline versus ceftriaxone in paediatric patients, ages 2 months to < 18 years, with CAP requiring hospitalization).

The study is described briefly below (for further details please refer to the full CSR).

Study D3720C00007

Study design

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

Subjects were stratified by age cohort and region and were randomly assigned to treatment in a 3:1 ratio, ceftaroline fosamil to ceftriaxone. The following age cohorts were defined:

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

A minimum of 7 intravenous (IV) doses was required for subjects randomized to ceftaroline fosamil. A switch to open label oral study drug (amoxicillin clavulanate) was allowed on or after Study Day 4 if a subject met the protocol-specified criteria.

Study site and dates

The study was conducted by Cerexa, US between 14/01/2013 and 10/04/2014. The study had appropriate ethics approval and was performed according to GCP. Fifty sites were enrolled but only 34 actually enrolled patients for the study.

Study Objectives

Primary
-To evaluate the safety and tolerability of ceftaroline versus ceftriaxone in pediatric subjects, ages 2 months to < 18 years, with community-acquired bacterial pneumonia (CABP) requiring hospitalization

Secondary
-To evaluate the efficacy of ceftaroline versus ceftriaxone in pediatric subjects with CABP requiring hospitalization
-To evaluate the pharmacokinetics (PK) of ceftaroline in pediatric subjects ages 2 months to < 18 years with CABP requiring hospitalization (**This analysis is reported separately**)

Study population

Male and female subjects 2 months to < 18 years of age; CABP (meeting the protocol-specified criteria) requiring hospitalization and IV antibacterial therapy; acute onset or worsening within 5 days before randomization of at least 2 clinical signs or symptoms of CABP (ie, cough, tachypnea, dyspnea, grunting, sputum production, chest pain, cyanosis, evidence of pneumonia with parenchymal consolidation, increased work of breathing) and at least 1 of the following: organism consistent with a typical respiratory pathogen identified or isolated from a respiratory or blood culture, leukocytosis, > 15% immature white blood cells, leukopenia or hypoxemia.

Study medications

Investigational Product, Dose, and Mode of Administration:
IV ceftaroline fosamil infused over 60 (± 10) minutes every 8 hours (q8h [± 1 hour]) as follows:
Children ≥ 6 months: ceftaroline fosamil 12 mg/kg for subjects weighing ≤ 33 kg or 400 mg for subjects weighing > 33 kg
Children < 6 months: ceftaroline fosamil 8 mg/kg

Reference Therapy, Dosage, and Mode of Administration:
IV ceftriaxone at a total daily dose of 75 mg/kg/day up to a maximum of 4 g/day, given in equally divided doses, each infused over 30 (± 10) minutes every 12 hours (q12h [± 2 hours]).

Optional Oral Switch, Dose and Mode of Administration:
Amoxicillin clavulanate was the drug specified to be administered for the optional oral therapy. A recommended total daily dose of up to 90 mg/kg/day amoxicillin clavulanate was to be divided equally q12h.

Duration of Treatment

Total duration of study drug therapy was 5 to 14 days, inclusive; a minimum of 3 days (7 infusions for subjects randomized to ceftaroline fosamil) of IV study drug therapy was required. The total duration of subject participation was expected to be 26 to 50 days, inclusive.

Criteria for Evaluation

Efficacy:
-Clinical response (defined as improvement in at least two and worsening of none of the following symptoms compared to baseline: Cough, Dyspnea, Sputum production, Chest pain, Chills or rigors, Feeling of warmth/feverish, Exercise intolerance or lethargy) at Study Day 4 by subject and by baseline pathogen in the MITT and the mMITT populations
-Clinical stability (defined by having met all of the following criteria: Afebrile (temperature ≤ 38.0°C by any measurement method), Age-appropriate normal pulse and respiratory rates, Oxygen saturation ≥ 92% on room air, Worsening of none of the following symptoms relative to baseline: cough, dyspnea,chest pain, sputum production, chills or rigors, feeling of warmth / feverish, and exercise intolerance or lethargy) at Study Day 4 by subject and by baseline pathogen in the MITT and mMITT populations
-Clinical outcome at End of IV Study Drug (EOIV), End of Therapy (EOT), and Test-of-Cure (TOC) in the MITT and CE populations
-Clinical and microbiological outcomes by subject and by baseline pathogen at TOC in the mMITT and ME populations
-Clinical relapse at Late Follow-up (LFU) in the MITT Population
-Emergent infections in the mMITT Population
-30-day all-cause mortality in the MITT Population

Safety:
Adverse events (AEs), serious adverse events (SAEs), deaths, and discontinuations due to AEs; clinical laboratory parameters; vital signs measurements

Statistical methods

The following study populations were defined:
-ITT Population: all randomized subjects with study drug assignment designated according to initial randomization, regardless of whether subjects receive study drug according to the randomization schedule, or receive a different drug from that to which they were randomized
-Safety Population: all randomized subjects who received any amount of study drug
-MITT Population: all randomized subjects who receive any amount of IV study drug and who have a confirmed diagnosis of CABP.
-CE Population: a subset of the MITT Population and will include subjects who meet minimal disease criteria for CABP and all evaluability criteria as specified in the Statistical Analysis Plan.
-mMITT Population: a subset of the MITT Population, including subjects for whom at least 1 typical bacterial pathogen had been identified from an adequate microbiological specimen at baseline
-ME Population: all subjects who met the criteria for both the CE and mMITT populations.
-PK Population: all randomized subjects who received a known amount of ceftaroline fosamil and who had had at least 1 PK sample collected (excluding those who received blood or blood component transfusions within 24 hours before any PK sample was drawn)

Efficacy: Efficacy response was analyzed using the MITT, CE, mMITT, and ME populations. Proportions of subjects with favorable efficacy responses were displayed by treatment group, both overall and within each age cohort. The difference between treatment groups in efficacy response rates was calculated, along with 95% confidence intervals (CI) for both the within-group response rates and the between-group difference for each efficacy response.

Safety: Safety parameters (AEs, SAEs, deaths, clinical laboratory parameters, and vital signs measurements) were summarized for the Safety Population.

Study monitoring

An external Data and Safety Monitoring Board (DSMB) was established to review safety data from this study, and other ongoing pediatric studies of ceftaroline fosamil, at prespecified intervals to ensure safety of all subjects enrolled.

Results

Study Disposition

Subjects were stratified by region and age cohort. A total of 161 subjects were randomized 3:1 to receive study drug (122 subjects to ceftaroline fosamil and 39 subjects to ceftriaxone) (ITT Population). All but 1 subject were treated with study drug and were included in the Safety Population.

Table 10.1–1. Subject Populations and Reasons for Exclusions—ITT Population

Study Populations *Reasons for Exclusion*	*Ceftaroline (N = 122) n (%)*	*Ceftriaxone (N = 39) n (%)*	*Total (N = 161) n (%)*
ITT Population	**122 (100.0)**	**39 (100.0)**	**161 (100.0)**
Safety Population	**121 (99.2)**	**39 (100.0)**	**160 (99.4)**
No study drug taken	1 (0.8)	0	1 (0.6)
MITT Population	**107 (87.7)**	**36 (92.3)**	**143 (88.8)**
No study drug taken	1 (0.8)	0	1 (0.6)
No confirmed CABP[a]	1 (0.8)	0	1 (0.6)
Sole atypical pathogen	14 (11.5)	3 (7.7)	17 (10.6)
mMITT Population	**24 (19.7)**	**9 (23.1)**	**33 (20.5)**
Not in MITT Population	15 (12.3)	3 (7.7)	18 (11.2)
No typical pathogen identified at baseline	98 (80.3)	30 (76.9)	128 (79.5)
CE Population	**98 (80.3)**	**36 (92.3)**	**134 (83.2)**
Not in MITT Population	15 (12.3)	3 (7.7)	18 (11.2)
Received < 80% of study drug	0	0	0
Less than the minimum number of days of IV or oral study drug	0	0	0
Test-of-Cure visit out of window	10 (8.2)	1 (2.6)	11 (6.8)
Concomitant antimicrobial violation	2 (1.6)	0	2 (1.2)
Received incorrect study drug	0	0	0
Unblinded prior to database lock	0	0	0
Additional inclusion/exclusion criteria violation[b]	3 (2.5)	0	3 (1.9)
ME Population	**23 (18.9)**	**9 (23.1)**	**32 (19.9)**
Not in mMITT Population	98 (80.3)	30 (76.9)	128 (79.5)
Not in CE Population	24 (19.7)	3 (7.7)	27 (16.8)

Demographics and Baseline Characteristics

The majority of subjects were white, with a mean age of 4.19 years (range 10 weeks through 17 years). Demographics and baseline characteristics were generally balanced between the 2 treatment groups. The majority of subjects had normal renal function, and no subjects had moderate or severe renal impairment.

Efficacy

-The clinical response and stability at Study Day 4 were similar between the 2 treatment groups in the MITT Population: 69.2% and 66.7% of subjects were responders and 34.6% and 36.1% of subjects were clinically stable in the ceftaroline and ceftriaxone groups, respectively.

Table 11.4.1.1–1. Clinical Response and Stability at Study Day 4—MITT Population

Response/Stability	*Ceftaroline (N = 107) n (%)*	*Ceftriaxone (N = 36) n (%)*	*Difference (%)*
Clinical response			
Responder	74 (69.2)	24 (66.7)	2.5
95% CI	(59.5, 77.7)	(49.0, 81.4)	(-13.9, 20.9)
Non-Responder	24 (22.4)	11 (30.6)	
Incomplete Data	9 (8.4)	1 (2.8)	
Clinical stability			
Stability	37 (34.6)	13 (36.1)	-1.5
95% CI	(25.6, 44.4)	(20.8, 53.8)	(-20.1, 15.3)
No stability	60 (56.1)	23 (63.9)	
Incomplete Data	10 (9.3)	0	

-Clinical cure rates at the TOC visit were high for both the ceftaroline and ceftriaxone treatment groups in both the MITT (87.9% and 88.9%, respectively) and CE populations (91.8% and 88.9%, respectively). Similar results in clinical outcomes were seen at the EOIV and EOT assessments. No subjects had relapse in either treatment group at the LFU assessment.

Table 11.4.1.2–1. 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	

Table 11.4.1.2–2. Clinical Outcomes at the TOC Visit—CE Population

Outcome	*Ceftaroline (N = 98) n (%)*	*Ceftriaxone (N = 36) n (%)*	*Difference (%)*
Clinical cure	90 (91.8)	32 (88.9)	2.9
95% CI	(84.5, 96.4)	(73.9, 96.9)	(-7.0, 17.9)
Clinical failure	8 (8.2)	4 (11.1)	
At EOIV	7 (7.1)	3 (8.3)	
At EOT	0	1 (2.8)	
At TOC	1 (1.0)	0	

Table 11.4.1.2–3. Clinical Outcome at the LFU Visit MITT Population

Outcome	*Ceftaroline (N = 107) n (%)*	*Ceftriaxone (N = 36) n (%)*	*Difference (%)*
Clinical cure at TOC visit, N1	94	32	
Sustained clinical cure	94 (100.0)	32 (100.0)	0.0
95% CI	(96.2, 100.0)	(89.1, 100.0)	(-4.0, 10.8)
Clinical relapse	0	0	
Indeterminate	0	0	

-Microbiological outcomes by subject and by baseline pathogen at TOC in the mMITT Population showed a favorable microbiological response (presumed eradication or eradication) for most subjects in both treatment groups (79.2% and 77.8% in the ceftaroline and ceftriaxone groups, respectively).

Table 11.4.1.4.1–1. Microbiological Outcome at the Test-of-Cure Visit—mMITT Population

	Ceftaroline (N = 24) n (%)	*Ceftriaxone (N = 9) n (%)*	*Difference (%)*
Favorable microbiological outcome	**19 (79.2)**	**7 (77.8)**	**1.4**
95% CI	(57.8, 92.9)	(40.0, 97.2)	(-25.7, 37.6)
Eradication	0	0	—
Presumed eradication	19 (79.2)	7 (77.8)	—
Unfavorable microbiological outcome	**4 (16.7)**	**2 (22.2)**	—
Persistence	0	0	—
Presumed persistence	4 (16.7)	2 (22.2)	—
Indeterminate	1 (4.2)	0	—

Safety results

Study drug exposure was similar between the ceftaroline and ceftriaxone groups. The median duration of IV treatment was 5.0 and 6.0 days, respectively. More than half of the subjects switched to oral study drug; the median duration of oral study drug treatment was 6 days in both the ceftaroline and ceftriaxone groups.

Similar percentages of subjects in each treatment group reported at least 1 TEAE. (45.5% and 46.2% in the ceftaroline and ceftriaxone groups, respectively). The incidence of SAEs was low. Seven subjects reported SAEs, with the overall percentage in each group low (5% in the ceftaroline group and 2.6% in the ceftriaxone group). No SAEs were related to study drug. Two subjects in the ceftaroline group discontinued IV study drug due to an AE. No deaths were reported during the study.

Table 12.2.1–1. 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

Table 12.3.1.2–1. Incidence of Serious Adverse Events—Safety Population

System Organ Class[a] Preferred Term	*Ceftaroline (N = 121)*		*Ceftriaxone (N = 39)*	
	n (%)	*Related*	*n (%)*	*Related*
Subjects with any SAE(s)	6 (5.0)	0	1 (2.6)	0
Infections and infestations				
Gastroenteritis	2 (1.7)	0	0	0
Bronchitis	1 (0.8)	0	0	0
Infectious pleural effusion	1 (0.8)	0	0	0
Pneumonia	1 (0.8)	0	0	0
Pneumonia respiratory syncytial viral	1 (0.8)	0	0	0
Metabolism and nutritional disorders				
Dehydration	1 (0.8)	0	0	0
Respiratory, thoracic and mediastinal disorders				
Pulmonary thrombosis	0	0	1 (2.6)	0

No trends were seen in changes from baseline for clinical laboratory parameters. The incidence of potentially clinically significant laboratory abnormalities was low and no subject met potential Hy's law criteria. Mean changes over time in vital signs measurements were similar between both treatment groups and consistent with improvement in the underlying infection over the course of the study.

Applicant's Conclusion

Safety data indicate that treatment of pediatric subjects with CABP with ceftaroline fosamil was well tolerated. The clinical outcomes in the ceftaroline treatment group were comparable to those in the ceftriaxone treatment group.

2.3 Discussion

The study was designed to primarily look at safety and tolerability of ceftaroline in the mentioned doses in patients with CABP requiring hospitalisation. Ceftriaxone was selected as an active comparator agent for its microbiological spectrum of activity, effectiveness as treatment for CABP, its widespread global use, and acceptance as a therapy for CABP based on expert opinion and national adult CAP

guidelines. The switch to oral therapy at the investigator's discretion is based on normal clinical practice.

In the study there were no unexpected safety issues, the tolerability was good and efficacy was similar to the comparator. Although PK results will be reported separately, it appears the choice of doses for the various cohorts was appropriate based on the efficacy seen.

In addition to this study, further studies are planned as part of PIP. Therefore no further action is proposed at this stage.

2.4 Changes to the product information

The MAH proposed no changes to the Product Information, which is acceptable at this stage as further paediatric studies are planned.

3. Overall conclusion and impact on the benefit/risk balance

Based on the results of the newly completed study which evaluates the safety and tolerability of ceftaroline versus ceftriaxone in paediatric patients, ages 2 months to < 18 years, with CAP requiring hospitalization, it is considered that the safety and efficacy of ceftaroline in this population is acceptable and no unexpected concerns have been identified.

Therefore this does not change the benefit/risk balance.

3. Rapporteur's overall conclusion and recommendation

Overall conclusion

The benefit/risk balance remains positive in the approved indications at present. A final decision regarding any change to the product literature related to the paediatric population will be taken upon completion of all the clinical studies planned in this population under the PIP.