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Assessment of Time to Clinical Response, a Proxy for Discharge Readiness, among Hospitalized Patients with Community-Acquired Pneumonia Who Received either Ceftaroline Fosamil or Ceftriaxone in Two Phase III FOCUS Trials

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The primary driver of health care costs for patients with community-acquired pneumonia (CAP) is the hospital length of stay (LOS). Unfortunately, hospital LOS comparisons are difficult to make from phase III CAP trials because of their structured designs and prespecified treatment durations. However, an opportunity still exists to draw inferences about potential LOS differences between treatments through the use of surrogates for hospital discharge. The intent of this study was to quantify the time to a clinical response, a proxy for the time to discharge readiness, among hospitalized CAP patients who received either ceftaroline or ceftriaxone in two phase III CAP FOCUS clinical trials. On the basis of the Infectious Diseases Society of America and American Thoracic Society CAP management guidelines and recent FDA guidance documents for community-acquired bacterial pneumonia, a *post hoc* adjudication algorithm was constructed *a priori* to compare the time to a clinical response, a proxy for the time to discharge readiness, between patients who received ceftaroline or ceftriaxone. Overall, 1,116 patients (ceftaroline, $n = 562$; ceftriaxone, $n = 554$) from the pooled FOCUS trials met the selection criteria for this analysis. Kaplan-Meier analyses showed that ceftaroline was associated with a shorter time, measured in days, to meeting the clinical response criteria ($P = 0.03$). Of the patients on ceftaroline, 61.0, 76.1, and 83.6% achieved a clinical response by days 3, 4, and 5, compared to 54.3, 69.8, and 79.3% of the ceftriaxone-treated patients. In the Cox regression, ceftaroline was associated with a shorter time to a clinical response (HR, 1.16, $P = 0.02$). The methodology employed here provides a framework to draw comparative effectiveness inferences from phase III CAP efficacy trials. (The FOCUS trials whose data were analyzed in this study have been registered at ClinicalTrials.gov under registration no. NCT00621504 and NCT00509106.)

Community-acquired pneumonia (CAP) remains the leading infection-related cause of death in the United States (1–3). Treatment of CAP places a tremendous burden on the health care system. It is estimated that the annual treatment cost of CAP exceeds $8.4 billion, largely because of hospitalization costs (4). This statistic is particularly concerning, given that hospitalization events due to all causes of pneumonia are projected to double to 2.6 million from 2004 to 2040, partly because of the aging population (5). Given that inpatient care for CAP costs approximately 20 times more than outpatient care (6), identifying therapies that facilitate the timely discharge of stable patients is essential to reducing the overall cost of CAP treatment.

Phase III international, multicenter, randomized, double-blind, comparative clinical trials are the current gold standard for establishing the efficacy and safety profiles of new antibiotics for CAP (7, 8). Although efficacy is established in such a design setting, it is difficult to infer meaningful economic or effectiveness differences between treatments in such trials. It is well documented that the primary driver of health care costs for patients with CAP is the hospital length of stay (LOS) (3, 6). Unfortunately, it is difficult to make direct hospital LOS comparisons in phase III registration studies. These studies are international, and the clinical practices and health care reimbursement policies in the countries represented dictate the hospital LOS of the study participants. Further mitigating LOS comparisons in most phase III trials are the fixed therapy duration requirements, lack of oral step-down therapy, and lack of predefined criteria for hospital discharge (9–11).

Although crude hospital LOS comparisons are difficult to interpret, it is possible to infer LOS differences between treatment groups of phase III trials through the use of proxy criteria for hospital discharge. Criteria for a dischargeable patient with CAP are well described in the American Thoracic Society/Infectious

Received 16 June 2014 **Returned for modification** 11 August 2014
Accepted 28 November 2014

Accepted manuscript posted online 8 December 2014

Citation Lodise TP, Anzueto AR, Weber DJ, Shorr AF, Yang M, Smith A, Zhao Q, Huang X, File TM. 2015. Assessment of time to clinical response, a proxy for discharge readiness, among hospitalized patients with community-acquired pneumonia who received either ceftaroline fosamil or ceftriaxone in two phase III FOCUS trials. Antimicrob Agents Chemother 59:1119–1126. doi:10.1128/AAC.03643-14.

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Supplemental material for this article may be found at http://dx.doi.org/10.1128/AAC.03643-14.

doi:10.1128/AAC.03643-14

Diseases Society of America (ATS/IDSA) CAP clinical management guidelines (4), which are consistent with the definitions of a favorable clinical response in the recent FDA CAP guidance documents (7, 8). Since data on vital signs, symptom resolution, laboratory values, and clinical responses are collected daily in most phase III CAP trials, it is possible to bridge trial results to the real-world practice setting by objectively defining the criteria for clinical response, a proxy for a dischargeable patient, with the existing clinical data.

The intent of this study was to quantify the time to a clinical response, a proxy for the time to discharge readiness, among hospitalized CAP patients who received either ceftaroline fosamil (ceftaroline here) or ceftriaxone in two phase III trials (9–11). To do so, we constructed an objective definition *a priori* (i.e., prior to the start of the present study) to *post hoc* adjudicate a dischargeable patient on the basis the criteria set forth in the ATS/IDSA guidelines and FDA briefing documents (4, 7, 8). To ensure uniformity with the recent FDA guidance for CAP, the definition of a dischargeable patient employed in this analysis was identical to the early clinical response outcome variable used in the FDA-specified day 4 clinical response analysis of ceftaroline versus ceftriaxone for community-acquired bacterial pneumonia (CABP) (12). With this definition in place at the start of the present study, we compared ceftaroline and ceftriaxone-treated patient groups for the time to a clinical response, a proxy for time to discharge readiness, by using time-to-event analyses. As secondary objectives, we compared treatment groups for the time to clinical stability and improvement of at least one symptom with no deterioration from the baseline.

(This study was presented in part at CHEST 2013 [26 to 31 October 2013, Chicago, IL], and at IDWeek 2013 [2 to 6 October 2013, San Francisco, CA].)

MATERIALS AND METHODS

Study population. Data from two phase III clinical trials with similar study designs were pooled for the present study. The trials of ceftaroline community-acquired pneumonia trial versus ceftriaxone in hospitalized patients (FOCUS 1 and FOCUS 2) were double-blind, randomized, multinational, multicenter studies that compared the safety and efficacy of intravenous (i.v.) ceftaroline versus i.v. ceftriaxone in adults who were hospitalized with CAP but not admitted to an intensive care unit (9–11). Both trials required patients to be in Pneumonia Outcomes Research Team (PORT) risk class III or IV at the time of hospital admission to be considered in the modified intent-to-treat efficacy (MITTE) analysis (19). Patients were randomized (1:1) to receive 600 mg of ceftaroline every 12 h or 1g of ceftriaxone every 24 h for 5 to 7 days. Patients in FOCUS 1 were also orally administered 500 mg of clarithromycin every 12 h on day 1 (10). The FOCUS trial protocols specified that daily clinical signs and symptoms be recorded on case report forms (CRFs) while patients were on the study drug; all patients were assessed as clinical cure, clinical failure, or indeterminate at the end-of-therapy (EOT) visit (9–11).

Details of the FOCUS trial designs and patient population definitions are available elsewhere (9–11). The sample used in the present study included all of the patients in the clinically evaluable (CE) population (n = 908), a subset of the MITTE population (n = 1,153). Additionally, 208 of the 245 patients in the MITTE population who did not meet the criteria for the CE population were included in our study sample because of the adequacy of data availability given the current focus on effectiveness evaluation for this analysis. These 208 patients included individuals with (i) an atypical sole causative pathogen or infection with *Legionella pneumophila*, (ii) less than 80% compliance, (iii) a test-of-cure (TOC) window (8 to 15 days after the EOT visit) violation, (iv) indeterminate response at TOC and not a clinical failure at EOT, and (v) missing assessment at TOC and not a clinical failure at EOT. The sample criteria of the present analysis were agreed upon by an adjudication committee (a panel of four physicians with expertise in CAP [Antonio Anzeuto, Andrew Shorr, David Weber, and Thomas File]) and the study's principal investigator (Thomas Lodise) prior to the blinded automated and manual adjudications.

TABLE 1 Clinical stability and symptom criteria for primary and sensitivity analyses of time to discharge readiness

Clinical stability criterion	Primary analysis	Sensitivity analyses[a]
Temp (°C)	≤37.8	≤37.8
Heart rate (beats/min)	≤100	≤100
Systolic blood pressure (mm Hg)	≥90	≥90
Respiratory rate (breaths/min)	≤24	≤30
% Oxygen saturation	≥90	≥90
Normal mental status[b]	Present	Not assessed
Symptom assessment[c]	At least 1 symptom improved and no deterioration from baseline	At least 2 symptom improved and no deterioration from baseline

[a] There were three individual sensitivity analyses for the following criteria: excluding normal mental status, a respiratory rate of ≤30 breaths/min, and at least two symptom improvements with no deterioration from the baseline.
[b] Defined as absence of confusion/disorientation.
[c] Cough, dyspnea, and chest pain were assessed as absent, mild, moderate, or severe. Sputum was assessed as absent or present. If present at the baseline, a change in character from the baseline was also recorded as improved, unchanged, or worsened.

Definitions of clinical response, clinical stability, symptom improvement and *post hoc* adjudication. The definitions of clinical response (a proxy for discharge readiness), clinical stability, and symptom improvement, and alternative criteria for sensitivity analyses are provided in Table 1. Consistent with the early clinical response outcome variable used in the FDA-specified day 4 clinical response analysis of ceftaroline versus ceftriaxone for CABP (12), achievement of a clinical response, or discharge readiness, required that both the clinical stability and symptom improvement criteria be met. Clinical vital signs included temperature, heart rate, systolic blood pressure, respiratory rate, oxygen saturation, and mental status. Symptoms included cough, dyspnea, chest pain, and sputum production. The adjudication algorithm was applicable up to day 7, after which clinical vital signs and symptoms were not available on CRFs. Sensitivity analyses were performed on the basis of discussions of the adjudication committee prior to finalization of the statistical analysis plan and initiation of the study. Since CAP often occurs in patients with baseline confusion or disorientation, the committee believed it was prudent to rerun the analyses with removal of this variable to assess the robustness of the findings. Given the reader variability in respiratory rate measurement in clinical practice, the committee also felt it was prudent to perform a sensitivity analysis that includes a more stringent definition of a high respiratory rate. The two-symptom improvement was another committee recommendation to assess the robustness of the data.

The adjudication algorithm was applied to the pooled FOCUS data by using a systematic approach to perform automated adjudication on a per-day basis starting on day 2 (see Appendix SA in the supplemental material). Patients were considered to have achieved a clinical response and to be dischargeable on the first day on which they met all of the criteria. If they failed to meet all of the criteria by day 7, patients were considered clinical failures on day 7 and censored in the time-to-event analyses. For patients with missing data on all of the criterion measures on any day and onward, the clinical response or dischargeability date was determined on the basis the EOT assessment on the CRF. If clinical cure or indeterminate was documented, the patient was censored on the last day

that data were available. If clinical failure was documented, the patient was censored at day 7. The automated process could not adjudicate those cases with partial missing data on any date. These cases were manually adjudicated by the adjudication committee by using the same adjudication algorithm along with clinical judgment. The entire adjudication process was blinded to treatment assignment.

Statistical analysis. Details of baseline patient characteristics were reported and compared between treatment arms, including demographics, medical history, physical examination, laboratory findings, prior antibiotic therapy, previous episodes of pneumonia, severity of illness (calculated by means of the PORT risk class scoring system and CURB-65 [confusion, urea, respiratory, blood pressure, age of ≥65 years] rating scale), microbiological culture results, and concomitant antibiotic treatment (19, 20). Kaplan-Meier time-to-event analyses (log rank test) were used to characterize the primary outcomes of interest stratified by treatment arm. In addition, sensitivity analyses were conducted (Table 1). Kaplan-Meier analyses of time to clinical response, a proxy for time to discharge readiness, were also conducted for the following subgroups: (i) Gram-positive infection only, (ii) Gram-negative infection only, (iii) typical pathogen(s) only, (iv) atypical pathogen(s) only, (v) no pathogen, (vi) *Streptococcus pneumoniae*, (vii) methicillin-susceptible *Staphylococcus aureus* (MSSA), (viii) PORT risk class III, (ix) PORT risk class IV, (x) CURB-65 score of ≥2, (xi) CURB-65 score of <2, (xii) FOCUS 1, and (xiii) FOCUS 2. Cox proportional-hazard models were used to estimate the hazards of time to clinical response, time to clinical stability, and time to symptom improvement, controlling for baseline characteristics (age of <65 years, gender, region of enrollment, prior pneumonia, current/recent alcohol abuse, prior antibiotic use, and PORT classification). All analyses were performed in SAS version 9.2 (SAS, Cary, NC).

RESULTS

Patient characteristics. There were 1,116 patients (ceftaroline, $n = 562$ [50.4%]; ceftriaxone, $n = 554$ [49.6%]) from the pooled FOCUS trials who met the selection criteria and were included in the study sample. The clinical-stability and symptom data for 1,002 (89.8%) of the 1,116 patients included were complete. The majority of these patients ($n = 947$, 84.9% of the total study population) achieved a clinical response (i.e., were ready to discharge) by day 7. There were 89 patients (8.0%) with missing vital and symptom data on a day before day 7. Among these patients, 50 had a clinical cure or indeterminate result documented on CRFs at the EOT visit and were censored on the last day when the vital and symptom data were available; 39 were documented in the CRFs with clinical failure at the EOT visit and were censored on day 7. The remaining 25 (2.2%) patients had partial missing data and were adjudicated manually.

The study sample baseline characteristics are summarized in Table 2. Nearly half of the patients were 65 years old or older (mean, 61 years old). Slightly over 60% of the patients were male, and more than 90% of them were white. Over one-third of the patients were in PORT risk class IV. The two treatment groups were comparable for all of the baseline characteristics except the percentage who had any prior incidents of pneumonia. More patients in the ceftaroline group than in the ceftriaxone group had a prior pneumonia diagnosis (21.4% versus 15.7%, $P = 0.015$).

Time to clinical response, clinical stability, and symptom improvement. Kaplan-Meier analyses showed that the time to a clinical response (i.e., discharge readiness) was statistically significantly shorter among patients treated with ceftaroline than among patients treated with ceftriaxone (Fig. 1, top; $P = 0.0335$). The time to clinical stability was also statistically significantly shorter among patients treated with ceftaroline (Fig. 1, middle; $P = 0.0190$). Patients treated with ceftaroline had a nonsignificantly shorter time to the improvement of at least one clinical symptom without deterioration from the baseline (Fig. 1, bottom). Of the 562 ceftaroline-treated patients, 61.0, 76.1, and 83.6% achieved a clinical response by days 3, 4, and 5, compared to 54.3, 69.8, and 79.3%, respectively, of the 554 ceftriaxone-treated patients. The corresponding Kaplan-Meier estimated median time to the achievement of a clinical response was 3 (2 to 3) days for the ceftaroline group and 3 (2 to 4) days for the ceftriaxone group.

Three sensitivity analyses of the time to a clinical response using alternative adjudication criteria (excluding mental health status, a respiratory rate of ≤30 breaths/min, and requiring two symptoms to improve from the baseline with no deterioration) showed consistent results; patients treated with ceftaroline had a shorter time to a clinical response than patients treated with ceftriaxone (for Kaplan-Meier plots of the sensitivity analyses, see Appendix SB in the supplemental material).

Table 3 presents the results of the subgroup analyses for the median time to a clinical response. For Kaplan-Meier plots of subgroups, see Appendix SC in the supplemental material. Among patients with Gram-positive infections only and patients in PORT risk class III, patients who received ceftaroline had a shorter median time to a clinical response. While the difference was not statistically significant, the time to a clinical response was numerically in favor of ceftaroline in the following subsets: *Streptococcus pneumoniae* ($P = 0.0585$), no baseline pathogen lab results ($P = 0.0680$), CURB-65 score of ≥2 ($P = 0.0533$), and FOCUS 1 ($P = 0.0578$). Similar median numbers of days to a clinical response were noted for other subgroups (Table 3).

Cox proportional-hazard models. Table 4 presents the results of the study outcomes using Cox proportional-hazard models adjusting for baseline characteristics. The findings are consistent with the Kaplan-Meier analyses. After adjustment for potential confounding factors, ceftaroline was associated with a 16% greater chance of a clinical response at any time point starting on day 2 (hazard ratio [HR], 1.161; 95% confidence interval [CI], 1.022 to 1.319 [$P = 0.022$]) compared with ceftriaxone. Ceftaroline was associated with an 18% greater chance of achieving clinical stability at any time point than ceftriaxone (HR, 1.179; 95% CI, 1.040 to 1.338 [$P = 0.010$]).

DISCUSSION

Given the exigent clinical need for meaningful comparative effectiveness data on CAP therapies, this study compared patients receiving ceftaroline and patients receiving ceftriaxone in two phase III FOCUS CAP registration trials for the time to a clinical response, a proxy for the time to discharge readiness. To ensure uniformity with the ATS/IDSA CAP clinical management guidelines and recent FDA guidance for CAP, the definition of a clinical response, a proxy for a dischargeable patient, employed in this analysis was determined prior to the start of the study and was identical to the early clinical response outcome variable used in the FDA-specified day 4 clinical response analysis of ceftaroline versus ceftriaxone for CABP (12). Through the use of the *a priori*-constructed *post hoc* adjudication algorithm, patients who received ceftaroline were found to have shorter overall times to a clinical response and clinical stability relative to patients who received ceftriaxone. Of the 562 ceftaroline-treated patients, 61.0, 76.1, and 83.6% achieved a clinical response by days 3, 4, and 5, compared to 54.3, 69.8, and 79.3%, respectively, of the 554 ceftri-

TABLE 2 Patient baseline characteristics

Characteristic	Ceftaroline ($n = 562$)	Ceftriaxone ($n = 554$)	P value[d]
Mean age (yr) ± SD	60.65 ± 16.30	61.31 ± 15.69	0.5291
No. (%) ≥65 yr old	261 (46.44)	266 (48.01)	0.5987
No. (%) of males	351 (62.46)	354 (63.90)	0.6172
No. (%) of following race:			0.9924
Caucasian	520 (92.53)	515 (92.96)	
Asian	19 (3.38)	19 (3.43)	
Black	17 (3.02)	14 (2.53)	
Native American/Alaskan	5 (0.89)	5 (0.90)	
Other	1 (0.18)	1 (0.18)	
No. (%) from following enrollment region:			0.9987
Africa	17 (3.02)	17 (3.07)	
Asia	18 (3.20)	18 (3.25)	
Eastern Europe	255 (45.37)	257 (46.39)	
Latin America	62 (11.03)	59 (10.65)	
USA	11 (1.96)	12 (2.17)	
Western Europe	199 (35.41)	191 (34.48)	
No. (%) with following most-common comorbidities:			
Structural lung disease[a]	154 (27.40)	139 (25.09)	0.3802
Any prior pneumonia	120 (21.35)	87 (15.70)	0.0152
Asthma	48 (8.54)	37 (6.68)	0.2410
Current or recent alcohol abuse	23 (4.09)	12 (2.17)	0.0649
Gastroesophageal reflux	23 (4.09)	16 (2.89)	0.2733
No. (%) with following smoking history:			
Never smoked	265 (47.15)	278 (50.18)	
Smoked but not current smoker	148 (26.33)	143 (25.81)	0.5359
Current smoker	149 (26.51)	133 (24.01)	
No. (%) in PORT risk class:			
III	351 (62.46)	344 (62.09)	0.9008
IV	211 (37.54)	210 (37.91)	
No. (%) with CURB-65 score of:[b]			
0	70 (12.46)	58 (10.47)	0.2983
1	213 (37.90)	233 (42.06)	
2	222 (39.50)	195 (35.20)	
3	51 (9.07)	59 (10.65)	
4	6 (1.07)	9 (1.62)	
No. (%) with bacteremia	22 (3.91)	19 (3.43)	0.6667
No. (%) with renal impairment[c]			
Mild (CL_{CR},[f] 51–80 ml/min)	187 (33.27)	178 (32.13)	0.6838
Moderate (CL_{CR}, 31–50 ml/min)	80 (14.23)	78 (14.08)	0.9406
No. (%) with WBC count (cells/mm^3) of:[c]			
<4,500	25 (5.48)	28 (6.25)	0.6233
4500–10,000	207 (45.39)	215 (47.99)	0.4340
>10,000	224 (49.12)	205 (45.76)	0.3112
No. (%) with immature-neutrophil (band) percentage of:			
>10	9 (1.99)	5 (1.13)	0.2965
>15	6 (1.33)	3 (0.68)	0.5058
No. (%) with prior antibiotic use[e]	229 (40.75)	248 (44.77)	0.1749

[a] Defined as any chronic parenchymal or airway disease (e.g., chronic obstructive pulmonary disease [emphysema, chronic bronchitis], bronchiectasis, or interstitial fibrosis).
[b] Scores ranged from 0 to 5, and the presence of each of the following contributed 1 unit to the score: new onset of confusion, urea greater than 7 mmol/liter, respiratory rate ≥30 breaths/min, systolic blood pressure of <90 mm Hg or diastolic blood pressure of ≤60 mm Hg, age of ≥65 years.
[c] Proportions for white blood cell (WBC) and immature neutrophil counts do not account for patients with missing data.
[d] P values were calculated by using Wilcoxon rank sum tests for continuous variables and chi-square tests for categorical variables.
[e] Antibiotic use within 96 h prior to first dose of study drug.
[f] CL_{CR}, creatinine clearance.

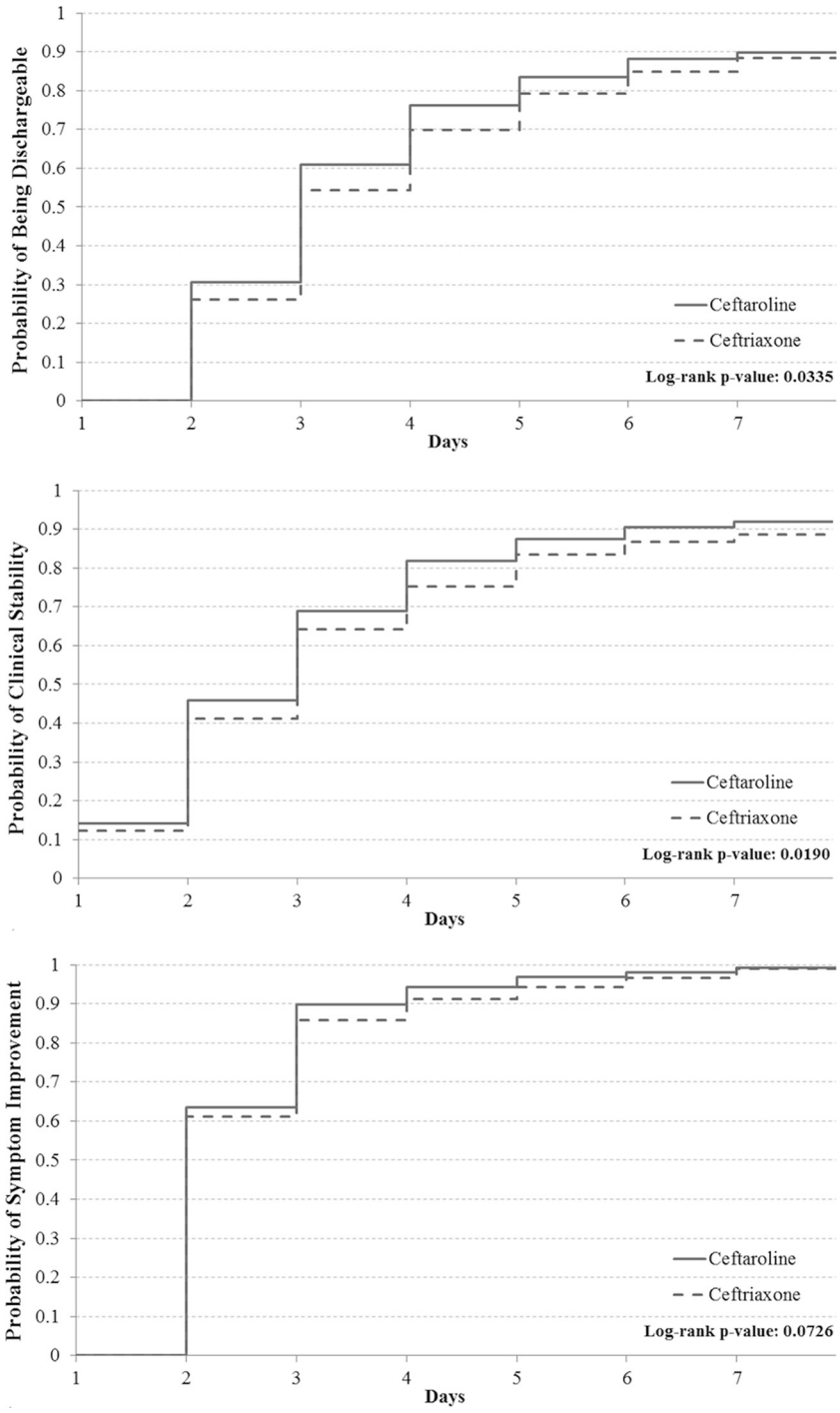

FIG 1 Times to discharge readiness, clinical stability, and the improvement of at least one symptom. Top, time to discharge readiness; middle, time to clinical stability; bottom, time to the improvement of at least one symptom with no symptom deterioration from the baseline.

axone-treated patients. The results of the sensitivity analyses were consistent with the core analyses, and the relationship between ceftaroline and the time to a clinical response persisted in the Cox regression analysis after adjustment for potential confounding factors. Compared to ceftriaxone, ceftaroline was associated with a 16% greater chance of a patient achieving a clinical response or being discharged at any time starting on day 2. In the subgroup analyses, patients with only a Gram-positive organism(s) at the baseline and patients in PORT risk class III who received ceftaroline took less time to meet the clinical response criteria, while the other subgroups showed comparable findings across the treatment arms. Collectively, these findings indicate that ceftaroline may be associated with a shorter time to a clinical response, a proxy for the time to discharge readiness, relative to that seen with

TABLE 3 Subgroup analyses of time to discharge readiness

Subgroup	Ceftaroline $n = 562$		Ceftriaxone $n = 554$		Log rank *P* value
	Median time (Q1, Q3)[b]	No. (%) of samples	Median time (Q1, Q3)[b]	No. (%) of samples	
Baseline infection					
Gram staining result[a]					
Positive only	3 (2, 4)	71 (12.6)	4 (3, 6)	68 (12.3)	0.0094
Negative only	3 (3, 5)	109 (19.4)	3 (3, 5)	103 (18.6)	0.9250
Type of pathogen					
Typical only	3 (2, 5)	143 (25.4)	3 (3, 5)	140 (25.3)	0.3046
Atypical only	3 (2, 5)	69 (12.3)	3 (2, 5)	60 (10.8)	0.7825
No baseline pathogen	3 (2, 4)	327 (58.2)	3 (2, 5)	327 (59.0)	0.0680
Streptococcus pneumoniae	3 (2, 4)	67 (11.9)	3 (2, 6)	68 (12.3)	0.0585
MSSA	4 (3, 6)	26 (4.6)	4 (3, 6)	28 (5.1)	0.5083
PORT risk score of:					
III	3 (2, 4)	351 (62.5)	3 (2, 5)	344 (62.1)	0.0185
IV	3 (2, 5)	211 (37.5)	4 (3, 5)	210 (37.9)	0.6313
CURB-65 score of:					
<2	3 (2, 4)	283 (50.4)	3 (2, 5)	291 (52.5)	0.3073
≥2	3 (2, 5)	279 (49.6)	4 (2, 5)	263 (47.5)	0.0533
Trial					
FOCUS 1	3 (2, 4)	281 (50.0)	3 (3, 5)	289 (52.2)	0.0578
FOCUS 2	3 (2, 4)	281 (50.0)	3 (2, 5)	265 (47.8)	0.2559

[a] Excluding *Mycoplasma pneumoniae*.
[b] Median number of days to achievement of a clinical response. Q1, quartile 1; Q3, quartile 3.

ceftriaxone. While cumulative daily achievement of a clinical response was only marginally different between treatment groups overall, more pronounced differences in the time to a clinical response between treatment groups were observed among patients with *S. pneumoniae* or other non-methicillin-resistant *S. aureus* (MRSA) susceptible Gram-positive organisms at the baseline.

These findings have important implications for clinicians. Time to clinical stability has been widely accepted as a tool to guide the switch from i.v. to oral antibiotic therapy in hospitalized patients, as well as to judge appropriateness for hospital discharge (4). A number of studies have demonstrated that there is a clear link between the time to a clinical response (e.g., clinical stability and symptom improvement) and subsequent hospital discharge and outcomes among hospitalized patients with CAP (13–15). Using a definition of response nearly identical to our time to discharge readiness criterion, Zasowski and colleagues were able to conclusively demonstrate a monotonic relationship between the time to a clinical response and the hospital LOS among PORT risk class III and IV hospitalized adult CAP patients who received ceftriaxone and azithromycin (15). On average, patients were dis-

TABLE 4 Cox proportional-hazard models for primary and secondary outcomes

Parameter	Time to being dischargeable			Time to clinical stability			Time to one symptom improving		
	HR	95% CI	*P* value[a]	HR	95% CI	*P* value[a]	HR	95% CI	*P* value[a]
Ceftaroline vs ceftriaxone	1.161	(1.022, 1.319)	0.022[d]	1.179	(1.040, 1.338)	0.010[d]	1.123	(0.992, 1.271)	0.068
Age ≥65 vs age <65	1.030	(0.899, 1.179)	0.672	1.172	(1.027, 1.339)	0.019[d]	0.828	(0.727, 0.944)	0.005[d]
Male vs female	1.023	(0.895, 1.169)	0.743	1.032	(0.905, 1.177)	0.636	1.065	(0.935, 1.213)	0.342
Region of enrollment[b]									
Western Europe	1.147	(0.990, 1.329)	0.068	1.202	(1.041, 1.387)	0.012[d]	1.227	(1.063, 1.416)	0.005[d]
United States	1.689	(1.083, 2.635)	0.021[d]	2.199	(1.407, 3.437)	0.001[d]	1.146	(0.735, 1.787)	0.549
Other[c]	1.205	(1.004, 1.448)	0.046[d]	1.204	(1.005, 1.443)	0.044[d]	1.244	(1.040, 1.489)	0.017[d]
Any prior pneumonia	1.019	(0.864, 1.202)	0.819	1.007	(0.856, 1.184)	0.933	0.984	(0.837, 1.157)	0.847
Current/recent alcohol abuse	0.731	(0.498, 1.073)	0.110	0.908	(0.627, 1.316)	0.611	0.742	(0.515, 1.068)	0.108
Prior antibiotic use	1.106	(0.970, 1.260)	0.132	1.050	(0.923, 1.194)	0.458	1.026	(0.903, 1.165)	0.694
PORT risk class III vs IV	1.284	(1.114, 1.480)	0.001[d]	1.353	(1.176, 1.556)	<0.001[d]	0.922	(0.804, 1.057)	0.243

[a] *P* values were obtained by chi-square test.
[b] Reference category, Eastern Europe.
[c] Including Africa, Asia, and Latin America.
[d] Significant difference at the 5% level.

charged 2 days following the achievement of a clinical response. The lag between the time to a clinical response and subsequent hospital discharge was not unexpected and was likely related to administrative and social factors that often determine the ultimate day of hospital discharge (16). Similarly, Halm et al. found a clear link between the time to clinical stability, defined as normalization of temperature, heart rate, and oxygen saturation, and the subsequent hospital LOS among hospitalized CAP patients (14). Similar to the study by Zasowski and colleagues (15), they also observed a predictable lag between the achievement of stability and subsequent hospital discharge (14). There are also some indications that time to clinical stability and being dischargeable may be important determinants of subsequent hospital readmission and death. Collectively, several recent studies (13–15) and the criteria for a dischargeable CAP patient in the ATS/IDSA CAP clinical management guidelines (4), which are nearly identical to the early clinical response outcome variable used in the FDA-specified day 4 clinical response analysis of ceftaroline versus ceftriaxone for CABP (12), lay the foundation for the clinical relevance of our *post hoc* adjudication analyses.

Several issues should be taken into consideration when interpreting these findings. First, we applied a *post hoc* adjudication algorithm to the data collected in the FOCUS trials, which is subject to all of the limitations inherent to a *post hoc* study. To minimize the potential biases associated with this approach, we constructed a set of objective criteria for the time to a clinical response, a proxy for discharge readiness, prior to conducting the study and made the discharge readiness definition identical to the early clinical response outcome variable used in the FDA-specified day 4 clinical response analysis of ceftaroline versus ceftriaxone for CABP (12). Furthermore, we applied an automated adjudication process for nearly 98% of the patients included. For the remaining 2% of the cases, a standardized, treatment-blinded manual adjudication process was created to evaluate the time to a clinical response or discharge readiness. The low percentage of manual reviews, combined with the standardization of the process, minimized the risk of biases resulting from the manual adjudication process. Multivariate analyses were also performed to control for any residual baseline differences.

This study was constrained by the original clinical trial study design, which only required the collection of daily clinical information for up to 7 days (the maximum dosing duration). Ideally, a prospectively designed trial to address the analysis employed here would have followed subjects daily until all of the discharge criteria were met, well beyond 7 days, if necessary. Since the overwhelming majority of the patients were adjudicated through an automated process to be dischargeable by day 7, the available data were still valuable in our study. In addition, measurements that were used to determine clinical response were made daily but not necessarily at the same time each day. While it is likely that clinical response assessments were performed at similar times each day, the intervals between daily clinical response measurements could have been as short as $<$12 h or as long as $>$36 h. Therefore, caution should be exercised when interpreting and differentiating daily findings across treatments.

It is also important to recognize that concomitant clarithromycin therapy was only permitted in FOCUS 1 and limited to the initial 24 h of hospital admission (9–11). Dual beta-lactam–macrolide therapy is the standard of care for CAP in the United States, as recommended by the Joint Commission on Accreditation of Health Care Organizations, Centers for Medicare & Medicaid Services, and ATS/IDSA (4, 17). Cognizant of this, we incorporated two analyses in this study to examine the potential effect of 1 day of concomitant clarithromycin therapy. First, we compared the time to a clinical response by trial (FOCUS 1 versus FOCUS 2). Second, we did a restricted analysis that included patients only with atypical pathogens and examined the time to a clinical response or readiness to discharge (non-treatment specific) by trial. Overall, similar times to a clinical response were noted across the trials. When restricted to only atypical pathogens by trial (FOCUS 1, $n = 63$; FOCUS, 2 $n = 66$), the result favored FOCUS 1 ($P = 0.0267$). At day 4, 81% of the patients in FOCUS 1 were clinical responders or discharge ready, compared to 64% of the patients in FOCUS 2. This result was consistent with the subset analysis by File et al. that demonstrated that 1 day of clarithromycin therapy was beneficial to CAP patients with atypical pathogens only (18). Clearly, these findings highlight the need for additional randomized studies to assess the true effect of dual beta-lactam–macrolide therapy on reported outcomes of the patients with CAP due to atypical pathogens only. Beyond the considerations mentioned above, it is important to recognize that no patients with MRSA were included in this study. Therefore, no inferences can be made about patients with CAP due to MRSA from this study. Statistically significant differences were noted between study groups, but the absolute differences between groups tended to be moderate. Lastly, one must consider the overall cost of hospital care, the comparative ceftaroline and ceftriaxone acquisition costs, and potential resistance implications of using ceftaroline or ceftriaxone when applying these study results to their clinical practice.

In conclusion, the findings of this *post hoc* examination of the clinical data collected from the FOCUS trials show that patients who received ceftaroline took statistically significantly less time, albeit modest, to meet the criteria for a clinical response, a proxy for discharge readiness, than those who received ceftriaxone. Given the clear link between the time to clinical stability and hospital discharge (13–15), these findings may have implications for clinical practice, as ceftaroline may be associated with a shorter time to hospital discharge than that achieved with ceftriaxone among hospitalized patients with CAP, particularly those with only a Gram-positive pathogen(s) at the baseline. The methodology employed here also provides a framework from which to draw comparative effectiveness inferences from phase III CAP efficacy trials. Since this was a *post hoc* examination of phase III clinical trial data, the findings need to be validated in the clinical arena to truly delineate their real-world implications.

ACKNOWLEDGMENTS

M. Yang had full access to all of the data in the study and takes responsibility for the integrity of the data and accuracy of the data analysis. The study concept and design were provided by T. P. Lodise, X. Huang, Q. Zhao, and M. Yang. Analysis and interpretation of data were performed by T. P. Lodise, A. Anzueto, D. J. Weber, A. Shorr, M. Yang, A. Smith, Q. Zhao, X. Huang, and T. M. File. The manuscript was drafted by T. P. Lodise and M. Yang. The manuscript was critically revised for important intellectual content by T. P. Lodise, A. Anzueto, D. J. Weber, A. Shorr, M. Yang, A. Smith, Q. Zhao, X. Huang, and T. M. File. Statistical analysis was done by M. Yang and A. Smith. Funding was obtained by X. Huang, Q. Zhao, and T. P. Lodise. Study supervision was performed by T. P. Lodise and M. Yang. Administrative, technical, or material support was provided by X. Huang, Q. Zhao, and A. Smith.

Outstanding assistance with data preparation and analysis was provided by Darren Thomason, Mariah Koh, Dendy MaCaulay (employees of Analysis Group, Inc.), and Ganesh Tamarana (employee of Cerexa, Inc.).

T. P. Lodise has received research grants from or served on scientific advisory boards for Forest, Cubist, Theravance, Medicines Company, and Pfizer. He is also a consultant for Forest, Cubist, and Medicines Company. T. M. File has received recent research grants from or served on scientific advisory boards for Pfizer, GlaxoSmithKline, Durata, Merck, Tetraphase, Trius, and Cempra and is also a consultant for Cubist, Astellas, and Forest. A. Anzueto has received recent research grants from or served on scientific advisory boards for Novartis, Boehringer Ingelheim, GlaxoSmithKline, and Forest. D. J. Weber has received research funding from NIH and CDC and is also a consultant for Pfizer, Merck, Germitec, Clorox, Johnson & Johnson, and Forest. A. Shorr has served as a consultant to and a speaker for or reviewed research support from AZ, Astellas, Bayer, Cubist, Forest, Pfizer, Cardeas, and Tetraphase. M. Yang is an employee at Analysis Group, which receives consulting fees from Forest. X. Huang and Q. Zhao are employed by the Forest Research Institute and hold stock in the company. A. Smith is employed by Cerexa, Inc., and holds stock in the company. The original FOCUS trials were funded by Cerexa, Inc. Support for this report was provided by the Forest Research Institute.

The Forest Research Institute reviewed the manuscript prior to submission but had no other involvement with the study.

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