STUDY REPORT SUMMARY

ASTRAZENECA PHARMACEUTICALS

FINISHED PRODUCT:
ACTIVE INGREDIENT:

Study No:
NIS-ICN-DUM-2010/1

Developmental Phase: phase IV
Study Completion Date: 31 Oct 2012
Date of Report: 23 Dec 2012

OBJECTIVES:

Mainly to evaluate the effectiveness and safety of CUBICIN® in routine clinical practice in Chinese patients

METHODS:

This is a multi-center, observational, non-interventional registry study to collect the clinical data in Chinese patients actually treated by daptomycin in clinical practice.

All the Chinese patients who are decided by treating physicians to receive CUBICIN® have the eligibility to participate in this registry study. First of all, confirm whether patients should receive the treatment with daptomycin, then re-evaluate whether patients should be enrolled in this study.

RESULTS:

General Information:

This trial started from July 2010 and submitted ethic application to 55 centers. A total of 203 patients were registered and all were enrolled. All the patients received treatment and finished the study, and were included in ITT, PPS and SS dataset. 94 subjects of them containing Gram-positive bacteria in the results of microbiological culture at enrollment (Day 0) were included in MITT analysis set.

The overall average age of subjects was 50.6 years (6～95 years). There were more males than females in enrolled patients, including 130 males (64.0%) and 73 females (36.0%), and all the subjects were Chinese.

The average height of subjects was 166.73cm (110.0-187.0cm), the average weight was 64.22Kg (24.0-110.0Kg) and average BMI was 23.04Kg/m^2 (13.8-39.0Kg/m^2).

The average systolic pressure of subjects was 120.41mmHg (82.0-198.0) and average diastolic pressure was 70.55mmHg (44.0-106.0).The average oral temperature was 38.16℃ (35.7-40.6). The average heart beat was 97.91beats/min (45.0-187.0).

Effectiveness Outcome:

Clinical efficacy outcome was shown in ITT set and was calculated by the time of treatment start with daptomycin. The clinical effective rate was 67.17% (133/198), 77.65% (132/170), 78.57% (88/112) and 76.19% (64/84) on Day 3, Day 7, Day 14 and after Day 14 after treatment, respectively. 143/203 patients (70.44%) had an effective clinical treatment as the final outcome at discharge. The median time from the start of treatment to the onset time of clinical effectiveness was 3.0 days.

It was shown in microbiological efficacy outcome that the bacterial clearance was 55.32% (52/94) in MITT on discharge day.

In MITT, *staphylococcus aureus* was predominant (33.0%, 31/94) in the 94 subjects with Gram-positive bacteria in bacterial cultures (including the results of blood culture and infective site culture) at enrollment, including MRSA (14.9%, 14/94), resistance-undefined *staphylococcus aureus* (14.9%, 14/94) and MSSA (4.3%, 4/94). The percentage of Gram-negative bacteria was 34.0% (32/94) and 3.2% (3/94) for fungi. In the results of infective site culture, the percentage of Gram-positive bacteria was 37.2% (35/94) and 31.9% (30/94) for Gram-negative bacteria. *Staphylococcus aureus* was predominant (11.7%, 11/94) in Gram-positive bacteria, including 6 MRSAs, 5 resistance-undefined *staphylococcus aureus*. In the results of blood culture, Gram-positive bacteria were predominant (78.7%, 74/94) followed by Gram-negative bacteria (6.4%, 6/94) and fungi (1.1%, 1/94).And the most of Gram-positive bacteria was *staphylococcus aureus* (25.5%，24/94), including MRSA (10.6%, 10/94), resistance-undefined *staphylococcus aureus* (10.6%, 10/94) and MSSA (4.3%, 4/94).

In the results of microbiological culture (including blood culture and infective site culture) after treatment (on discharge day), Gram-negative bacteria were predominant (31.9%, 30/94) followed by Gram-positive bacteria (9.6%, 9/94) and fungi (3.2%, 3/94). In the results of infective site culture, Gram-negative bacteria were predominant (31.9%, 30/94) followed by Gram-positive bacteria (5.3%,

5/94). In the results of blood culture, it was followed by Gram-negative bacteria (5.3%, 5/94), Gram-positive bacteria (4.3%, 4/94) and fungi (3.2%, 3/94).2/4 Gram-positive bacteria were resistance-undefined *staphylococcus aureus*, and the other 2 were enterococcus gallinarum (group D). Compared with that before treatment, the Gram-positive bacteria clearance was the highest among the positive rates of pathogen culture in microbiological, infective site and blood cultures after treatment. Results of ITT and PPS analysis were basically consistent with that of MITT.

At enrollment, simple bloodstream infection (42.9%, 87/203) was the most disease infected in 203 subjects, followed by other infections (18.2%, 37/203) and skin soft tissue infection (14.3%, 29/203) in ITT. And in bloodstream infection with other infections, i.e., complicated bloodstream infection, there were 13 (27.7%, 13/47) bloodstream infections with endocardial infection and 7 (14.9%, 7/47) blood infections with skin soft tissue infection. And blood flow is the most infective site (42.9%, 87/203).

In addition, in order to understand the effect of daptomycin on different infection type and different pathogens, a total of 17 subgroup analyses were performed in this study. The results showed there were 23 patients in the subgroup of *staphylococcus aureus* bloodstream infection, and the clinical effective rate (including clinical assessment “cure” and “improvement”) was 81.82% (18/22), 95% (19/20), 93.33% (14/15) and 100.0% (10/10) on Day 3, Day 7, Day 14 and after Day 14, respectively, calculated by the time of daptomycin therapy. The efficacy was improved with the prolongation of treatment duration, and the clinical effective rate reached 100.0% (10/10) on Day 14 after treatment.21/23 patients (91.3%, 21/23) had an effective clinical treatment as the final outcome at discharge.10 patients of them with bloodstream infection caused by MRSA (methicillin resistant *staphylococcus aureus*) had a clinical effective rate (including cure and improvement) of 100.0% (10/10) on Discharge Day after daptomycin treatment, and the clinical effective rate (including cure and improvement) was also 100.0% (5/5) in 5 patients with bloodstream infection caused by MSSA (methicillin sensitive *staphylococcus aureus*) on Discharge Day after daptomycin treatment, indicating a good efficacy in *staphylococcus aureus*, including MRSA and MSSA where the clinical effective rate reached as high as 100.0%. (See Section 9.4 for details)

5 patients with *staphylococcus aureus* bloodstream infection combined with IE had a clinical effective rate (including cure and improvement) of 100.0% (5/5) on Discharge Day after daptomycin treatment. 18 patients were included in the subgroup of *staphylococcus aureus* bloodstream infection without IE, and had a clinical effective rate (including cure and improvement) of 88.89% (16/18) on

Discharge Day after daptomycin treatment. (See Section 9.8 for details). The data above indicated that daptomycin had a comparable clinical efficacy for *staphylococcus aureus* bloodstream infection with or without IE.

The data in this study can demonstrate that the application range includes *staphylococcus aureus* bloodstream infection in post-marketing clinical practice, including simple bloodstream infection and complicated bloodstream infection. And it was found in the subgroup analysis by pathogens that daptomycin had a good efficacy for bloodstream infections caused by *staphylococcus aureus*.

Safety Outcome:

A total of 203 subjects were enrolled in safety analysis set in this study.

The total incidence of adverse events (AE) was 12.8% (26/203) in this study, including 7 AEs (3.4%) judged by investigators to be related with the drug, 3 AEs (1.5%) leading to the discontinuation of the investigational drug. There were 2 serious adverse events (SAE) (1.0%), which were judged by investigators to be unrelated with the investigational drug.

Adverse events with high frequency during treatment included hypoalbuminemia, hypocalcemia, hypokalemia, nausea, skin rashes, elevated AST, decreased platelet and increased serum CPK. Most adverse events were mild.

7 AEs judged by investigators to be related with the investigational drug included 6 mild AEs in severity and only 1 moderate AE (skin pruritus). 5 of these AEs were resolved during follow-up, the other 2 AEs that had not been recovered at follow-up were mild decreased platelet. Investigators still gave daptomycin at initial dose.

3 AEs leading to the drug discontinuation were mild hypokalemia, mild increase in serum CPK and moderate rashes with pruritus, respectively. The AE was resolved after discontinuation of the investigational drug.

2 SAEs were death due to multiple organ failure, and these SAEs were judged by investigators to be unrelated with daptomycin treatment.

The safety outcome in this study showed a good tolerability of daptomycin and consistency of safety data with foreign published results.

Conclusion:

The results in this non-interventional study showed daptomycin had a good clinical efficacy and bacterial clearance in the treatment of a variety of Gram-positive bacterial infection (including bloodstream infection, endocarditis, skin soft tissue infection) in Chinese patients, especially a significant efficacy in the treatment of serious infection, such as bloodstream infection caused by *staphylococcus aureus* (including MRSA and MSSA) and concomitant

endocarditis. Meanwhile, this drug was well tolerated and the safety data was consistent with foreign published results.