AstraZeneca

Clinical Study Report Synopsis

Drug Substance	Daptomycin
Study Code	D1790C00003
Edition Number	Final
Date	25 March 2011

A Phase 3, Multicentre, Randomised, Investigator-blinded, Parallel-group Study of the Safety and Efficacy of Intravenous Daptomycin (Cubicin®) Compared with that of Comparator (Vancomycin or Vancomycin Followed by Semi-synthetic Penicillin-cloxacillin) in the Treatment of Chinese Subjects with Complicated Bacterial Skin and Skin Structure Infection (cSSSI) due to Gram-Positive Pathogens

Study dates: First subject enrolled: 22 September 2008
Last subject completed: 09 September 2010

Phase of development: Therapeutic confirmatory (IIIa)

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

Study centres

A total of 29 centres in China participated in this study.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables	Type
Primary To evaluate safety and tolerability of daptomycin in Chinese patients with known or suspected Gram-positive cSSSI and compare with that of comparators by assessment of AEs, changes in laboratory measurements (haematology, clinical chemistry, urinalysis and CPK levels), and changes in the ECG.	**Primary** AEs, changes in laboratory measurements (haematology, clinical chemistry, urinalysis and CPK levels) and changes in the ECG.	Safety
Secondary To evaluate efficacy of daptomycin compared with comparator (vancomycin or vancomycin followed by a semi-synthetic penicillin [cloxacillin]) in Chinese patients with known or suspected Gram-positive cSSSI by evaluation of the blinded investigator's assessment of clinical response at the TOC evaluation, the blinded investigator's assessment of clinical response at EOT, microbiological response at EOT and TOC, pathogen specific clinical and microbiological response at EOT and TOC, time to defervescence and relapse rate.	**Secondary** Blinded investigator's assessment of clinical response at the TOC evaluation; the blinded investigator's assessment of clinical response at EOT; microbiological response at EOT and TOC; pathogen specific clinical and microbiological response at EOT and TOC; time to defervescence; and relapse rate.	Efficacy

AE: Adverse event; CPK: Creatine phosphokinase; cSSSI: Complicated skin and skin structure infection; ECG: Electrocardiogram; EOT: End of therapy; TOC: Test of cure.

Study design

This was a Phase IIIa, multicentre, randomised, investigator-blinded, parallel-group study comparing the safety and efficacy of intravenous (IV) daptomycin (4 mg/kg every 24 hours) with IV vancomycin (1 g every 12 hours) or vancomycin followed by semi-synthetic penicillin (cloxacillin) in Chinese patients with known or suspected complicated skin and skin structure infection (cSSSI).

Target patient population and sample size

The patient population included male and non-pregnant, non-lactating female Chinese patients aged 18 to 75 years who had a diagnosis of cSSSI known or suspected to be due to

Gram-positive bacteria. Patients were to have had at least 3 of the following clinical signs or symptoms of skin infection: temperature >38.0°C (rectal) or >37.5°C (oral); white blood cell count >10 x 10^9/L or with ≥10% band neutrophils; pain; tenderness on palpation; erythema (extending at least 1 cm beyond the wound edge); swelling; induration; or pus formation. Patients with a known bloodstream infection were to be excluded from the study.

In this study it was planned to include approximately 240 randomised patients, with 120 patients in each treatment group (daptomycin or comparator). With this sample size it was expected to obtain 100 evaluable patients in each treatment group so as to meet the State Food and Drug Administration requirements for registration studies.

Investigational product and comparator(s): dosage, mode of administration and batch numbers

Table S2 Details of investigational product and comparators

Investigational product or comparator	Dosage form, strength, dosing schedule and route of administration	Manufacturer	Batch number
Daptomycin	Powder for IV administration, 500 mg, 4 mg/kg every 24 hours IV	Hospira, USA	H2008-01-01-02 H2008-01-01-03
Vancomycin	1 g every 12 hours IV	Sourced and labelled locally	Not applicable
Cloxacillin	4 to 6 g per day IV in 3 to 4 equally divided doses (1 g every 6 hours or 2 g every 8 hours). Serious infection: 4 to 12 g per day IV (in 3 to 4 equally divided doses)	Sourced and labelled locally	Not applicable

IV: Intravenous; USA: United States of America.

Duration of treatment

The duration of IV therapy was to be 7 to 14 days for both regimens (daptomycin or comparator), with the actual duration based on the investigator's judgment of the patient's response. If, in the investigator's opinion, a patient required more than 14 days of therapy, the duration of therapy could be extended following discussion with the medical monitor.

Statistical methods

Safety analyses included all patients who received at least 1 dose of study treatment and were based on comparison of adverse events (AEs), laboratory analyses, vital signs, electrocardiograms (ECG) and physical examination. AEs were summarised for each treatment group by system organ class and preferred term. The proportions of patients with at least 1 AE, treatment-related AEs, severe AEs, serious adverse events (SAEs), death, discontinuation due to an AE, discontinuation due to a treatment-related AE, or other

significant AEs were summarised by treatment group. For the analysis of continuous safety variables including haematology, serum chemistry (including creatine phosphokinase [CPK]), ECG and vital signs, change from baseline to each post-treatment visit was summarised for each treatment group. Where appropriate, shift tables were created to describe the shift change from baseline to each post-baseline visit for the categorical variables reported by case report form or derived categorical variables based on laboratory or vital signs normal ranges.

The assessment of clinical response (success rate) was performed primarily on the Clinically Evaluable (CE) population; secondary analysis of clinical response was carried out on the Full Analysis Set (FAS), FAS subset, Microbiologically Evaluable (ME) and CE subset population. The assessment of microbiologic response was performed on the FAS subset, ME population and CE subset population. A 2-sided 95% confidence interval (CI) was constructed for the difference in the success rates of clinical or microbiologic outcomes by patient between the daptomycin and vancomycin groups at Test of cure (TOC) and End of Therapy (EOT). The CIs were computed using the method proposed by Miettinen and Nurminen (1985). Pathogen-specific clinical and microbiological response at EOT and TOC were analysed using the same method.

Time to defervescence was analysed by treatment group for all patients in the FAS and CE populations using a Kaplan-Meier survival approach, with the log-rank test to determine whether the treatment groups differed.

Rates of Relapse were calculated in the FAS, FAS subset and CE population by treatment group and a 2-sided 95% CI was constructed for the difference in rate of relapse between groups.

Patient population

The first patient was enrolled on 22 September 2008 and the last patient completed the study on 09 September 2010. Overall 277 patients consented; of these, 12 patients were not randomised (11 patients were incorrectly enrolled and 1 patient voluntarily discontinued). Overall, 265 patients were randomised, with 264 patients receiving study treatment (Table S3).

Table S3 Summary of analysis sets

Analysis sets	Number (%) of patients		
	Treatment group		
	Daptomycin (N=131)	Comparator (N=134)	Overall (N=265)
All patients randomised	131 (100)	134 (100)	265 (100)
Patients included in the safety population	131 (100)	133 (99.3)	264 (99.6)
Patients excluded from the safety population[a]	1 (0.8)	0	1 (0.4)
Patients included in the FAS population	130 (99.2)	134 (100)	264 (99.6)
Patients included in the CE population	110 (84.0)	104 (77.6)	214 (80.8)
Patients included in the ME population	81 (61.8)	82 (61.2)	163 (61.5)

[a] Randomised but did not receive study drug.
Note: One patient was randomised to the comparator group but instead received treatment with daptomycin; as per the definition for the safety population, this patient was therefore analysed according to the treatment actually received (daptomycin). This patient was included in the comparator group for the FAS population.
CE: Clinically evaluable; FAS: Full analysis set; ME: Microbiologically evaluable.

Over 80% of randomised patients completed the study (111 patients [84.7%] in the daptomycin group versus 110 patients [82.1%] in the comparator group). The rates of discontinuation from the study (daptomycin: 20/131 patients [15.3%], comparator: 24/134 patients [17.9%]) were also similar between treatment groups. Over 85% of randomised patients completed study treatment (114 patients [87.0%] in the daptomycin group versus 116 patients [86.6%] in the comparator group) and the rates of study treatment discontinuation (daptomycin: 17/130 patients [13.1%], comparator: 18/134 patients [13.4%]) were balanced between treatment groups.

The demographic and patient characteristics were representative of the intended population and the 2 patient groups were well balanced.

Summary of efficacy results

This study successfully demonstrated that the efficacy of daptomycin was clinically and statistically comparable to standard therapy for the treatment of cSSSI due to Gram-positive bacteria. Clinical and microbiological success rates at the EOT and TOC evaluations were high and comparable for the daptomycin and comparator treatment groups (Table S4). The lower bounds of the 95% CIs for the difference in the clinical or microbiological success rates (daptomycin – comparator) were >-10%. For the TOC visit clinical success rates were comparable for both treatment groups for patients infected with *Staphylococcus aureus* (*S. aureus;* the most commonly isolated pathogen at baseline) (daptomycin: 42/44 [95.5%]; comparator: 39/44 [88.6%]; 95% CI: -5.5%, 20.2%). Similar results were observed at the EOT visit.

For the TOC visit the clinical success rate for patients infected with methicillin-resistant *S. aureus* (MRSA) was 100% (14/14 patients) for the daptomycin group compared with 90.9% (10/11 patients) for the comparator group (95% CI: -14.3, 38.4).

Table S4 Summary of analysis of clinical and microbiological response rates (CE and ME population)

	Number (%) of patients		
	Treatment group		
Response	**Daptomycin**	**Comparator**	**95% CI[a]**
Clinical success at TOC[b]	100/110 (90.9)	92/104 (88.5)	-6.0, 11.2
Clinical success at EOT[b]	100/110 (90.9)	95/104 (91.3)	-8.5, 7.7
Microbiological success at TOC[c]	73/78 (93.6)	72/80 (90.0)	-5.5, 13.0
Microbiological success at EOT[c]	72/81 (88.9)	71/82 (86.6)	-8.2, 12.9

[a] Difference = daptomycin – comparator.
[b] Analysis based on the CE population.
[c] Analysis based on the ME population.
CI: Confidence interval; CE: Clinically evaluable; EOT: End of therapy; ME: Microbiologically evaluable; TOC: Test of cure.

The proportion of patients in each treatment group who became defervescent during the study was similar (86.7% in the daptomycin group and 83.3% of patients in the comparator group). The median time to first defervescence was also similar between the 2 treatment groups (5 days in the daptomycin group and 4.5 days in the comparator group).

A low rate of clinical relapse was observed in both treatment groups (2.0% in the daptomycin group and 1.1% in the comparator group).

Summary of safety results

Reflective of the different dosing regimens (daptomycin 4 mg/kg every 24 hours versus vancomycin 1 g every 12 hours), the median number of doses of comparator received was twice as many as the number of daptomycin doses received (9 doses for daptomycin versus 18 doses for comparator). The mean number of days on treatment was the same for both treatment groups (9.7 days). A similar proportion of patients were withdrawn from study treatment in each treatment group; with a small proportion of patients being withdrawn due to AEs in each group (2.3% of patients in the daptomycin group and 6.8% of patients in the comparator group.

Overall, the number of patients reporting AEs was low and consistent between the 2 treatment groups (22.9% of patients in the daptomycin group versus 29.3% of patients in the comparator group). A higher proportion of patients in the comparator group had AEs that were considered treatment-related by the investigator compared with the daptomycin group (9.9% of patients in the daptomycin group compared with 21.1% of patients in the comparator

group). The incidence of severe AEs and SAEs was low in both treatment groups. AEs of alanine aminotransferase increased (5.3% of patients overall) and aspartate aminotransferase increased (4.5% of patients overall) were each reported for >10 patients overall; these AEs were well balanced between the 2 treatment groups. A higher proportion of patients in the comparator group had an AE in the skin and subcutaneous tissue disorder SOC (including AEs of drug eruption, pruritus, rash and rash generalised) compared with the daptomycin group (1.5% of patients in the daptomycin group compared with 6.0% of patients in the comparator group). There were no AEs of rhabdomyolysis. There was an imbalance in the occurrence of the AE blood CPK increased between the 2 treatment groups; 4 patients with blood CPK increased in the daptomycin group (all considered treatment-related and non-serious by the investigator) compared with no patients in the comparator group. Increases in CPK activities were reversible in all patients and were consistent with previously reported experience of this adverse reaction.

One patient in each treatment group had an SAE during the study that had an outcome of death (comparator group: hepatic cirrhosis; daptomycin group: pneumonia): neither death was considered related to the study treatment. The incidence of AEs leading to discontinuation from the study was low (3.1% in the daptomycin group and 6.0% in the comparator group). The incidence of discontinuation of study treatment due to an AE was also low (2.3% in the daptomycin group and 6.8% in the comparator group); study treatment was stopped due to an AE for these patients but some of these patients remained in the study. There were no other significant AEs reported during the study.

In general, CPK activities fluctuated throughout the study and several patients in each treatment group had high CPK activities (outliers), which resulted in a skewed data set. There was no evidence to suggest any clinically significant population changes in any of the clinical chemistry, haematology or urinalysis parameters during the study; any small changes were consistent between the 2 treatment groups. There were no findings of clinical concern and no trends in vital signs, electrocardiograms or physical examinations during the study.