Supplementary Appendix

Efficacy and Safety of Ceftaroline Fosamil in Patients with Community-Acquired Pneumonia in China: Subset Analysis of an International Phase 3 Randomized Controlled Trial

Chao Zhuo[1], Yijiang Huang[2], Wenyuan Liu[3], Jin-Fu Xu[4], Wei Yun Zhu[5], Gregory G. Stone[6], Jean Li Yan[7], Naglaa Mohamed[8]

[1]State Key Laboratory of Respiratory Disease, National Clinical Research Center of Respiratory Diseases, Guangzhou Institute of Respiratory Health, The First Affiliated Hospital of Guangzhou Medical University, Guangzhou, China; [2]Respiratory Clinical Medical Center, Hainan Cancer Hospital, Hainan, China; [3]Respiratory Department, Sichuan Provincial People's Hospital, Chengdu, China; [4]Department of Respiratory and Critical Care Medicine, Shanghai Pulmonary Hospital, Tongji University School of Medicine, Shanghai, China; [5]Medical Department, Pfizer Investment Co. Ltd., Beijing, China; [6]Biopharmaceuticals Group, Pfizer Inc., Groton, Connecticut, USA; [7]Biopharmaceuticals Group, Pfizer Inc., Cambridge, Massachusetts, USA; [8]Biopharmaceuticals Group, Pfizer Inc., New York, New York, USA

Supplementary Methods

Participating study sites: ASIA CAP China subset

1st Affiliated Hospital of Guangzhou Medical College

Beijing Hospital

Ruijin Hospital

The First Hospital of China Medical University

Beijing Chaoyang Hospital

Zhongshan Hospital Fudan University

Hainan Provincial People’s Hospital

Shengjing Hospital

Sichuan Provincial People’s Hospital

The Central Hospital of China Aerospace Corporation

Chengdu Military General Hospital

The Second Hospital of Hebei Medical University

Shanghai Pulmonary Hospital

Northern Jiangsu People's Hospital

Anhui Provincial Hospital

Wuxi People's Hospital

General Hospital of the Second Artillery Force of PLA

1st Affiliated Hospital of Nanchang University

Huadong Hospital Affiliated to Fudan University

Shanghai East Hospital

Jiangyin People's Hospital

Shenzhen People's Hospital

The First People's Hospital of Hangzhou

Analysis populations: ASIA CAP China subset

Analysis population	Definition	Site 1314 included[a]
Safety population	All randomized patients who received any study drug	Yes
MITT population	All randomized patients who received any study drug and had PORT risk class III or IV CAP	No
mMITT population	Patients in the MITT population who had at least one bacterial pathogen identified at baseline (excluding *Mycoplasma pneumoniae*, *Chlamydophila pneumoniae* and *Legionella pneumophila*)	No
CE population	Patients in the MITT population who met predefined evaluability criteria, including minimum disease criteria, and having sufficient information to determine clinical outcome	No
ME population	Patients who met all criteria for both the mMITT and the CE populations	No

Notes: [a]Patients randomised at study site 1314 were excluded from all efficacy analysis populations for the China subset analysis.

Abbreviations: CAP, community-acquired pneumonia; CE, clinically evaluable; ME, microbiologically evaluable; MITT, Modified intention-to-treat; mMITT, microbiological modified intention-to-treat; MRSA methicillin-resistant *Staphylococcus aureus*; PORT, Pneumonia Outcomes Research Team.

Investigator-determined clinical response categories at the TOC visit

Response category	Definition
Clinical cure	Total resolution of all signs and symptoms of community-acquired pneumonia or improvement[a] to such an extent that further antimicrobial therapy was not necessary.
Clinical failure[b]	Any of the following: • Persistence, incomplete clinical resolution or worsening in signs and symptoms of CAP that required alternative antimicrobial therapy • Treatment-limiting AE leading to discontinuation of the study drug when patient required alternative antimicrobial therapy to treat the pneumonia • Death wherein pneumonia (i.e., CAP) was considered causative.
Indeterminate	Study data were not available for the evaluation of efficacy for any reason including treatment change prior to completing at least 48 h of the study treatment; death wherein pneumonia was clearly non-contributory, lost to follow-up, or extenuating circumstances precluding classification as a cure or failure.

Notes: [a]Clinical improvement included the absence of fever (temperature ≤38 °C oral or ≤38.5 °C rectally or tympanically) for at least 24 continuous hours, with temperature recorded twice daily, in addition to a substantial improvement in the signs and symptoms of CAP. Substantial improvement included a return to the pre-CAP baseline levels for patients with decreased pulmonary function (e.g. patients with COPD). [b]Clinical failures at EOT visit were carried forward to the TOC visit. Deaths occurring within 28 days of the EOT visit were to be classified as failures.

Abbreviations: AE, adverse event; CAP, community-acquired pneumonia; COPD, chronic obstructive pulmonary disease; EOT, end-of-treatment; TOC, test-of-cure.

Microbiological response categories at the TOC visit

Response category	Microbiological outcome	Definition[a]
Favourable	Eradication	An adequate source specimen demonstrated absence of the original baseline pathogen.
	Presumed eradication	An adequate source specimen was not available to culture and the patient was assessed as a clinical cure.
Unfavourable	Persistence	Source specimen demonstrated continued presence of the original baseline pathogen.
	Presumed persistence	An adequate source specimen was not available to culture and the patient was assessed as a clinical failure.
Indeterminate	Indeterminate	An adequate source specimen was not available to culture and the patient's clinical response was assessed as indeterminate.

Notes: [a]An adequate source specimen was defined as any sample that yielded growth of a CAP pathogen, e.g., blood, respiratory specimens, or pleural fluid.

Abbreviations: CAP, community-acquired pneumonia; TOC, test-of-cure.

Supplementary Results

Table S1 Adverse events by system organ class and preferred term reported in ≥2 patients in either treatment group in the China subset (safety population, including site 1314)

System organ class[a] Preferred term	Ceftaroline fosamil (n=150)	Ceftriaxone (n=150)
Patients with ≥1 AE	57 (38.0)	58 (38.7)
Blood and lymphatic system disorders	6 (4.0)	2 (1.3)
Leukopenia	3 (2.0)	1 (0.7)
Anaemia	2 (1.3)	1 (0.7)
Cardiac disorders	4 (2.7)	1 (0.7)
Palpitations	2 (1.3)	0
Gastrointestinal disorders	11 (7.3)	13 (8.7)
Constipation	3 (2.0)	4 (2.7)
Diarrhoea	3 (2.0)	1 (0.7)
Gastritis	2 (1.3)	0
Abdominal pain	0	2 (1.3)
General disorders and administration site conditions	3 (2.0)	7 (4.7)
Pyrexia	3 (2.0)	2 (1.3)
Oedema peripheral	0	4 (2.7)
Hepatobiliary disorders	8 (5.3)	14 (9.3)
Hepatic function abnormal	5 (3.3)	3 (2.0)
Liver injury	2 (1.3)	5 (3.3)
Investigations	6 (4.0)	7 (4.7)
White blood cell count decreased	3 (2.0)	1 (0.7)
Metabolism and nutrition disorders	14 (9.3)	11 (7.3)
Hypoalbuminaemia	3 (2.0)	0
Hypokalaemia	3 (2.0)	4 (2.7)
Hyperglycaemia	2 (1.3)	0
Type 2 diabetes mellitus	0	2 (1.3)
Nervous system disorders	4 (2.7)	4 (2.7)
Dizziness	1 (0.7)	2 (1.3)
Reproductive system and breast disorders	0	2 (1.3)
Benign prostatic hyperplasia	0	2 (1.3)
Respiratory, thoracic and mediastinal disorders	7 (4.7)	6 (4.0)
Hypoxia	1 (0.7)	2 (1.3)
Skin and subcutaneous tissue disorders	5 (3.3)	5 (3.3)
Rash	3 (2.0)	3 (2.0)

Notes: Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories. [a]Patients could have one or more preferred terms reported under a given system organ class.

Abbreviation: AE, adverse event.

Table S2 Serious adverse events by system organ class and preferred term in the China subset (safety population, including site 1314)

System organ class[a] Preferred term	Ceftaroline fosamil (n=150)	Ceftriaxone (n=150)
Patients with ≥1 SAE	10 (6.7)	6 (4.0)
Cardiac disorders	2 (1.3)	0
Cardiac failure	1 (0.7)	0
Cardiac failure acute	1 (0.7)	0
Gastrointestinal disorders	1 (0.7)	0
Upper gastrointestinal haemorrhage	1 (0.7)	0
General disorders and administration site conditions	0	1 (0.7)
Pyrexia	0	1 (0.7)
Hepatobiliary disorders	1 (0.7)	0
Cholecystitis chronic	1 (0.7)	0
Cholelithiasis	1 (0.7)	0
Infections and infestations	1 (0.7)	3 (2.0)
Lung infection	1 (0.7)	1 (0.7)
Bronchitis	0	1 (0.7)
Pneumonia	0	1 (0.7)
Pulmonary tuberculosis	0	1 (0.7)
Metabolism and nutrition disorders	2 (1.3)	0
Gout	1 (0.7)	0
Hypernatraemia	1 (0.7)	0
Neoplasms benign, malignant and unspecified (including cysts and polyps)	1 (0.7)	1 (0.7)
Small cell lung cancer	1 (0.7)	0
Hepatic cancer	0	1 (0.7)
Respiratory, thoracic and mediastinal disorders	2 (1.3)	0
Bronchiectasis	1 (0.7)	0
Chronic obstructive pulmonary disease	1 (0.7)	0
Vascular disorders	2 (1.3)	1 (0.7)
Arteriosclerosis	1 (0.7)	0
Shock haemorrhagic	1 (0.7)	0
Venous thrombosis limb	0	1 (0.7)

Notes: Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories. [a]Patients could have one or more preferred terms reported under a given system organ class.

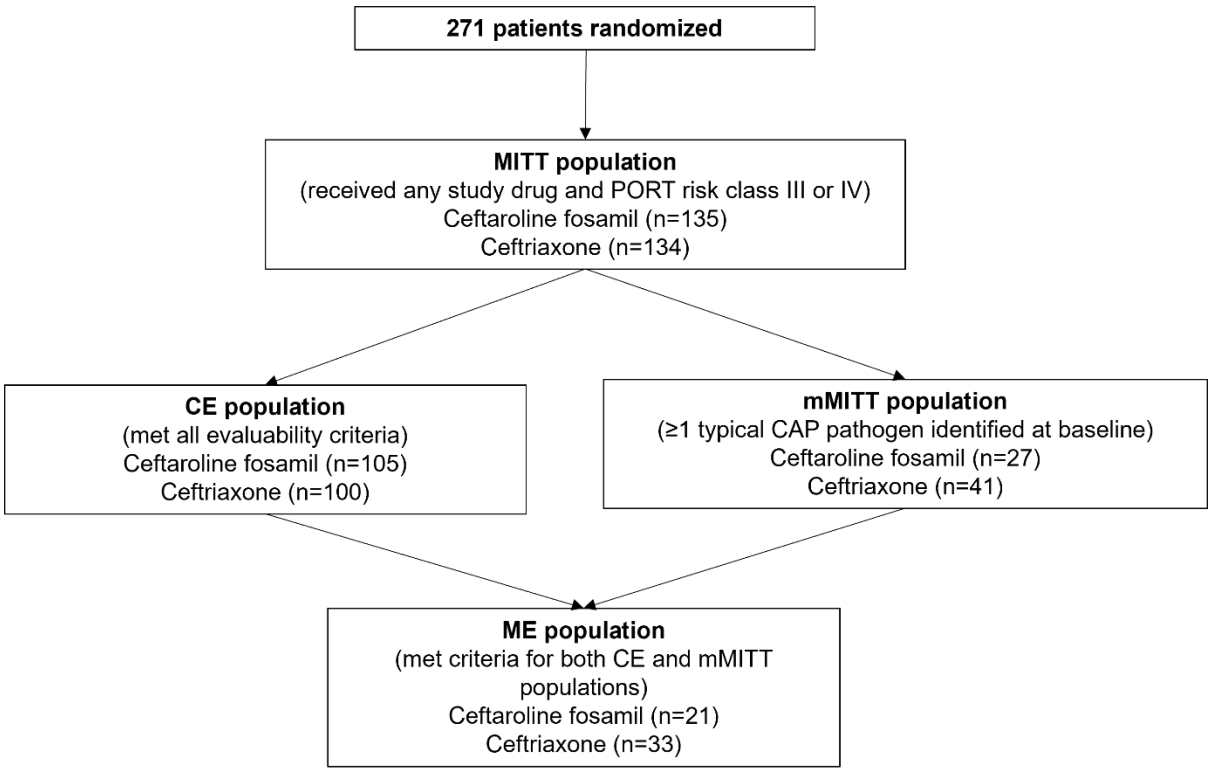
Abbreviation: SAE, serious adverse event.

Table S3 Potentially clinically significant post-baseline clinical chemistry, vital signs and Coombs direct test in the China subset (safety population, including site 1314)

Variable	Ceftaroline fosamil (n=150)	Ceftriaxone (n=150)
Alanine aminotransferase (ukat/L)		
>3.0 x ULN and >200% increase from baseline	0/136	6/143 (4.2)
Alkaline phosphatase (ukat/L)		
>2.0 x ULN and >100% increase from baseline	2/143 (1.4)	1/145 (0.7)
Aspartate aminotransferase (ukat/L)		
>3.0 x ULN and >200% increase from baseline	1/132 (0.8)	3/142 (2.1)
Gamma glutamyl transferase (ukat/L)		
>3.0 x ULN and >200% increase from baseline	3/143 (2.1)	2/144 (1.4)
Systolic blood pressure		
≥180 mmHg and increase ≥20 mmHg	1/149 (0.7)	2/149 (1.3)
≤90 mmHg and decrease ≥20 mmHg	2/149 (1.3)	3/149 (2.0)
Diastolic blood pressure		
≥105 mmHg and increase ≥15 mmHg	2/149 (1.3)	0/149
≤50 mmHg and decrease ≥15 mmHg	3/149 (2.0)	6/149 (4.0)
Heart rate		
≥120 bpm and increase ≥15 bpm	2/149 (1.3)	4/149 (2.7)
≤50 bpm and increase ≥15 bpm	4/149 (2.7)	0/149 (0)
ECG parameters		
QTcB >500 msec and change from baseline ≥60 ms	0/150	1/48 (0.7)
QTcF >500 msec and change from baseline ≥60 ms	0/150	0/148
Coombs DAGT seroconversion from negative to positive		
Baseline to EOT	11/132 (8.3)	1/137 (0.7)
Baseline to TOC	9/132 (6.8)	1/137 (0.7)

Abbreviations: DAGT; direct antiglobulin test; ECG, electrocardiogram; EOT, end of treatment; QTcB, corrected QT interval using Bazett's formula; QTcF, corrected QT interval using Frederica's formula; TOC, test-of-cure; ULN, upper limit of normal.

Figure S1 ASIA CAP China subset analysis populations (excluding site 1314)



Abbreviations: CE, clinically evaluable; ME, microbiologically evaluable; MITT, Modified intention-to-treat; mMITT, microbiological modified intention-to-treat.