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Efficacy and safety of ceftobiprole in patients aged 65 years or older: a *post hoc* analysis of three Phase III studies

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Aim: To evaluate the efficacy and safety of ceftobiprole in patients aged ≥65 years. **Materials & methods:** We conducted a *post hoc* analysis of three randomized, double-blind, Phase III studies in patients with acute bacterial skin and skin structure infections, community-acquired pneumonia and hospital-acquired pneumonia. **Results:** Findings for patients aged ≥65 years (n = 633) were consistent with those for the overall study populations, although a trend toward improved outcomes was reported in some subgroups, for example, patients aged ≥75 years with community-acquired pneumonia were more likely to achieve an early clinical response with ceftobiprole than comparator (treatment difference 16.3% [95% CI:1.8–30.8]). The safety profile was similar between treatment groups in all studies. **Conclusion:** This analysis further supports the efficacy and safety of ceftobiprole in older patients with acute bacterial skin and skin structure infections or pneumonia.

Clinicaltrials.gov trial identifiers: NCT03137173, NCT00326287, NCT00210964, NCT00229008

Lay abstract: Infections are a common cause of severe disease and death in older patients. Antibiotic treatment may also be complicated by age-related changes within the body. The present study analyzed results from three large clinical trials that assessed the benefits of the novel antibiotic ceftobiprole in the older population. In patients aged over 65 years with skin infections or with pneumonia acquired either in the community or in a hospital setting, ceftobiprole offered similar benefits to established antibiotics. There was also some preliminary evidence that older patients may respond more quickly to ceftobiprole compared with the other antibiotics used in these studies. Overall, ceftobiprole was well tolerated and will be a useful treatment option for infections in older patients.

Clinical trial registration: NCT03137173, NCT00326287, NCT00210964, NCT00229008 (Clinicaltrials.gov)

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Keywords: acute bacterial skin and skin structure infections • ceftobiprole • community-acquired pneumonia • elderly • hospital-acquired pneumonia • older • Phase III

Infectious diseases occur frequently in older persons and are associated with significant morbidity and mortality [1]. The increased susceptibility to infection that occurs with aging is multifactorial, with immunosenescence, comorbid conditions, nutritional deficiencies, swallowing difficulties, decreased mucociliary clearance and residence in a long-term care facility, all potentially contributing to the risk of infection [2]. Outcomes for older patients are generally worse than for younger individuals due to the presence of chronic underlying diseases and reduced physiologic reserve capacity [1]. Furthermore, use of antimicrobial therapy in older patients can be complicated by age-related physiological changes affecting the pharmacokinetics and pharmacodynamics of a drug, and by potential interactions with concomitant therapies [3]. These patients may also be at a higher risk of acquiring multidrug-

resistant organisms, as they typically have higher exposure to hospitals and long-term care facilities where such organisms are more prevalent, and because healthcare providers tend to have a lower threshold for prescribing antimicrobial agents for older patients [4,5].

Community-acquired pneumonia (CAP) is a common infection in older adults, with increasing age reported as a significant risk factor for the development of CAP across multiple studies [6]. Hospitalization may be required for up to 80% of patients aged over 65 years with CAP and it remains a major cause of death in this age group [2,7]. Older age is also a significant risk factor for hospital-acquired pneumonia (HAP), as older patients often have longer hospital stays and are more likely to aspirate oropharyngeal material due to swallowing dysfunction [8]. Outcomes for HAP in the elderly can be extremely poor, with length of stay in hospital significantly increased and in-hospital mortality rates approaching 30% reported [8,9]. The etiology of pneumonia in older patients can be difficult to establish and it has been estimated that a causative pathogen may not be identified in up to 77% of cases [10], necessitating the need for empiric antibiotic therapy. *Streptococcus pneumoniae* is the most commonly isolated pathogen in patients with CAP, with *Haemophilus influenzae*, Gram-negative bacteria and respiratory viruses also identified frequently [10]. *Staphylococcus aureus* (including methicillin-resistant *S. aureus* [MRSA]) has been identified as a pathogen in both CAP and HAP [11,12], with 10% of HAP cases being shown to be attributable to MRSA in a meta-analysis of 23 studies [13]. MRSA infections in general have been associated with higher morbidity and mortality than methicillin-sensitive *S. aureus* infections; however, this may be due to confounding associations with other prognostic factors [14]. MRSA infections also pose an increased burden on healthcare services due to the need to treat patients empirically for MRSA in cases of severe nosocomial infections and also the costs associated with surveillance, screening and isolation of MRSA carriers [14]. Current guidelines recommend MRSA coverage for patients who are receiving empiric antibiotic therapy for HAP and who have additional risk factors for MRSA, for example, prior intravenous (iv.) antibiotic use [13].

Advanced age is associated with an increased risk of skin and skin structure infections due to the weakening integrity of the skin and delayed wound healing among other risk factors [4,15]. *S. aureus* is the most commonly isolated pathogen, and older age has been shown to be a risk factor for MRSA infections of the skin [16]. Outcomes can be worse for older individuals, with patients older than 65 years at significantly higher risk of initial treatment failure and mortality compared with younger patients [17,18].

As the numbers of people aged over 65 years continues to increase across the world, there is a growing need to improve therapeutic options for infectious diseases in this population [2]. Ceftobiprole is an advanced-generation cephalosporin with broad-spectrum activity against Gram-positive (including MRSA) and Gram-negative bacteria [19,20]. In two large, randomized, double-blind, multicenter, Phase III studies, ceftobiprole demonstrated noninferiority and similar tolerability to ceftriaxone ± linezolid for the treatment of adult patients hospitalized for CAP [21] and to the combination of ceftazidime + linezolid for the treatment of adult patients with HAP excluding ventilator-associated pneumonia (VAP) [22]. As a result, it is now approved in many European and several non-European countries for the treatment of CAP and HAP excluding VAP [23]. The efficacy of ceftobiprole has also been demonstrated in the Phase III TARGET study in acute bacterial skin and skin structure infections [24], and it is currently being evaluated in patients with *S. aureus* bacteremia including infective endocarditis [25].

In order to assess the efficacy and tolerability of ceftobiprole versus comparators in older (defined as 65–74 years) and elderly (defined as ≥75 years) patients, we conducted a *post hoc* analysis of the ABSSSI, CAP and HAP (excluding VAP) Phase III studies.

Materials & methods

Study design

This was a *post hoc* analysis of three randomized, double-blind, multicenter, Phase III studies in patients hospitalized with an ABSSSI (TARGET; NCT03137173), CAP (NCT00326287) or HAP (NCT00210964 and NCT00229008). The study designs of the three trials have been previously published [21,22,24] and are summarized below in brief. For all studies, institutional review board/ethics committee approval of the protocol was obtained, and all participants provided signed written informed consent before enrollment.

ABSSSI study

The TARGET study was conducted at 32 sites in the USA and Europe and randomized a total of 679 patients with an ABSSSI. Patients were eligible if they were aged ≥18 years and had a diagnosis of ABSSSI (either a wound infection, cellulitis or erysipelas, or a major cutaneous abscess) requiring iv. antibacterial treatment. Patients were

also required to have at least one regional or systemic sign of infection. All eligible patients were randomized (1:1) to receive either ceftobiprole (administered every 8 h as a 2-h 500-mg iv. infusion) or vancomycin (administered every 12 h as a 2-h 1000-mg [or 15 mg/kg] iv. infusion). Patients in the vancomycin arm also received treatment with aztreonam (administered every 12 h as a 0.5-h 1000-mg iv. infusion), although this could be halted after 72 h if Gram-negative coverage was no longer deemed necessary. To maintain blinding, patients in the ceftobiprole-treatment group received placebo infusions that were matched in frequency, duration and volume to the aztreonam infusion. Patients were treated for 5–10 days with a possible extension to 14 days if clinically required.

CAP study

This study was conducted at 103 study sites worldwide and randomized 666 patients, with 638 of these included in the intent-to-treat (ITT) population. Patients aged ≥18 years with CAP severe enough to require hospitalization and treatment with iv. antibiotics for ≥3 days were eligible for enrollment. CAP was defined as pneumonia occurring while residing in the community, not in a chronic care facility, and with no history of hospitalization within 14 days of symptom onset. Patients were required to have new lung infiltrates on chest radiography that were consistent with bacterial pneumonia, fever/hypothermia, or leukocytosis/leukopenia, and two or more of the following signs or symptoms: cough, purulent sputum, auscultatory findings of pulmonary consolidation, dyspnea or tachypnea, or new onset/worsened hypoxemia. Patients were randomized (1:1) to receive either ceftobiprole (administered every 8 h as a 2-h 500-mg iv. infusion) or ceftriaxone (administered once daily as a 30-min 2000-mg iv. infusion). If an MRSA infection was suspected, linezolid 600 mg every 12 h was added to ceftriaxone, while a matched placebo infusion was added to ceftobiprole. Target treatment duration was 7 days, but this could be extended to 14 days at the investigator's discretion.

HAP study

This study randomized 781 patients with HAP (including 571 patients with nonventilator HAP) from 157 different study sites worldwide. Eligible patients were aged ≥18 years and had a radiologically-confirmed diagnosis of pneumonia ≥72 h after hospitalization or stay in a chronic care facility and demonstrated two or more clinical signs or symptoms of pneumonia (purulent respiratory secretion, tachypnea or hypoxemia), fever or leukocytosis/leukopenia, new or persistent radiographic infiltrates, and an Acute Physiology and Chronic Health Evaluation II score ≥8 and ≤25. Patients were randomized (1:1) to receive either ceftobiprole (administered every 8 h as a 2-h 500-mg iv. infusion) or ceftazidime (administered every 8 h as a 2-h 2000-mg iv. infusion). Patients in the ceftazidime treatment group also received linezolid (administered every 12 h as a 1-h 600-mg iv. infusion) while patients in the ceftobiprole group received a matched placebo infusion. Target treatment duration was 7 days, but could be extended to 14 days if required.

Post hoc analysis

This *post hoc* analysis included subgroups of patients aged 65–74 years (older patients) and aged ≥75 years (elderly patients) at enrollment. These age ranges were selected for this analysis based on the US FDA and the EMA guidelines on studies in geriatric populations [3,26]. In these subgroups, ceftobiprole was evaluated against the comparators for early clinical response, clinical cure at the test-of-cure (TOC) visit and all-cause mortality (assessed at day 28 in the ABSSSI study and day 30 in the CAP and HAP studies).

For all efficacy end points, analyses were conducted in the ITT and clinically evaluable (CE) populations. The CE populations were defined as follows for each study: ABSSSI – patients with no major protocol deviations and a completed response outcome; CAP – all treated patients with a diagnosis of CAP, unless the duration of study drug therapy was <48 h or <80% of the intended dose, cure took place within <5 days, or if other prespecified exclusion criteria applied; and HAP – patients who received at least one dose of study medication and were CE at the TOC visit. All end points were analyzed descriptively with two-sided 95% CI for the treatment difference generated for the early clinical response and clinical cure end points. In the ABSSSI study, treatment differences and the 95% CIs were computed using the Cochran–Mantel–Haenszel weights method adjusted for geographical region and actual type of ABSSSI. In the CAP and HAP studies, the 95% CIs for each end point were based on the normal approximation to the difference of the two proportions. Safety and tolerability were evaluated by assessment of adverse events (AEs) in the safety population (defined as all randomized patients who received at least one dose of study drug).

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Table 1. Number of patients aged 65–74 years and ≥75 years from the acute bacterial skin and skin structure infection, community-acquired pneumonia and hospital-acquired pneumonia (excluding ventilator-associated pneumonia) Phase III studies (intent-to-treat population).

Age group (years)	ABSSSI		CAP		HAP (excluding VAP)		ABSSSI + CAP + HAP (excluding VAP)		Total
	Ceftobiprole n = 335	Vancomycin + aztreonam n = 344	Ceftobiprole n = 314	Ceftriaxone ± linezolid n = 324	Ceftobiprole n = 287	Ceftazidime + linezolid n = 284	Ceftobiprole n = 936	Comparator n = 952	n = 1888
65–74	27 (8.1)	36 (10.5)	57 (18.2)	64 (19.8)	74 (25.8)	63 (22.2)	158 (16.9)	163 (17.1)	321 (17.0)
≥75	14 (4.2)	16 (4.7)	54 (17.2)	62 (19.1)	78 (27.2)	88 (31.0)	146 (15.6)	166 (17.4)	312 (16.5)
Total	41 (12.2)	52 (15.1)	111 (35.4)	126 (38.9)	152 (53.0)	151 (53.2)	304 (32.5)	329 (34.6)	633 (33.5)

All values are n (% of total population).
ABSSSI: Acute bacterial skin and skin structure infection; CAP: Community-acquired pneumonia; HAP: Hospital-acquired pneumonia; VAP: Ventilator-associated pneumonia.

Results

Patient disposition & baseline characteristics

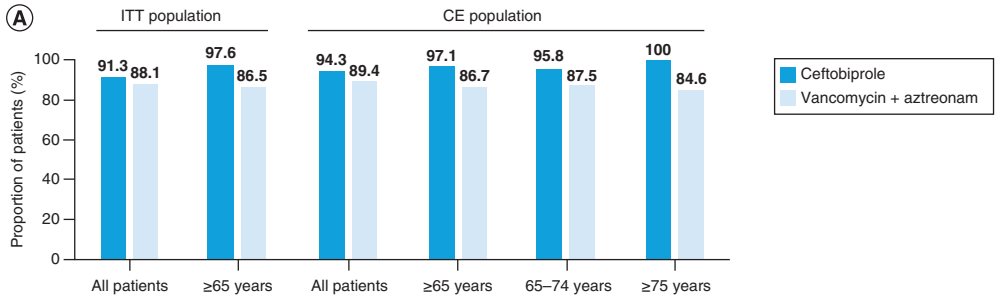
Overall, 633 patients from the three studies were ≥65 years of age at enrollment, representing 13.7%, 37.1% and 53.1% of all patients included in the ITT populations of the ABSSSI, CAP and HAP (excluding VAP) studies, respectively (Table 1). In the CAP study, similar numbers of patients aged 65–74 years and aged ≥75 years were enrolled (65–74 years, n = 121; ≥75 years, n = 116), whereas in the HAP study, a slightly higher proportion of patients were aged ≥75 years (65–74 years, n = 137; ≥75 years, n = 166). Conversely, the ABSSSI study enrolled a relatively small number of patients aged ≥75 years (n = 30, 4.4%). Across the ITT populations of all three studies, 304 patients were randomized to ceftobiprole (ABSSSI, n = 41; CAP, n = 111; and HAP, n = 152) and 329 patients were randomized to comparators (ABSSSI, n = 52; CAP, n = 126; and HAP, n = 151). In the ABSSSI and CAP studies, all patients received at least one dose of study drug. In the HAP study, two patients randomized to ceftobiprole did not receive study treatment; both patients were in the 65–74 years subgroup.

Baseline characteristics of all patients aged ≥65 years from the ABSSSI, CAP and HAP studies are presented in Table 2. Baseline characteristics were largely similar between treatment groups, with only a few notable numerical differences observed. First, in the ABSSSI study, a higher proportion of patients in the ceftobiprole treatment group were diabetic compared with the vancomycin + aztreonam treatment group (31.7% vs 11.5%). Second, in the CAP study, a lower proportion of patients in the ceftobiprole treatment group had received systemic antibacterial treatment in the previous 24 h compared with patients in the ceftriaxone ± linezolid treatment group (55.9% vs 65.9%). Finally, in the HAP study, a higher proportion of patients in the ceftobiprole treatment group were male compared with the ceftazidime + linezolid treatment group (63.2% vs 51.0%). High-risk factors were highly prevalent in patients aged ≥65 years in the pneumonia studies, with 84.0% of patients in the CAP study having a Pneumonia Outcomes Research Team score ≥3 and 45.5% of patients in the HAP study having an Acute Physiology and Chronic Health Evaluation II score ≥15. Overall, in the CAP and HAP studies, respectively, 36.7% and 28.1% of patients had underlying chronic obstructive pulmonary disease, and 10.1% and 33.0% were in intensive care at enrollment. Furthermore, the majority of CAP (64.6%) and HAP (82.8%) patients aged ≥65 years had received systemic antibacterial treatment in the previous 30 days.

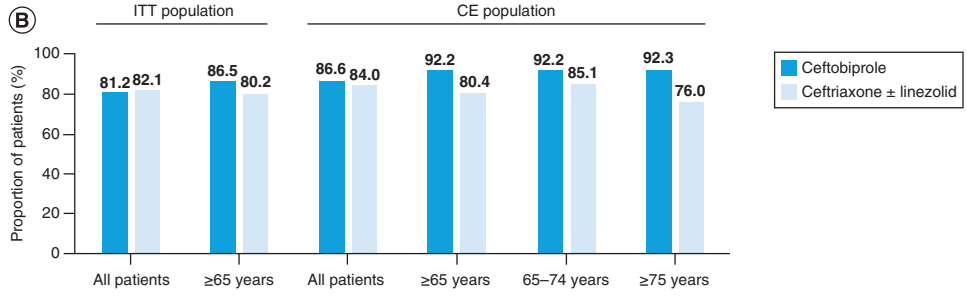
Efficacy

Early clinical response

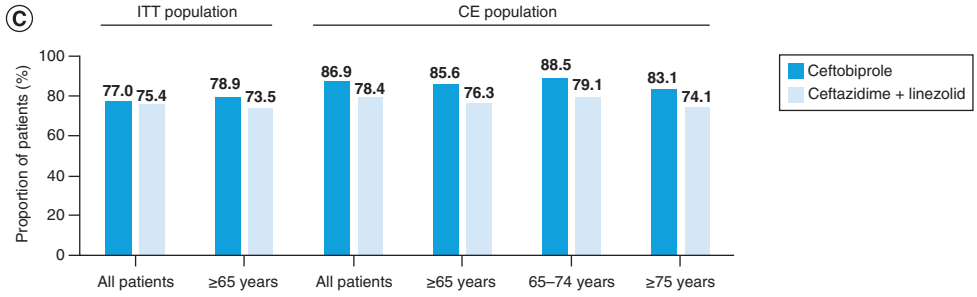
In all three studies, treatment differences for the overall CE population favored ceftobiprole, but were all <10% (ABSSSI, 5.0%; CAP, 2.5%; and HAP, 8.5%). For the subgroups of older and elderly patients, treatment differences were broadly consistent with those reported for all patients, with some evidence of improved clinical outcomes with ceftobiprole in some subgroups. In the ABSSSI study (Figure 1A), treatment differences favoring ceftobiprole of 9.7%, 9.1% and 10.2% were reported for patients in the CE population aged ≥65, 65–74 and ≥75 years, respectively. However, patient numbers in these subgroups were low and the treatment differences were not statistically significant. For patients in the CE population in the CAP study (Figure 1B), treatment differences >10% were observed for all patients aged ≥65 years (11.8%) and for the smaller subgroup of patients aged ≥75 years (16.3%). All of these treatment differences favored ceftobiprole and were statistically significant. In the HAP study (Figure 1C), treatment differences for all subgroups consistently favored ceftobiprole in the CE



Number of patients: ceftobiprole/vancomycin + aztreonam	335/344	41/52	283/293	34/45	24/32	10/13
Treatment difference, % (95% CI)	**3.3** (-1.2, 7.8)	**11.2** (0.4, 22.1)	**5.0** (0.6, 9.4)	**9.7** (-1.8, 21.1)	**9.1** (-4.6, 22.9)	**10.2** (-8.7, 29.0)



Number of patients: ceftobiprole/ceftriaxone ± linezolid	314/324	111/126	231/238	90/97	51/47	39/50
Treatment difference, % (95% CI)	**-0.9** (-6.9, 5.1)	**6.3** (-3.1, 15.8)	**2.5** (-3.9, 8.9)	**11.8** (2.2, 21.5)	**7.1** (-5.5, 19.6)	**16.3** (1.8, 30.8)



Number of patients: ceftobiprole/ceftazidime + linezolid	287/284	152/151	198/185	111/97	52/43	59/54
Treatment difference, % (95% CI)	**1.7** (-5.3, 8.6)	**5.4** (-4.1, 15.0)	**8.5** (0.9, 16.1)	**9.3** (-1.4, 20.0)	**9.4** (-5.5, 24.3)	**9.0** (-6.1, 24.1)

Figure 1. Early clinical response in the overall population and in subgroups of patients aged ≥65 years, 65–74 years and ≥75 years in the three Phase III studies. (A) Acute bacterial skin and skin structure infection. **(B)** Community-acquired pneumonia. **(C)** Hospital-acquired pneumonia (excluding ventilator-associated pneumonia). Between-treatment difference was calculated as ceftobiprole minus comparator. For the ABSSSI study, early clinical response was assessed at 48–72 h after the start of treatment and success was defined as meeting all of the following: ≥20% reduction from baseline in the area of the primary lesion, survival for ≥72 h from initiation of treatment, no use of concomitant systemic or topical antibacterials on the primary lesion and no unplanned surgical procedures for the ABSSSI after the start of treatment. For the pneumonia studies, early clinical response was assessed at day 3 (CAP) or day 4 (HAP) and was defined as improvement or cure based on an assessment by the investigator of signs and symptoms using standardized criteria.
ABSSSI: Acute bacterial skin and skin structure infection; CAP: Community-acquired pneumonia; CE: Clinically evaluable; HAP: Hospital-acquired pneumonia; ITT: Intent-to-treat.

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Table 2. Demographic and baseline characteristics of patients aged ≥65 years from the acute bacterial skin and skin structure infection, community-acquired pneumonia and hospital-acquired pneumonia (excluding ventilator-associated pneumonia) Phase III studies (intent-to-treat population).

Characteristics	ABSSSI		CAP		HAP (excluding VAP)	
	Ceftobiprole n = 41	Vancomycin + aztreonam n = 52	Ceftobiprole n = 111	Ceftriaxone ± linezolid n = 126	Ceftobiprole n = 152	Ceftazidime + linezolid n = 151
Gender						
Females	22 (53.7)	26 (50.0)	49 (44.1)	61 (48.4)	56 (36.8)	74 (49.0)
Males	19 (46.3)	26 (50.0)	62 (55.9)	65 (51.6)	96 (63.2)	77 (51.0)
Geographic regions						
USA	11 (26.8)	13 (25.0)	18 (16.2)	16 (12.7)	23 (15.1)	23 (15.2)
Europe	30 (73.2)	39 (75.0)	39 (35.1)	48 (38.1)	76 (50.0)	68 (45.0)
Other	0	0	54 (48.6)	62 (49.2)	53 (34.9)	60 (39.7)
Diabetes mellitus	13 (31.7)	6 (11.5)	23 (20.7)	26 (20.6)	47 (30.9)	44 (29.1)
Systemic antibacterial treatment in previous 24 h	0	0	62 (55.9)	83 (65.9)	93 (61.2)	94 (62.3)
Systemic antibacterial treatment in previous 30 days	0	0	66 (59.5)	87 (69.0)	125 (82.2)	126 (83.4)
High-risk factors at baseline						
Any high-risk factors[†]	–	–	108 (97.3)	119 (94.4)	141 (92.8)	138 (91.4)
Age ≥75 years	14 (34.1)	16 (30.8)	54 (48.6)	62 (49.2)	78 (51.3)	88 (58.3)
PORT ≥III (CAP) or APACHE ≥15 (HAP)	–	–	97 (87.4)	102 (81.0)	68 (44.7)	70 (46.4)
Bacteremia	–	–	3 (2.7)	3 (2.4)	14 (9.2)	13 (8.6)
COPD	–	–	41 (36.9)	46 (36.5)	46 (30.3)	39 (25.8)
ICU at baseline	–	–	12 (10.8)	12 (9.5)	47 (30.9)	53 (35.1)

All values are n (%).
[†]Other than age ≥75 years, high-risk factors at baseline were not available for patients in the ABSSSI study.
ABSSSI: Acute bacterial skin and skin structure infection; APACHE: Acute Physiology and Chronic Health Evaluation; CAP: Community-acquired pneumonia; COPD: Chronic obstructive pulmonary disease; HAP: Hospital-acquired pneumonia; ICU: Intensive care unit; ITT: Intent-to-treat; PORT: Pneumonia Outcomes Research Team; VAP: Ventilator-associated pneumonia.

population but were all <10% (overall population, 8.5%; ≥65 years, 9.3%; 65–74 years, 9.4%; and ≥75 years, 9.0%) and were not statistically significant. Results for the ITT population were broadly consistent with the CE population for all three studies.

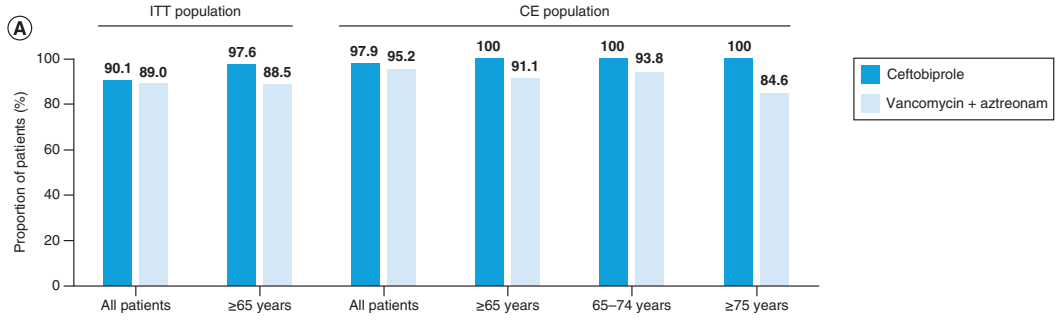
Clinical cure at TOC visit

In all three studies, clinical cure rates were broadly similar across treatment groups and age-stratified subgroups. In the ABSSSI study (Figure 2A), a trend for a higher treatment difference favoring ceftobiprole was observed in the subgroup of patients aged ≥75 years compared with all patients in the CE population (10.2% vs 2.7%) although the results were not statistically significant. In both the CAP and HAP studies (Figure 2B & C), no treatment differences >10% were observed. Similar results were observed in the ITT population.

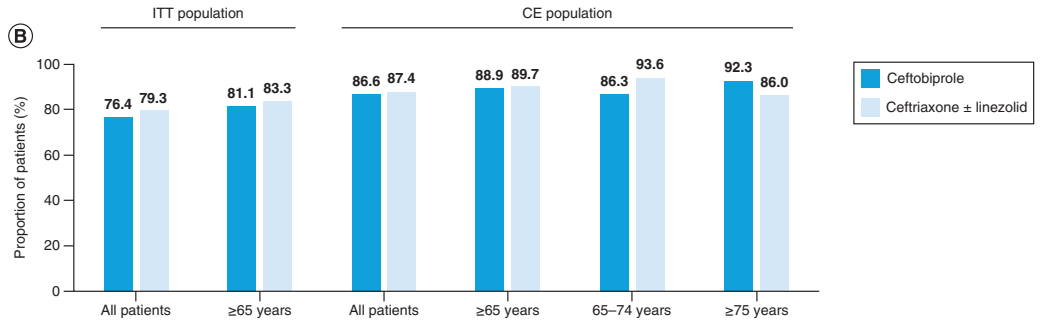
Mortality

All-cause mortality rates in the ABSSSI and CAP studies were generally low. In the ABSSSI study, three (0.4%) deaths were reported by day 28 in the ITT population, all of which occurred in patients under 65 years of age. There were no deaths in the ceftobiprole-treated group and mortality rates in patients treated with vancomycin + aztreonam were very low (ITT population, 0.9%; CE population, 0.7%). In the CAP study, 13 (2.0%) deaths were reported by day 30 in the ITT population (Figure 3A). Most deaths (11 out of 13) occurred in patients aged ≥65 years and were equally split between the treatment groups (five [4.5%] vs six [4.8%]).

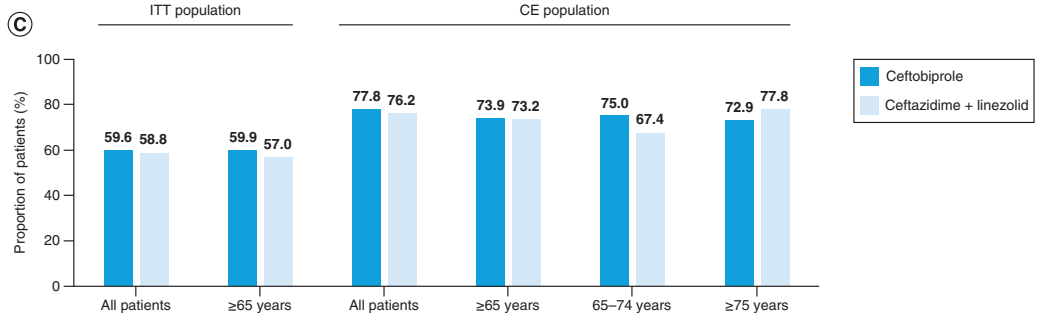
As expected, all-cause mortality rates were considerably higher in the HAP study, with 99 (17.3%) deaths occurring in the ITT population by day 30 (Figure 3B). For the overall patient population, no differences were reported in mortality rates between the treatment groups. However, for patients aged ≥65 years there was a trend for reduced mortality with ceftobiprole versus ceftazidime + linezolid (ITT population, 20.4% vs 24.5%). This



	ITT population		CE population			
Number of patients: ceftobiprole / vancomycin + aztreonam	335/344	41/52	283/293	34/45	24/32	10/13
Treatment difference, % (95% CI)	**1.0** (-3.5, 5.6)	**8.8** (-1.3, 18.9)	**2.7** (-0.3, 5.6)	**8.3** (-0.1, 16.7)	**6.5** (-2.3, 15.3)	**10.2** (-8.7, 29.0)



	ITT population		CE population			
Number of patients: ceftobiprole / ceftriaxone ± linezolid	314/324	111/126	231/238	90/97	51/47	39/50
Treatment difference, % (95% CI)	**-2.9** (-9.3, 3.6)	**-2.3** (-12.0, 7.5)	**-0.8** (-6.9, 5.3)	**-0.8** (-9.7, 8.1)	**-7.3** (-19.1, 4.4)	**6.3** (-6.4, 19.1)



	ITT population		CE population			
Number of patients: ceftobiprole / ceftazidime + linezolid	287/284	152/151	198/185	111/97	52/43	59/54
Treatment difference, % (95% CI)	**0.8** (-7.3, 8.8)	**2.9** (-8.2, 14.0)	**1.6** (-6.9, 10.0)	**0.7** (-11.3, 12.7)	**7.6** (-10.7, 25.9)	**-4.9** (-20.8, 11.0)

Figure 2. Clinical cure in the overall population and in subgroups of patients aged ≥65 years, 65–74 years and ≥75 years in the three Phase III studies. (A) Acute bacterial skin and skin structure infection. **(B)** Community-acquired pneumonia. **(C)** Hospital-acquired pneumonia (excluding ventilator-associated pneumonia). Between-treatment difference was calculated as ceftobiprole minus comparator. For all three studies, clinical cure was investigator assessed and was defined as complete, or near complete, resolution of baseline signs and symptoms of the primary infection, with no further need for antibacterial treatment at the TOC visit (for the ABSSSI study this was 15–22 days after randomization; for the CAP and HAP studies this was 7–14 days after end of treatment).

ABSSSI: Acute bacterial skin and skin structure infection; CAP: Community-acquired pneumonia; CE: Clinically evaluable; HAP: Hospital-acquired pneumonia; ITT: Intent-to-treat; TOC: Test of cure.

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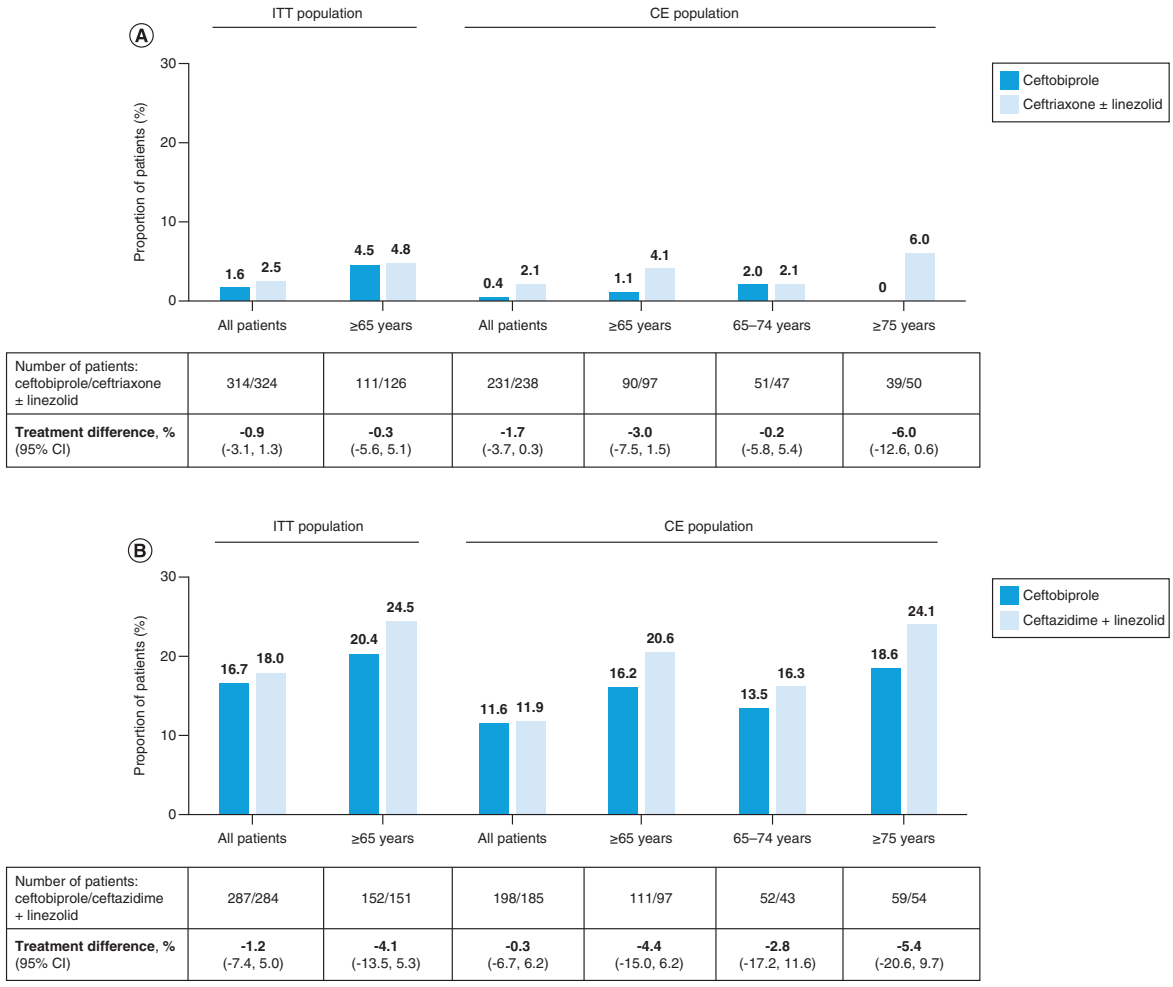

Figure 3. 30-day all-cause mortality in the overall population and in subgroups of patients aged ≥65 years, 65–74 years and ≥75 years in the two Phase III pneumonia studies. (A) Community-acquired pneumonia. **(B)** Hospital-acquired pneumonia (excluding ventilator-associated pneumonia). Between-treatment difference was calculated as ceftobiprole minus comparator.
CE: Clinically evaluable; ITT: Intent-to-treat.

trend was also observed for the subgroups of patients aged 65–74 years (13.5% vs 16.3%) and ≥75 years (18.6% vs 24.1%) in the CE population. Treatment differences were not statistically significant in any subgroup.

Safety

Safety data for all three studies are reported in Table 3. In the ABSSSI study, treatment-emergent AEs were reported in a higher proportion of patients treated with ceftobiprole versus vancomycin + aztreonam in the overall population (44.3% vs 38.6%) and in the subgroup of patients aged 65–74 years (48.1% vs 33.3%). In patients aged ≥75 years, no differences between treatment groups were observed (35.7% vs 37.5%). Serious AEs (SAEs) and treatment-related AEs occurred at a similar rate between treatment groups in both the overall patient population and in patients aged ≥65 years. Although based on small patient numbers, in the subgroup of patients ≥75 years, the proportion of ceftobiprole-treated patients with an AE or treatment-related AE was lower than in the overall population (AE, 35.7% vs 44.3%; treatment-related AE, 0 vs 19.8%). Irrespective of treatment, SAEs occurred at a slightly higher rate in patients ≥75 years compared with the overall patient population (ceftobiprole, 7.1% vs 1.8%; vancomycin + aztreonam, 6.3% vs 3.5%).

In the CAP study, the rates of treatment-emergent AEs were broadly similar between treatment groups and age categories. Treatment-related AEs occurred more frequently in patients treated with ceftobiprole versus ceftriaxone ± linezolid in the overall population (35.8% vs 25.8%) and in patients aged 65–74 years (36.8% vs

Table 3. Incidence of adverse events in the overall population and in subgroups of patients aged ≥65 years, 65–74 years and ≥75 years from the acute bacterial skin and skin structure infection, community-acquired pneumonia and hospital-acquired pneumonia (excluding ventilator-associated pneumonia) Phase III studies (safety population).

ABSSSI	All patients		≥65 years		65–74 years		≥75 years	
	Ceftobiprole n = 334	Vancomycin + aztreonam n = 342	Ceftobiprole n = 41	Vancomycin + aztreonam n = 52	Ceftobiprole n = 27	Vancomycin + aztreonam n = 36	Ceftobiprole n = 14	Vancomycin + aztreonam n = 16
AE	148 (44.3)	132 (38.6)	18 (43.9)	18 (34.6)	13 (48.1)	12 (33.3)	5 (35.7)	6 (37.5)
SAE	6 (1.8)	12 (3.5)	1 (2.4)	3 (5.8)	0	2 (5.6)	1 (7.1)	1 (6.3)
Treatment-related AE	66 (19.8)	62 (18.1)	4 (9.8)	6 (11.5)	4 (14.8)	4 (11.1)	0	2 (12.5)
Treatment-related SAE	1 (0.3)	2 (0.6)	0	0	0	0	0	0
CAP	**All patients**		**≥65 years**		**65–74 years**		**≥75 years**	
	Ceftobiprole n = 310	Ceftriaxone ± linezolid n = 322	Ceftobiprole n = 111	Ceftriaxone ± linezolid n = 126	Ceftobiprole n = 57	Ceftriaxone ± linezolid n = 64	Ceftobiprole n = 54	Ceftriaxone ± linezolid n = 62
AE	217 (70.0)	208 (64.6)	78 (70.3)	90 (71.4)	42 (73.7)	44 (68.8)	36 (66.7)	46 (74.2)
SAE	35 (11.3)	37 (11.5)	22 (19.8)	21 (16.7)	12 (21.1)	8 (12.5)	10 (18.5)	13 (21.0)
Treatment-related AE	111 (35.8)	83 (25.8)	36 (32.4)	29 (23.0)	21 (36.8)	13 (20.3)	15 (27.8)	16 (25.8)
Treatment-related SAE	3 (1.0)	4 (1.2)	2 (1.8)	2 (1.6)	1 (1.8)	2 (3.1)	1 (1.9)	0
HAP (excluding VAP)	**All patients**		**≥65 years**		**65–74 years**		**≥75 years**	
	Ceftobiprole n = 283	Ceftazidime + linezolid n = 284	Ceftobiprole n = 150	Ceftazidime + linezolid n = 151	Ceftobiprole n = 72	Ceftazidime + linezolid n = 63	Ceftobiprole n = 78	Ceftazidime + linezolid n = 88
Any AE	214 (75.6)	219 (77.1)	123 (82.0)	126 (83.4)	59 (81.9)	50 (79.4)	64 (82.1)	76 (86.4)
SAE	92 (32.5)	83 (29.2)	57 (38.0)	51 (33.8)	27 (37.5)	19 (30.2)	30 (38.5)	32 (36.4)
Treatment-related AE	80 (28.3)	68 (23.9)	47 (31.3)	43 (28.5)	28 (38.9)	13 (20.6)	19 (24.4)	30 (34.1)
Treatment-related SAE	9 (3.2)	3 (1.1)	5 (3.3)	2 (1.3)	4 (5.6)	0	1 (1.3)	2 (2.3)

All values are n (%).
ABSSSI: Acute bacterial skin and skin structure infection; AE: Adverse event; CAP: Community-acquired pneumonia; HAP: Hospital-acquired pneumonia; SAE: Serious AE; VAP: Ventilator-associated pneumonia.

20.3%). However, no difference between treatment groups was observed for treatment-related AEs in patients aged ≥75 years (27.8% vs 25.8%). In both treatment groups, SAEs occurred more frequently in patients aged ≥65 years compared with the overall population (ceftobiprole, 19.8% vs 11.3%; ceftriaxone ± linezolid, 16.7% vs 11.5%), and this trend was also noted in the subgroups of patients aged 65–74 years and ≥75 years.

For patients with HAP (excluding VAP), rates of treatment-emergent AEs and SAEs were similar between treatment groups. Irrespective of treatment, a slight increase in the rates of AEs and SAEs were noted for patients aged ≥65 years compared with the overall population. This trend was consistent in the subgroups of patients aged 65–74 and ≥75 years. Treatment-related AEs occurred more frequently with ceftobiprole than ceftazidime + linezolid in both the overall patient population (28.3% vs 23.9%) and in patients aged 65–74 years (38.9% vs 20.6%). However, for patients aged ≥75 years, the opposite was observed, with 24.4% of ceftobiprole-treated patients experiencing a treatment-related AE versus 34.1% of ceftazidime + linezolid-treated patients.

In all three studies, treatment-related SAEs occurred infrequently and no correlation with age was observed. Treatment-related AEs for patients in the ceftobiprole treatment group were consistently lower in patients aged ≥75 years compared with the overall population.

Discussion

The findings of this large *post hoc* analysis of three Phase III studies indicated that ceftobiprole is effective and has a good safety profile as a treatment for ABSSSIs or pneumonia in patients aged 65 years or older, including in elderly patients (aged ≥75 years).

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A potential for improved outcomes with ceftobiprole versus each comparator was observed for the early clinical response end point in both the ABSSSI and CAP studies. This effect was slightly more pronounced in the subgroups of patients aged ≥75 years than in the patients aged 65–74 years. In the HAP study, treatment differences were broadly similar between the overall patient population and the subgroups stratified by age, although a numerical increase in the treatment difference was noted in patients aged ≥65 years compared with all patients in both the ITT and CE populations. This is consistent with previous findings from a *post hoc* analysis demonstrating that ceftobiprole may have some advantages over other antibiotics for achieving early improvements in high-risk patients [27], perhaps reflecting its rapid bactericidal activity [28]. Clinical cure rates at the TOC visit were broadly similar between patients aged ≥65 years and the overall patient population in both the CAP and HAP studies. For patients with an ABSSSI, a treatment difference >10% was reported for the subgroup of patients aged ≥75 years; however, this was based on a very small patient population.

Mortality rates in patients with HAP were relatively high in the overall ITT population (17.3%) but were consistent with recent studies reporting mortality rates in patients with nonventilator HAP, including a large database of more than 100,000 patients in the USA (13.1%) and a case–control, single-center study (15.5%) [9,29]. As expected, mortality rates were higher in patients aged ≥65 years, reaching 22.4% across both treatment groups. This reflects the prevalence of high-risk factors in this patient population and is broadly similar to other studies assessing mortality in older patients with HAP [8,30]. Of note, mortality rates were numerically lower in patients treated with ceftobiprole compared with ceftazidime + linezolid in patients aged ≥65 years and in the smaller subgroup of patients aged ≥75 years. This is consistent with the signal for improved early clinical outcomes and supports the potential benefits of ceftobiprole in this population particularly. In the CAP study, numerically lower rates of all-cause mortality were reported with ceftobiprole versus ceftriaxone ± linezolid in patients aged ≥65 years in the ITT population. However, mortality rates were generally low in this study and results must be interpreted with caution.

For older and elderly patients, additional care must be taken when administering any pharmacological agent due to physiological changes that may affect the pharmacokinetics of a drug, for example, renal impairment. In this analysis, the safety profile of ceftobiprole was broadly similar in older and elderly patients compared with the overall patient population in all three studies. Overall, the proportions of patients with an SAE increased with age in all three studies. However, this occurred in all treatment groups and likely reflects a worse health state in elderly patients. Reassuringly, few differences in the rates of treatment-related SAEs were noted in older and elderly patients compared with the overall patient population. For ceftobiprole-treated patients, the incidence of treatment-related AEs was slightly lower in elderly patients compared with the overall population across all three studies. However, the numbers of events are low and results must therefore be interpreted with caution.

Across the world, the number of adults over 65 years of age is expected to double over the next 30 years, reaching 1.5 billion in 2050 [4]. This is expected to have a significant impact on healthcare costs and resource utilization in both the developed and developing world. Older and elderly patients will continue to be vulnerable to infectious diseases and it will be essential to optimize antimicrobial treatments to reduce the morbidity and mortality burden in these populations. Ceftobiprole is a valuable addition to the antimicrobial treatment armamentarium and may be a particularly useful treatment option in patients at risk of infection with MRSA.

Limitations of this *post hoc* analysis include the relatively small sample size for the individual age-stratified subgroups, most notably for the older and elderly patients with an ABSSSI. In addition, the ABSSSI, CAP and HAP studies were not powered to detect statistical treatment differences between subgroups, and patients enrolled in these controlled trials may not be fully representative of the real-world older and elderly patient populations.

Conclusion

This *post hoc* analysis of over 300 ceftobiprole-treated patients from three Phase III studies of ABSSSI and pneumonia further supports the efficacy and safety of ceftobiprole in older and elderly patients.

Author contributions

All authors contributed to the acquisition of data, and to the development, critical review and final approval of this manuscript.

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Summary points

- Infectious diseases pose a significant risk to the health of older individuals and remain one of the leading causes of death in this population.
- Older patients are particularly at risk of infection with multidrug-resistant organisms due to higher exposure to hospitals and long-term care facilities and more frequent use of antimicrobial therapies compared with younger individuals.
- Ceftobiprole is an advanced-generation cephalosporin with broad-spectrum activity against Gram-positive (including methicillin-resistant *Staphylococcus aureus*) and Gram-negative bacteria.
- The efficacy of ceftobiprole has previously been demonstrated in three large, randomized controlled trials in patients with acute bacterial skin and skin structure infections (ABSSSIs), community-acquired pneumonia and hospital-acquired pneumonia (HAP).
- In this *post hoc* analysis, the efficacy of ceftobiprole in older (aged 65–74 years) and elderly (aged ≥75 years) patients was broadly consistent with its efficacy in the overall patient populations in the ABSSSI, community-acquired pneumonia and HAP studies.
- A trend for improved outcomes with ceftobiprole versus comparator antibiotics was observed for the end point of early clinical response in all three studies.
- In patients with HAP, mortality rates were numerically lower in patients treated with ceftobiprole compared with ceftazidime + linezolid in patients aged ≥65 years and in the smaller subgroup of patients aged ≥75 years.
- The safety profile of ceftobiprole in older and elderly patients was similar to that of the overall patient population in all three studies.
- Ceftobiprole may be a valuable treatment option for older and elderly patients with an ABSSSI or pneumonia, particularly for patients at risk of infection with methicillin-resistant *Staphylococcus aureus*.

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Data sharing statement

The authors certify that this manuscript reports the secondary analysis of clinical trial data that have been shared with them, and that the use of these shared data is in accordance with the terms (if any) agreed upon their receipt. The sources of these data are: NCT03137173, NCT00326287, NCT0021096 and NCT00229008. Data for the overall study populations of the ABSSSI, CAP and HAP studies are previously published [21,22,24]. Study details are also available at clinicaltrials.gov (ABSSSI: https://clinicaltrials.gov/ct2/show/NCT03137173; CAP: https://clinicaltrials.gov/ct2/show/NCT00326287; and HAP: https://clinicaltrials.gov/ct2/show/NCT00210964 and https://clinicaltrials.gov/ct2/show/NCT00229008). Raw data for the subgroups of older and elderly patients enrolled in the ABSSSI, CAP and HAP studies were generated by Basliea Pharmaceutica International Ltd, Basel, Switzerland. Derived data supporting the findings of this study are available from the corresponding author (K Hamed) on request.

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