AstraZeneca

Clinical Study Report Synopsis

Drug Substance	Ceftaroline fosamil
Study Code	D3720C00002
Edition Number	1

A Phase III, Multi-Centre, Randomised, Double-Blind, Comparative Study to Evaluate the Efficacy and Safety of Intravenous Ceftaroline Fosamil Versus Intravenous Ceftriaxone in the Treatment of Adult Hospitalised Patients with Community-Acquired Bacterial Pneumonia in Asia

Study dates: First patient enrolled: 22 December 2011
Last patient last visit: 29 May 2013

Phase of development: Therapeutic confirmatory (III)

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

Publication

None at the time of writing this report.

Objectives and criteria for evaluation

The objectives and variables of this study are summarised in Table S 1.

Table S 1 Objectives and outcome variables

Objectives			Outcome variable
Priority	**Type**	**Description**	**Description**
Primary	Efficacy	To determine the non-inferiority in the clinical cure rate of ceftaroline treatment compared with that of ceftriaxone treatment at the TOC visit in the clinically evaluable (CE) population of adult hospitalised patients with community acquired bacterial pneumonia (CAP).	Clinical response at the TOC visit in the CE population.
Secondary	Efficacy	To evaluate clinical response at the EOT visit.	Clinical response at the EOT visit in the MITT and CE populations.
	Efficacy	To evaluate clinical response at the TOC visit in the MITT, mMITT, and ME populations.	Clinical response at the TOC visit in the MITT, mMITT, and ME populations.
	Efficacy	To evaluate microbiological response at the TOC visit.	Microbiological response at the TOC visit in the mMITT and ME populations.
	Efficacy	To evaluate the overall (clinical and radiographic) response at the TOC visit in the MITT and CE populations.	Overall (clinical and radiographic) response at the TOC visit in the MITT and CE populations.
	Efficacy	To evaluate the clinical and microbiological response by pathogen at the TOC visit.	Per-pathogen clinical and microbiological response at the TOC visit in the mMITT and ME populations.
	Efficacy	To evaluate the clinical relapse at the LFU visit.	Clinical relapse at the LFU visit (clinically cured at TOC) in the CE population.
	Efficacy	To evaluate the microbiological re-infection/recurrence at the LFU visit.	Microbiological re-infection/recurrence at the LFU visit (clinical and microbiologically favourable outcome at the TOC visit) in the mMITT and ME populations.
	Safety	To evaluate the safety of ceftaroline.	AEs, ECG, laboratory assessments, physical examination, and vital signs in the safety population.
	Exploratory/ PK[a]	To evaluate ceftaroline PK in a sub-group of patients.	PK parameters derived from population PK analysis.

Table S 1 Objectives and outcome variables

Objectives			Outcome variable
Priority	**Type**	**Description**	**Description**
	Exploratory/ PK/PD[a]	To evaluate ceftaroline exposure and the antimicrobial response relationship.	Any potential PK/PD relationships.
	Exploratory/ HEOR	To quantify the length of stay in hospital and rates of ICU admission by clinical outcome.	Length of hospital stay and admission and duration of stay in an ICU as measured at the LFU visit.
	Exploratory/ PRO	To characterise and explore resolution of patient-reported symptoms of CAP.	CAP-SYM 18 scores at baseline, Day 2, Day 4, EOT, TOC, and LFU visits.

[a] Results of these objectives are reported in a separate report.

AE Adverse event; CAP-SYM 18 Community-Acquired Pneumonia-Symptom 18 questionnaire; CSR Clinical Study Report; ECG Electrocardiogram; EOT End-of-therapy; HEOR Health Economics and Outcomes Research; ICU Intensive care unit; LFU Late follow-up; ME Microbiologically evaluable; MITT Modified intent-to-treat; mMITT Microbiological modified intent-to-treat; PD Pharmacodynamics; PK Pharmacokinetics; PRO Patient reported outcomes; TOC Test-of-cure.

Study design

This was a Phase III, multi-centre, randomised, double blind, comparative efficacy and safety study of ceftaroline fosamil[1] 600 mg intravenous (iv) every 12 hours (q12h) versus ceftriaxone 2 g iv every 24 hours (q24h) administered for 5 days to 7 days in hospitalised, adult Asian patients with community-acquired pneumonia (CAP)[2]. A block randomisation method using either an interactive voice response system or an interactive web response system, stratified by district, was used to assign patients in a 1:1 ratio to either the ceftaroline group or the ceftriaxone group. The study consisted of a baseline visit, a 5-day to 7-day treatment period, followed by the end-of-treatment (EOT), test-of-cure (TOC), and late follow-up (LFU) visits. Patient participation was required between 26 days to 42 days.

Target patient population and sample size

The target patient population comprised male and female hospitalised patients of age ≥18 years from the Asian region with CAP as defined by radiographic and microbiologic inclusion criteria and whose severity of disease is a Pneumonia Outcomes Research Team (PORT) Risk Class Determination III or IV. The patients were to have acute illness of ≤7 days duration with radiographic evidence of pneumonia and at least 3 clinical signs or symptoms consistent with a lower respiratory tract infection. Only those patients whose severity of disease was determined as a PORT Risk Class III or IV were eligible for the study.

[1] In this document, "ceftaroline fosamil" is used when necessary to clearly differentiate the prodrug from the bioactive form and when specifically referring to the form of the drug administered to patients (when describing dosages). However, for brevity, the name "ceftaroline" is used in all other instances (eg, in descriptions of treatment groups, in table headers and footnotes, and in general results discussion).

[2] This CSR synopsis uses CAP to represent all instances of community-acquired bacterial pneumonia and community-acquired pneumonia.

Assuming a point estimate for the clinical cure rate of 85% in the ceftriaxone treatment group and 85% in the ceftaroline group in the clinically evaluable (CE) population, a non-inferiority margin of 10%, a power of 90%, and an evaluability rate of 77.5%, a total sample size of 692 patients was required (346 patients in each of the treatment groups). However, in accordance with standard practice in infection studies, evaluability of patients on blinded data was assessed on an on-going basis and it was identified that the evaluability rate was lower than expected (<77.5%), thus recruitment was increased to 770 patients.

Investigational product and comparator: Dosage, mode of administration, and batch numbers

Ceftaroline fosamil for injection was supplied as 600 mg of the prodrug of ceftaroline, a sterile, pale yellowish-white to light yellow crystalline powder in a single-dose, clear glass 20-mL vial. Patients randomised to ceftaroline fosamil received 600 mg iv q12h (±2 hours) of this study drug, infused over 60 (±20) minutes for 5 days to 7 days. To maintain study blinding, each 60-minute infusion was divided into 2 sequential 30 (±10)-minute infusions containing 50% of the total dose.

Ceftriaxone for injection was supplied as 1 g/vial (2 vials for a 2 g dose) using commercially available material. Patients randomised to ceftriaxone received a dose of 2 g of this study drug, infused over 30 (±10) minutes immediately followed by iv saline placebo infused over 30 (±10) minutes, q24h (±2 hours), for 5 days to 7 days. Twelve hours after each dose of ceftriaxone and saline placebo, patients in this group received 2 consecutive saline placebo infusions, each infused over 30 (±10) minutes q24h (±2 hours). The ceftriaxone and saline placebo infusions corresponded to the q12h (±2 hours) infusions of ceftaroline, thereby maintaining the blinding.

The dosage, mode of administration, and batch numbers are provided in Table S 2.

Table S 2 Details of the study drugs

Study drug	Dosage form, strength, and mode of administration	Manufacturer	Batch number
Ceftaroline fosamil.	Powder for concentrate for solution for infusion, 600 mg.	FACTA Pharmaceutical SpA.	**China:** 0001D0, 0004D2, 0013D1, 0019D2, 205263/9 **India:** 0004D2, 0012D1, 0012D2, 0013D1, 0019D2, 205263/9 **Korea:** 0001D0, 0004D2, 0012D2, 0013D1, 0019D2, 205263/9 **Taiwan:** 0001D0, 0004D2, 0012D2, 0013D1, 205263/9 **Vietnam:** 0004D2 and 001D0.

Table S 2 Details of the study drugs

Study drug	Dosage form, strength, and mode of administration	Manufacturer	Batch number
Ceftriaxone	Powder for iv solution, 1 g/vial (2 g in total), iv administration.	Roche	**China:** 205263/10, B3621, B3691, B3691B01F0282, B3704, B3714, B3777 **India:** 205263/10, B3621, B3691, B3691B01F0282, B3704, B3714, B3777 **Korea:** 205263/10, B3456, B3621, B3691, B3691B01F0282, B3704, B3714, B3777 **Taiwan:** 205263/10, B3621, B3691, B3704, B3714. **Vietnam:** B3691, B3704, B3777.

iv Intravenous.

Duration of treatment

The duration of treatment for both ceftaroline and ceftriaxone was 5 days to 7 days.

Statistical methods

The efficacy analysis populations were as follows: Modified intent-to-treat (MITT, received any study drug and had PORT Risk Class III or IV), microbiological modified intent-to-treat (mMITT, ≥1 typical[3] bacterial baseline pathogen), clinically evaluable (CE, met all evaluability criteria), and microbiological evaluable (ME, met criteria of both CE and mMITT populations). The safety population included all patients who received at least 1 dose of the study drug.

For the primary efficacy outcome measure, the clinical cure rate of ceftaroline was compared with that of ceftriaxone at the TOC visit in the CE population, a 2-sided 95% confidence interval (CI) for the observed difference in the cure rate (ceftaroline group minus ceftriaxone group) was computed using the method proposed for unstratified designs by Miettinen and Nurminen. Non-inferiority of ceftaroline was to be concluded if the lower limit of the 95% CI for the difference for the CE population was greater than -10%. If the clinical cure rate for ceftaroline was higher than that seen in the ceftriaxone group and non-inferiority was established in the CE population, a test of superiority was to be conducted. Superiority of ceftaroline was to be concluded if the lower limit of the 95% CI for the difference in the CE population exceeded 0%.

For each secondary efficacy outcome measure, a 2-sided 95% CI was computed using the method proposed for unstratified designs by Miettinen and Nurminen, where appropriate.

[3] In this document, the term typical is used for Gram-positive and Gram-negative bacterial pathogens commonly associated with community-acquired pneumonia.

The safety analysis was to be performed using the safety population. The safety variables included adverse events (AEs), clinical laboratory parameters, vital signs, electrocardiogram parameters, and physical examinations. For each safety variable, the last assessment made prior to the first dose of the study drug was to be used as the baseline for all analyses.

Subject population

The disposition of the patients in this study is summarised in Table S 3. Across treatment groups, the disposition of the patients was balanced, except for discontinuations.

Overall, 847 patients were enrolled from 64 centres in 5 Asian districts in this study. Of these, 771 patients were randomised; 385 in the ceftaroline group and 386 patients in the ceftriaxone group. The proportion of patients randomised from each district were 39.2% from China, 25.9% India, 18.8% Korea, 7.5% Taiwan, and 8.6% Vietnam. Overall, 62/771 [8%] patients discontinued study treatment and 115/771 [14.9%] from the study. There was a higher percentage of discontinuations in the ceftriaxone group than in the ceftaroline group. The most common reason for discontinuing the study treatment and study was patient decision.

In both the MITT and CE populations, the demographic characteristics of the patients were balanced across treatment groups and were consistent with the inclusion and exclusion criteria of the study. In the MITT population, all patients were Asian with a higher percentage of male patients (70.4% patients) compared with female patients (29.6% patients). The mean age of the patients was 66 years (range: 19 years to 94 years), the majority of patients were elderly patients with 60.6% patients in the age group of ≥65 years, including 31.6% patients being in the age group ≥75 years. India, China, Korea, and Vietnam enrolled patients aged >18 years; Taiwan enrolled patients aged ≥20 years. An upper age limit was applied by India (≤75 years) as per the Indian regulatory authority approval letter. All patients were PORT Risk Class III (68%) or Class IV (32%). A high percentage of patients had a history of underlying lung disease: COPD (27.7%), asthma (5.6%), tuberculosis (6.6%), chronic bronchitis (3.9%), and bronchiectasis (3.4%) and a low percentage (<25%) of patients had received prior systemic antibacterial medication.

In the mMITT population, the most commonly isolated Gram-positive pathogen was *Streptococcus pneumoniae* (42/176 [23.9%] patients), followed by *Staphylococcus aureus* (12/176 [6.8%] patients). The most commonly isolated Gram-negative pathogens were *Klebsiella pneumoniae*, followed by *Haemophilus influenzae,* and *Escherichia coli*. The majority of infections were monomicrobial (77.8%) and were caused by Gram-negative pathogens (ie, 69% of monomicrobial infections were caused by Gram-negative pathogens).

Table S 3 Patient disposition (All patients)

	Number (%) of patients[b]		
	Ceftaroline	**Ceftriaxone**	**Total**
Patients enrolled[a]			847
Patients randomized	385	386	771

Table S 3 Patient disposition (All patients)

	Number (%) of patients[b]		
	Ceftaroline	**Ceftriaxone**	**Total**
Patients who were not randomized			76
Withdrawn from study due to eligibility criteria not fulfilled			68
Withdrawn from study due to other			4
Withdrawn from study due to subject decision			4
Patients who received treatment	381 (99.0)	383 (99.2)	764 (99.1)
Patients who did not receive treatment	4 (1.0)	3 (0.8)	7 (0.9)
Withdrawn from study due to severe non-compliance to protocol	2 (0.5)	2 (0.5)	4 (0.5)
Withdrawn from study due to subject decision	2 (0.5)	1 (0.3)	3 (0.4)
Patients who completed treatment	358 (93.0)	344 (89.1)	702 (91.1)
Patients who discontinued treatment	23 (6.0)	39 (10.1)	62 (8.0)
Treatment stopped due to subject decision	14 (3.6)	20 (5.2)	34 (4.4)
Treatment stopped due to adverse event	7 (1.8)	8 (2.1)	15 (1.9)
Treatment stopped due to other	2 (0.5)	7 (1.8)	9 (1.2)
Treatment stopped due to death	0	2 (0.5)	2 (0.3)
Treatment stopped due to subject lost to follow-up	0	2 (0.5)	2 (0.3)
Patients who completed study	332 (86.2)	317 (82.1)	649 (84.2)
Patients who withdrew study	49 (12.7)	66 (17.1)	115 (14.9)
Withdrawn from study due to subject decision	27 (7.0)	33 (8.5)	60 (7.8)
Withdrawn from study due to subject lost to follow-up	10 (2.6)	20 (5.2)	30 (3.9)
Withdrawn from study due to other	6 (1.6)	9 (2.3)	15 (1.9)
Withdrawn from study due to death	3 (0.8)	4 (1.0)	7 (0.9)
Withdrawn from study due to severe non-compliance to protocol	3 (0.8)	0	3 (0.4)

[a] Informed consent received.
[b] Percentages were calculated from the number of randomised patients.

Summary of efficacy results

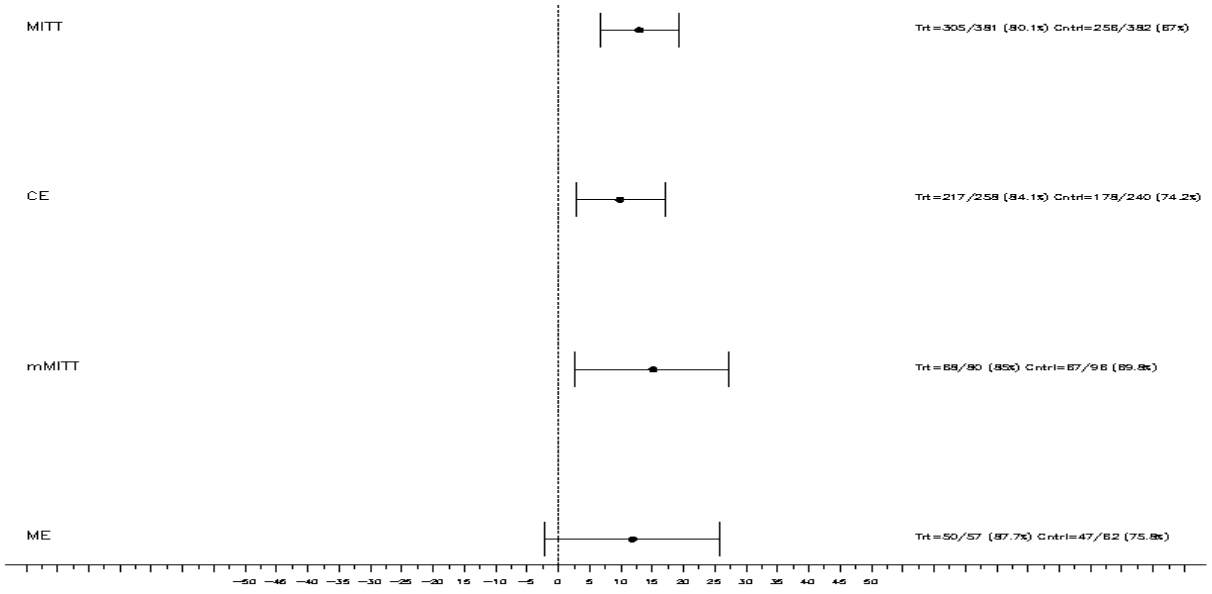
The non-inferiority of ceftaroline compared with ceftriaxone was demonstrated in the CE population, as the lower limit of the 95% CI around the treatment difference (ceftaroline - ceftriaxone) was greater than the pre-specified non-inferiority boundary of -10%. The clinical cure rates in the ceftaroline group vs the ceftriaxone group at the TOC visit were 84.1% vs 74.2% (difference: 9.9; 95% CI: 2.8 to 17.1). In addition, given that non-inferiority was

demonstrated and the lower limit of 95% CI was greater than pre-specified boundary of 0%, the superiority of ceftaroline compared with ceftriaxone was concluded.

The clinical response at the EOT visit in the CE and MITT populations were consistent with the results of the primary analysis. The lower limit of the 95% CIs around the treatment difference (ceftaroline - ceftriaxone) was greater than 0% in both the populations.

The clinical response at the TOC visit in the MITT, mMITT, and ME populations was consistent with the results of the primary analysis (see Figure 1).

Figure 1 **Forest plot of analysis of Clinical response at TOC (MITT, CE, mMITT and ME population)**



Difference: Ceftaroline treatment group minus ceftriaxone treatment group.
Confidence intervals were calculated using Miettinen and Nurminen method for unstratified designs.
Trt: Ceftaroline, Cntrl: Ceftriaxone.
CE Clinically evaluable; CI Confidence interval; ME Microbiologically evaluable; MITT Modified intent-to-treat; mMITT Microbiological modified intent-to-treat; TOC Test-of-cure.

Due to the absence of culture data, the microbiological response of all patients at the TOC visit was presumed from the clinical response. Thus, the microbiological response rates and treatment differences were the same as for the clinical response rates for both the ME population and mMITT population.

In the CE and MITT populations, the results of the overall response at the TOC visit were identical to the results of the primary analysis as the inclusion of radiographic responses did not impact the overall success rates. In both the populations, the lower limit of 95% CIs was greater than 0%.

The clinical response rates by baseline pathogen at the TOC visit in the ceftaroline group were high for all key pathogens. However, the small numbers of patients with each individual baseline pathogen precluded meaningful comparisons of the clinical response rates in the ceftaroline group versus the ceftriaxone group. The clinical cure rates associated with infections caused by both Gram-positive pathogens and by Gram-negative pathogens were higher in the ceftaroline group than the ceftriaxone group. Similarly, the clinical cure rates for the monomicrobial infections were higher in the ceftaroline group than in the ceftriaxone group. However, the clinical cure rates were similar between the treatment groups for the polymicrobial infections. Given the microbiological response of all patients/pathogens at the TOC visit was presumed from the clinical response at the TOC visit, the microbiological response rates at the TOC visit by pathogen in the mMITT and ME population were identical to the clinical response rates at the TOC visit by pathogen in the mMITT and ME populations.

In the MITT population, an analysis population that did not exclude patients due to presence of a sole atypical[4] pathogen or indeterminate *Mycoplasma* immunoglobulin M (IgM) immunofluorescent assay (IFA) serology [5], there was an evidence of a large treatment difference in patients without an atypical pathogen infection 81.1% vs 66.7% (difference:14.4; 95% CI: 7.2, 21.6). This level of difference was not evident in patients with an atypical infection for whom clinical cure rates were 76.9% vs 72.4% (difference: 4.5, 95% CI: -10.9, 20.1). In contrast, the results in patients who had indeterminate *Mycoplasma* IgM IFA serology results (78% vs 62.2%) demonstrated a treatment difference similar to that observed in patients with no evidence of atypical pathogens (difference: 15.8; 95% CI: 3.8, 34.2). This is consistent with the hypothesis that the patients who were classified with indeterminate serology had false positive *Mycoplasma* IgM IFA serology. These patients were generally excluded from the CE population.

In both the MITT and CE populations, of the patients who were clinically cured at the TOC visit, more than 91% of patients remained clinically cured at the LFU visit, with a low clinical relapse rate in both the treatment groups. In both the treatment groups and populations, the relapse rate at the LFU visit, following the clinical response of cure at the TOC visit, was <3%.

In the ME population, none of the patients in the ceftaroline group and 1 patient in the ceftriaxone group had microbiological re-infection/recurrence at the LFU visit. This was also observed in the mMITT population.

In the ME population, none of the patients in the ceftaroline group and 1 patient in the ceftriaxone group had a superinfection. In the mMITT population, none of the patients in the ceftaroline group and 2 patients in the ceftriaxone group had a superinfection. In both populations and treatment groups, none of the patients had a new infection or colonisation.

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[4] In this document, the term atypical is used for atypical CAP pathogens that included *Chlamydophila pneumoniae*, *Mycoplasma pneumoniae*, and *Legionella pneumophila.*

[5] The *Mycoplasma pneumoniae* IgM serology was classified as indeterminate if the immunofluorescence (IFA) serology was positive in the absence of a confirmatory positive serology result.

Summary of patient-reported outcome

Patient-reported symptoms were collected using the Community-Acquired-Pneumonia Symptom (CAP-SYM) 18 questionnaire. At the EOT visit, there were no major differences in the individual symptoms between the treatment groups.

Summary of health economic results

The overall median length of hospital stay was 8 days in both the treatment groups in both the CE and MITT populations. The 75th percentile of the length of stay in the hospital was slightly longer in the ceftriaxone group compared with the ceftaroline group (10 days vs 9 days). In the CE and MITT populations, there were few patients admitted to the ICU: 1 patient in the ceftaroline group and 5 patients in the ceftriaxone group.

Summary of pharmacokinetic results

A population PK analysis will be performed and the results will be reported separately. The plasma concentrations of ceftriaxone were not determined.

Summary of safety results

The median duration of exposure was 6.5 days in both the treatment groups. More than 85% of patients in both the treatment groups received study drug for at least 5 days.

Overall, the number of patients with AEs of any category was comparable across treatment groups (Table S 4).

Table S 4 Adverse events in any category - Patient level (Safety population)

AE category	Number (%) of patients[a]	
	Ceftaroline (N=381)	Ceftriaxone (N=383)
Any AE	172 (45.1)	163 (42.6)
Any AE causally related to study drug [b]	31 (8.1)	25 (6.5)
Any AE with outcome = Fatal	3 (0.8)	3 (0.8)
Any AE with outcome = Fatal, causally related to study drug [b]	0	0
Any SAE (including events with outcome = death) [d]	30 (7.9)	29 (7.6)
Any SAE (including events with outcome = death), causally related to study drug [d]	0	1 (0.3)
Any SAE upto EOT+1 Day (including events with outcome = death) [c]	16 (4.2)	20 (5.2)
Any SAE upto EOT+1 Day (including events with outcome = death), causally related to study drug [c]	0	1 (0.3)
Any AE leading to discontinuation of IP	7 (1.8)	7 (1.8)

Table S 4 Adverse events in any category - Patient level (Safety population)

AE category	Number (%) of patients[a] Ceftaroline (N=381)	Ceftriaxone (N=383)
Any AE leading to discontinuation of IP, causally related to study drug [b]	1 (0.3)	5 (1.3)
Any AE of severe intensity	13 (3.4)	15 (3.9)
Any AE of severe intensity, causally related to study drug [b]	0	0
AE of specific interest*	64 (16.8)	49 (12.8)

[a] Patients with multiple events in the same category were counted only once in that category. Patients with events in more than 1 category were counted once in each of those categories.
[b] As assessed by the investigator.
[c] As assessed by the investigator and included SAE's with an onset date between the date of first dose and EOT+1 day.
[d] Included SAE with an onset date from the date of first dose to the LFU visit or 30 days following the EOT visit in absence of the LFU visit.
Included adverse events with an onset date between the date of first dose and TOC visit or 20 days following the EOT visit in the absence of the TOC visit.
* See Table 11.3.2.8 for AEs of specific interest.
AE Adverse event; EOT End-of-therapy; IP Investigational product; LFU Late follow-up; SAE Serious adverse event; TOC Test-of-cure.

The most common AEs reported by preferred term in the ceftaroline and ceftriaxone groups, with the frequency of occurrence ≥2% in either of the 2 treatment groups were: Diarrhoea (6.3% patients vs 3.4% patients), constipation (4.7% patients vs 2.3% patients), vomiting (3.9% patients vs 1.8% patients), dizziness (3.7% patients vs 1% patient), nausea (2.1% patients vs 0.8% patient), and headache (1.6% patients vs 2.3% patients). The majority of the AEs were of mild intensity in both the ceftaroline and ceftriaxone groups (26% patients vs 23.8% patients). A small and comparable number of patients reported AEs with severe intensity in the ceftaroline and ceftriaxone groups (3.4% patients vs 3.9% patients). A total of 64 (16.8%) patients in the ceftaroline group and 49 (12.8%) patients in the ceftriaxone group experienced AEs of specific interest. The most common AEs of specific interest in the ceftaroline and ceftriaxone groups were diarrhoea (6.3% patients vs 3.7% patients) and liver disorder (3.7% patients vs 4.2% patients).

The most common causally-related AEs in the ceftaroline and the ceftriaxone groups with a frequency >1% in either of the 2 treatment groups were: Vomiting (1.3% patients vs 0.5% patients), hepatic function abnormal (1.3% patients vs 0.3% patient), diarrhoea (1% patients in each treatment group), pruritus (1% patients vs 0.3% patients), and rash (0.3% patients vs 1.6% patients).

Overall, there were 6 AEs with an outcome of death in the study (3 ceftaroline; 3 ceftriaxone), none of which were considered by the investigator to be related to study treatment. In

addition, there was 1 patient in the ceftriaxone group who died after the TOC visit. The primary cause of death was pneumonia (disease under study) and hence it was not recorded as an AE leading to death. The incidence of serious adverse events (SAEs) was similar between the treatment groups (7.9% patients in the ceftaroline group; 7.6% patients in the ceftriaxone group). There was no common trend observed in the incidence of SAEs across treatment groups. The incidence of DAEs was low in both the treatment groups (7 [1.8%] patients in each treatment group). The DAEs were distributed across a number of system organ classes and preferred terms with no obvious trend or pattern.

The most common potentially clinically significant (PCS) haematology findings in the ceftaroline and ceftriaxone groups was positive direct antiglobulin test, also known as positive direct Coombs' test (54/327 [16.5%] vs 27/330 [8.2%]). However, some patients had positive direct Coombs' test identified at baseline. Overall the post-baseline seroconversion of direct antiglobulin (Coombs test) from negative to positive during the study period occurred in a higher percentage of patients in the ceftaroline group (11.5% patients) compared with patients in the ceftriaxone group (4.2% patients). All the patients were screened for haemolytic anaemia via change in haemoglobin, lactate dehydrogenase, total and indirect bilirubin, and haptoglobin. None of the patients showed any evidence of haemolytic anaemia during the study. The other common PCS haematology findings in the ceftaroline and ceftriaxone groups (occurring in ≥1% patients in either of the treatment groups) were decreased haematocrit ratio (1.8% patients vs 1.3% patients), increased neutrophils (1.5% patients vs 2.4% patients), increased platelets (1.3% patients in each treatment group), and decreased haemoglobin count (0.6% patients vs 1.5% patients).

The most common PCS clinical chemistry findings in the ceftaroline and ceftriaxone groups (occurring in ≥1% patients in either of the treatment group) were increased aspartate aminotransferase (AST) (2.1% patients vs 2% patients), increased alanine aminotransferase (ALT) (1.4% patients vs 3.4% patients), increased alkaline phosphatase (1.1% patients vs 2.2% patients), increased creatinine kinase (1.5% patients vs 0.3% patients), increased gamma glutamyltransferase (0.8% patients vs 1.6% patients), decreased potassium (0.8% patients vs 1.4% patients), and increased sodium (0% patient vs 1.1% patients).

There were no clinically important changes or trends in the mean value of any haematology and clinical chemistry parameters during the study. Three patients in the ceftaroline group and 3 patients in the ceftriaxone group had elevations in ALT or AST >3xupper limit of normal (ULN) accompanied by elevations in total bilirubin >2xULN at timepoints during the study; although in 2 ceftaroline patients and 1 ceftriaxone patient, elevations of ALT, AST, or bilirubin were observed from baseline. Increase in transaminases is a known class effect of cephalosporins including ceftaroline. Since the elevations of transaminases and bilirubin either occurred at baseline, transient or at different timepoints, and/or could have been caused by other underlying medical conditions, it was concluded that none of these patients met the criteria of Hy's law.

There were no clinical changes of concern noted in the vital signs for either of the treatment groups during the study. Time-dependent decrease in heart rate, temperature, and respiratory

rate as well as increase in oxygen saturation was observed in both the treatment groups, consistent with the beneficial effect of the study drug. The percentage of patients with overall PCS vital sign values was low and balanced across the treatment groups.

There were low incidences of QT interval corrected for heart rate (QTc) (QT interval corrected for heart rate using Bazett's formula [QTcB] and QT interval corrected for heart rate using Fridericia's formula [QTcF]) increases to >500 msec with a change from baseline of ≥60 msec, observed at isolated timepoints. There were 2 patients in each of the treatment groups with QTcB increases to >500 msec with a change from baseline of ≥60 msec. There were no patients in the ceftaroline group and 2 patients in the ceftriaxone group who had QTcF increases to >500 msec with a change from baseline of ≥60 msec. None of the post-baseline PCS QTc prolongation was reported as AE in either of the treatment groups. There was no clinically meaningful trend or pattern in QT/QTc interval increases or decreases in either treatment groups.