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Pharmacokinetics and Target Attainment of Ceftobiprole in Asian and Non-Asian Subjects

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Abstract

Ceftobiprole is a broad-spectrum cephalosporin. The objective of this study was to test the hypothesis that the pharmacokinetics (PK) and exposure of ceftobiprole in Asian subjects are similar to those in non-Asian subjects. Three approaches were followed. The first compared the individual PK estimates between the 2 subgroups derived from a population PK model previously built. Next, it was determined whether "Asian subject" was a significant covariate. Finally, a pharmacodynamic analysis was performed by comparing measures of exposure and target attainment. No significant differences were found between PK parameter estimates for Asian and non-Asian subjects, with median values (range) for clearance of 4.82 L/h (2.12–10.47) and 4.97 L/h (0.493–20.6), respectively ($P = .736$). "Asian subject" was not a significant covariate in the population PK model. There were no significant differences between the measures of exposure. The geometric mean ratio for the *f*AUC was 1.022 (90%CI, 0.91–1.15), indicating bioequivalence. Taking a target of 60% coverage of the dose interval, more than 90% of the population in both subgroups was adequately exposed. This analysis demonstrated that there are no PK or pharmacodynamic differences between Asian and non-Asian subjects for a ceftobiprole dose of 500 mg every 8 hours as a 2-hour infusion.

Keywords

exposure, drug development, special patient population, cephalosporin, population pharmacokinetics

Ceftobiprole, a broad-spectrum cephalosporin derived from the prodrug ceftobiprole medocaril, is approved in adults in Europe for the treatment of community-acquired pneumonia and hospital-acquired pneumonia, excluding ventilator-associated pneumonia.[1] The antimicrobial spectrum includes a wide range of Gram-negative bacteria, as well as methicillin-resistant *Staphylococcus aureus* and penicillin-resistant *Streptococcus pneumoniae*.[2,3]

Before approval, the safety, efficacy, and pharmacokinetics (PK) of ceftobiprole were extensively studied in global populations. However, it is known for some drugs that the PK are different in specific populations or are race dependent.[4–7] For another cephalosporin, cephalexin, it was shown that differences in peptide transporter 2 polymorphism distribution exists between various populations. For cephalexin, these differences did not result in relevant PK differences.[8] This illustrates that PK differences between populations for cephalosporins may exist. Ceftobiprole is potentially a weak substrate of the renal tubule cell uptake transporters organic anion transporter 1 and organic cation transporter 2. Therefore, it is mandatory in some countries, including Asian countries, to show that the dosing regimen chosen is adequate in subjects in these specific countries before the drug can be registered. Studies on ceftobiprole PK in Asian people living in Asia are obligatory to prove that a dosing regimen similar to that in non-Asian subjects can be used.

Ceftobiprole is not metabolized and is primarily eliminated in its unchanged form by glomerular filtration. While PK differences of ceftobiprole between

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Asian and non-Asian subjects are therefore unlikely, the main objective of this study was to test the hypothesis that the PK and pharmacodynamics (PD) of ceftobiprole in Asian subjects are not significantly different from those in non-Asian subjects. In addition to evaluating whether differences exist in the PK of ceftobiprole in Asians, particularly Asians of Chinese origin, to determine whether dose adjustments would be required, the analysis also serves to demonstrate that additional clinical trials in Asian countries, commonly requested by local authorities, are not useful and even superfluous. To that purpose, we compared the PK parameter estimates of Asian subjects and non-Asian subjects from a population model we developed earlier.[9] We also evaluated whether the property "Asian" was significant as a covariate in this PK model. Finally, we calculated different PK/PD indices for exposure for the 2 subgroups to determine whether there were significant differences in target attainment.

Materials and Methods

Asian and Non-Asian Population

A total of 47 Asian subjects and 153 non-Asian subjects were included in the analysis. The PK data included 29 Asian individuals from the phase 3 complicated skin and soft tissue infection study (BAP00414, NCT00210899) and 18 subjects from a PK study published previously involving 171 patients with nosocomial pneumonia.[9] The BAP00414 phase 3 study compared ceftobiprole to vancomycin plus ceftazidime in the treatment of resistant *S aureus* skin and skin structure infections, taking into account clinical cure and safety.[10] Ceftobiprole monotherapy was shown to be as effective as vancomycin plus ceftazidime in these patients. The non-Asian subjects were all from the latter study. Thus, the new dataset consisted of a total of 200 patients for the analysis. The term "Asian subjects" refers to a subject of an Asian race treated at a clinical study site in the People's Republic of China, Taiwan, or the Republic of Korea. All other subjects were from various non-Asian countries (such as United States, Argentina, Honduras, Brazil, Mexico, and Czech Republic). Of the non-Asian subjects, 78 individuals with rich-sampling (7 samples or more) and of the Asian subjects, 23 individuals with rich sampling were included. Demographic data were included in the database (age, weight, body mass index, and creatinine clearance [CrCL], which was calculated using the Cockcroft-Gault equation). All data were provided to the authors by Basilea Pharmaceutica International Ltd. Information on the individual study sites and the Institutional Review Board is available in the supplementary data file. The studies were in accordance with the Declaration of Helsinki and all participants gave written informed consent.

Ceftobiprole Administration, Sampling, and Concentrations

Ceftobiprole was administered intravenously in doses of 500 mg infused over 2 hours every 8 hours. Blood samples were drawn at different time points and consisted of a median of 3 samples per patient (range 1–7), mostly during multiple dosing intervals. The exact sampling times were recorded and used in the analysis. Immediately after sampling, the samples were kept on ice and stored at −70°C until analysis.[9]

For the measurement of the concentrations of ceftobiprole, liquid chromatography tandem mass spectrometry was used, with a lower limit of quantification of 20 or 50 ng/mL in 2 different laboratories. The methodologies and controls used were comparable, making it unlikely that structural differences between the measurements of the 2 laboratories exist. Within every run, a set of quality controls was included, covering the entire range of the measurements. All relevant information on the methodology from the original validation reports is presented in the supplementary data.

Population PK Analysis

The population PK model of ceftobiprole has been described before.[9] Briefly, a 3-compartment model with age as covariate on the volume of the central compartment and CrCL as covariate on the systemic clearance was developed using Compaq Visual FORTRAN standard edition 6.6 (Compaq Computer Corp., Euston, Texas) and the NONMEM software package (version VI, release 2; Icon Development Solutions, Ellicott City, Maryland). The model was implemented in the NONMEM ADVAN5 subroutine and the analysis was performed using the FOCE method with INTERACTION.

The new dataset of 200 individuals was evaluated using the model. The criteria used to accept this model for the new dataset were as follows: no systematic deviation in the model fits or goodness-of-fit plots (visually inspected); no aberrant values in the basic structural PK parameter estimates or in their respective confidence intervals.

To determine whether the difference between Asian and non-Asian subjects was a significant covariate in the model, as an indication of potential PK differences between Asian and non-Asian subjects, the covariate "Asian" was incorporated into the model using the same method as for the other covariates. Briefly, all covariates were tested one by one in the basic model and only covariates with a significant improvement compared to the basic model were used in further analysis. To select

a covariate for further analysis, a level of significance of 0.05 was used (corresponding to a difference of at least 3.84 points in mean objective function value).

Exposure to Ceftobiprole in the Subgroups

Using individual PK parameter estimates from the final population PK model or correlations between the parameter estimates and the covariates (CrCL and age) as described earlier,[9] the exposure to ceftobiprole was calculated individually for all subjects. Values for fraction of dosing interval the unbound (free) drug concentration exceeds minimum inhibitory concentration ($\%fT_{>MIC}$), area under the unbound drug concentration-time curve (fAUC), maximal unbound drug concentration fC_{max}, and minimum unbound drug concentration fC_{min} were derived using KINFUN 1.06 (Medimatics, Maastricht, the Netherlands). The AUC presented is the AUC of a single dose in steady state. The $\%fT_{>MIC}$ was calculated for 4 fixed MIC values (MIC of 1, 2, 4, and 8 mg/L) for the dose of 500 mg every 8 hours administered intravenously over 2 hours. Protein binding of 16% was used in the analysis.[11]

Target Attainment Rates

The exposure to ceftobiprole was calculated for each individual for a range of fixed MIC values (0.5–32 mg/L), by determining the $\%fT_{>MIC}$ for each of the 200 patients in the analysis dataset, based on the individual PK parameter estimates using KINFUN 1.06. The target attainment rate was calculated for a range of PK/PD targets ($\%fT_{>MIC}$ values from 30%–100% of the dosing interval).

Statistical Analysis

Comparisons between groups were performed using the Mann-Whitney test (2-tailed, $P < .05$) in GraphPad prism v5.0 (Graphpad Inc, La Jolla, California). They were calculated based on the median to avoid influence of extreme outliers on the results. For the test of bioequivalence, the geometric mean ratio of fAUC with its 90%CI was calculated using SAS version 9.3 (SAS Institute Inc, Cary, North Carolina) using the TTest procedure. Results were interpreted following the US Food and Drug Administration *Statistical Approaches to Establishing Bioequivalence* guidance, which states that bioequivalence is shown if the 90%CI for the geometric mean ratio falls between 0.8 and 1.25.[12] A power calculation with an α of 0.05 would yield statistical power of 90% to detect a difference in $\%fT_{>MIC}$ of 10% after inclusion of 47 Asian subjects in a total sample of 200 individuals.

Results

Population and Demographics

The median values and the ranges for age, body weight, body mass index, and CrCL of the 47 Asian and 153 non-Asian subjects are represented in Table 1. The values for the 2 covariates of the population PK model, age and CrCL, were not significantly different between the 2 subgroups ($P = .657$ and $P = .553$, respectively). The median value for body weight for Asian subjects was significantly lower compared with non-Asian subjects (64 kg vs 75 kg, respectively; $P = .0005$), however, the ranges of the 2 subgroups were overlapping. Despite the difference in weight between the 2 subgroups, the body mass indices were similar, with median values of 24.0 kg/m^2 and 24.7 kg/m^2 for Asian and non-Asian subjects, respectively ($P = .983$).

Population PK Analysis

The dataset of the 200 patients was submitted to the previously published model.[9] The estimates of the structural PK parameter with the coefficient of variation for the published and current analysis are shown in Table 2. The current analysis did not result in aberrant values for the structural PK parameter estimates and were comparable to the previous analysis.[9] The goodness-of-fit plots demonstrated a good model fit and no deviation was introduced by adding patients to the dataset. Based on the predefined criteria, we accepted this model in further analyses.

The results from the population PK model were used to detect differences between the subgroups for several PK parameters. None of the determined means of the PK parameter estimates were significantly different between the subgroups, as is shown in Table 1.

The incorporation of the covariate "Asian" into the basic model did not improve it significantly: the difference in mean objective function value for the model with Asian as covariate on clearance and volume of distribution of central compartment compared to the basic model without other covariates was 0.002 and 0.099 points, respectively. The variability in clearance or volumes of distribution did not decrease after implementation of this covariate, indicating a lack of difference in PK between the 2 subgroups.

Exposure to Ceftobiprole in Asian vs Non-Asian

The exposure to ceftobiprole in the 2 subgroups, Asian and non-Asian, was calculated for each of the PK/PD indices ($\%fT_{>MIC}$, fAUC [single dose steady state], fC_{max}, fC_{min}). The results of the comparison are shown in Table 3 and a selection of the indices in shown in Figure 1. The exposure of one of the non-Asian subjects was extremely unrealistic (eg, fAUC of 30536), while the mean fAUC was 100 and the median fAUC

Table 1. Demographics and PK Parameter Estimates for Asian and Non-Asian Subjects

	Asian subjects (n=47)						Non-Asian subjects (n=153)						
Parameter	N	Mean#	SD	Median	Min value	Max Value	N	Mean#	SD	Median	Min value	Max value	p-value*
Age	47	51.6	16.6	52.0	19	78.0	153	50.6	20.3	51.0	17.0	92.0	0.657
Weight	47	67.6	13.6	64.0	51	100	152	74.8	13.7	75.0	40.0	115.0	0.0005
BMI	47	25.5	4.94	24.0	18.2	42.3	151	25.1	4.23	24.7	15.6	41.4	0.983
Creatinine clearance	47	106.1	37.6	99.0	39.0	194.5	144	111.5	67.9	107.0	11.8	612.1	0.553
CL	47	4.91	1.89	4.82	2.12	10.47	152	5.16	2.73	4.97	0.49	20.6	0.736
Vd1	47	15.3	6.16	15.3	7.51	43.8	152	18.4	14.1	14.6	6.21	138.2	0.658
Vd_{ss}	47	21.0	6.16	21.1	13.3	49.5	152	24.2	14.1	20.3	12.0	144.0	0.658
Vd(area)	47	32.8	8.5	30.1	19.7	63.7	152	36.1	16.1	31.8	14.4	144.8	0.193
T1/2	47	4.88	1.32	4.33	3.97	11.4	152	5.65	3.21	4.29	3.80	32.2	0.599

*p-value represents the significance between the median values of the Asian and non-Asian subjects. #arithmetic mean. Min value= minimum value of the range; max value- maximum value of the range; SD standard deviation, N= number of subjects; BMI=body Mass index (kg/m^2); CL=clearance (L/h), Vd1 volume of distribution of the central compartment (L); Vd_{ss}= volume of distribution at steady state (L). Vd, (area) was calculated based on the terminal half-life[20]

Table 2. PK Estimate Parameters of the Previously Published Model[9] vs Current Analysis

	Previously Published Model (N = 171)[9]			Current Analysis (N = 200)		
Parameter	Mean	SE	Relative SE (% SE)	Mean	SE	Relative SE (% SE)
Clearance (L/h)	4.74	0.24	5.06	4.71	0.22	4.73
Vd1 (L)	15.5	1.26	8.13	15.4	1.21	7.86
Vd2 (L)	1.93	0.34	17.6	1.89	0.34	17.7
Vd3 (L)	3.76	1.18	31.4	3.86	1.15	29.8
Intercompartmental clearance (Vd1 and Vd2) (L/h)	0.37	0.11	29	0.36	0.11	30.4
Intercompartmental clearance (Vd1 and Vd3) (L/h)	3.05	1.83	60	3.09	1.76	57
Covariate creatinine clearance on clearance	0.0052	0.0011	21.2	0.0053	0.0011	20.1
Covariate age on Vd1	0.012	0.0015	13.1	0.011	0.0015	13

Table 3. Data of the Various Measures of Exposure for the Subgroups Asian and Non-Asian Subjects

	Asian Subjects (n = 47)						Non-Asian Subjects (n = 153)						
Parameter	N	Mean[b]	SD	Median	Min Value	Max Value	N	Mean[b]	SD	Median	Min Value	Max Value	*P*[a]
$fT_{>MIC=1}$	47	100	0	100	100	100	152	99.6	2.68	100	78.2	100	NA
$fT_{>MIC=2}$	47	99.4	2.29	100	87.2	100	152	97.7	7.63	100	52.6	100	0.342
$fT_{>MIC=4}$	47	88.9	13.7	97.9	59.7	100	152	87.2	16.0	93.5	23.0	100	0.608
$fT_{>MIC=8}$	47	66.5	25.3	59.7	8.66	100	152	63.8	27.5	54.2	0.0	100	0.749
*f*AUC	47	117.6	46.4	103.7	47.7	235.8	152	135.9	116.5	100.7	24.3	1015	0.736
fC_{max}	47	23.2	5.90	22.9	8.82	36.8	152	24.6	13.0	23.0	5.95	95.8	0.585
$fCmin_{ss}$	47	5.67	4.34	3.85	1.46	19.9	152	7.78	11.4	3.52	0.50	98.7	0.902

f, free, unbound fraction; NA, not available; SD, standard deviation.
[a]*P* value represents the significance between median values for the Asian and non-Asian subjects.
[b]Arithmetic mean. Min value = minimum value of the range; max value = maximum value of the range.

was 135. This appeared to be the result of aberrant PK estimates, which were based on a single concentration of 387 mg/L at approximately 6 hours after the start of the infusion. This is most likely not correct, therefore this individual was excluded from the analysis. There is another high value for CrCL in the data. This value is outside the range for which the CrCL by using the Cockcroft-Gault equation is validated,

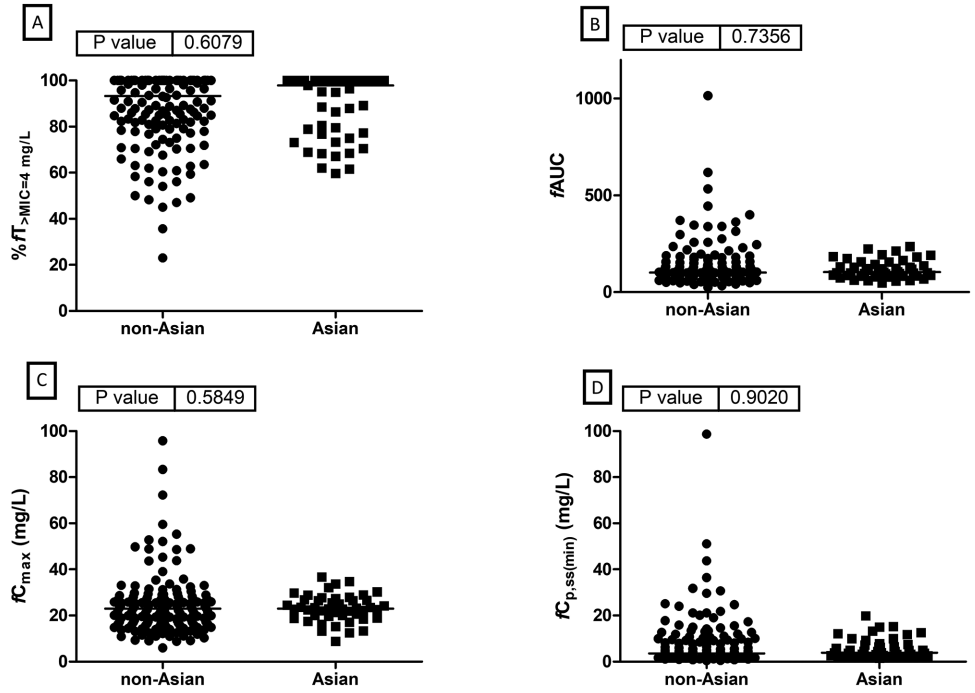

Figure 1. Distribution of $\%fT_{>MIC} = 4$ mg/L, *f*AUC, fC_{max}, and fC_{minss} in Asian (n = 47) and non-Asian (n = 152) subjects. *f*, free, unbound fraction.

usually up to 90 mL/min. This high value indicates that the CrCL was high, but the measurement is not precise. No other values were excluded. There were no significant differences in medians between the 2 subgroups. The values for the Asian subjects are within the range for the non-Asian subjects. This indicates no significant difference in exposure to ceftobiprole between Asian and non-Asian subjects. A further analysis showed that the geometric mean ratio for the *f*AUC of non-Asian and Asian subjects was 1.022 (90%CI, 0.91–1.15), indicating bioequivalence.

Target Attainment Rates

To determine whether the individuals in the 2 subgroups were treated appropriately and equally, target attainment rates were compared. The target attainment for the 2 subgroups is shown in Figure 2. There is no difference in observed target attainment between Asian and non-Asian subjects. For broad spectrum coverage targeting $\%fT_{>MIC\,=\,4\ mg/L}$ of 50% or 60% of the dosing interval, the probability of target attainment was at least 90% in both subgroups.

Discussion

Using several approaches, this analysis demonstrated there are no differences in the PK of ceftobiprole between Asian and non-Asian subjects. No significant differences were detected in the structural PK parameter estimates of the subgroups. Furthermore, the implementation of "Asian" as a covariate in the model did not improve the population model, indicating no difference between the Asian and non-Asian subgroups. Finally, we demonstrated that both subgroups were similarly exposed to ceftobiprole and that the probability of target attainment for Asian and non-Asian subjects did not differ for the recommended dosing regimen of 500 mg every 8 hours as a 2-hour infusion. This is also supported by the geometric mean ratio of *f*AUC and its 90%CI, indicating bioequivalence between non-Asian and Asian subjects.

The subgroups were comparable for the main demographic parameters. The only significant demographic parameter was body weight. Asian subjects had a lower body weight compared with non-Asian subjects. However, the PK of ceftobiprole is primarily driven by renal status, in this study estimated by CrCL. There was no significant difference in CrCL between Asian and non-Asian subjects. Difference in body weight was, therefore, unlikely to be of importance for renal elimination of ceftobiprole. It is also in agreement with the finding of no difference in exposure and $\%fT_{>MIC}$ between the 2 populations. Because the exposure did not differ between the 2 populations, the difference in body weight has no implications on recommended dose.

As for other cephalosporins, the PK/PD index that correlated best with microbiological eradication and clinical cure was $\%fT_{>MIC}$, as has been shown for ceftobiprole previously, both in preclinical evidence[13]

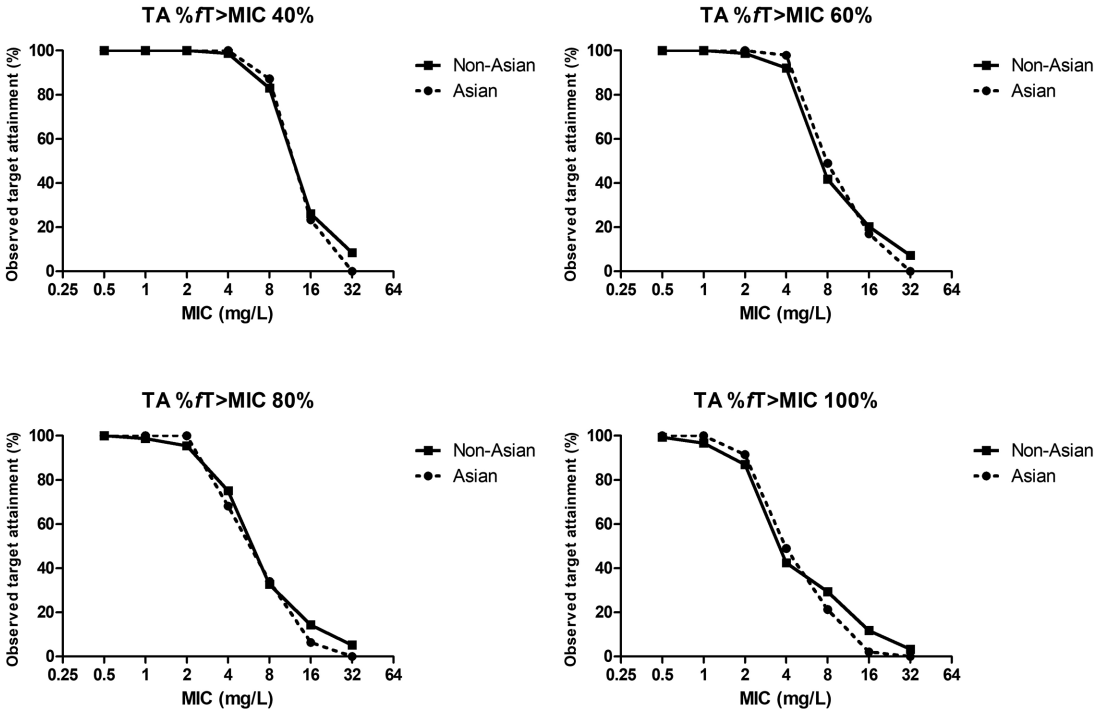

Figure 2. Observed target attainment rates for Asian (n = 47) and non-Asian (n = 152) subjects for targets of concentrations above the MIC, ranging from 40%–100% of the dosing interval. *f*, free, unbound fraction; TA, target attainment.

and in human data.[14] The exposure required to result in a likely favorable outcome is at least 45% $fT_{>MIC}$ for ceftazidime[15] and 50%-60% $fT_{>MIC}$ for ceftobiprole.[14] However, another study has shown that in some cases, 30% $fT_{>MIC}$ is sufficient, in particular for staphylococci.[16] We therefore calculated the exposure for $fT_{>MIC}$ to be 30%-100% and concluded that for all these different targets, the exposure in the 2 subgroups was comparable.

Because PK/PD indices other than $\%fT_{>MIC}$ might be of importance, these indices were also compared. The total exposure to ceftobiprole is best represented by *f*AUC/MIC and was found to be similar between the 2 subgroups. In general, the fC_{max} might be of importance for toxicity[17] and was also found to be similar for the 2 subgroups.

To determine clinical breakpoints, the European Committee on Antimicrobial Susceptibility Testing (EUCAST) uses 50%–60% as a PK/PD target for cephalosporins used to treat severe infections caused by Gram-negative infections.[18] For ceftobiprole, the EUCAST recently determined breakpoints: 4 mg/L for the PK/PD breakpoint, 0.25 mg/L for Enterobacteriaceae, 2 mg/L for *S aureus*, and 0.5 mg/L for *S pneumoniae*.[19] Taking a target attainment rate of 60% $fT_{>MIC}$ and the most conservative breakpoint of 4 mg/L, both Asian and non-Asian subjects reached the target in at least 90% of the cases.

Conclusion

There are no clinically relevant differences in exposure to ceftobiprole in Asian subjects compared with non-Asian subjects, therefore the dosing regimen as approved by the European Medicines Agency for its use in Europe can also be used in Asia.

Disclosures

M. Engelhardt and A.H. Schmitt-Hoffmann are employees of Basilea Pharmaceutica International Ltd.

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Supporting Information

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