Clinical Study Report Synopsis

Drug Substance	Daptomycin
Study Code	D1790C00002
Edition Number	1.0
Date	1 March 2010

A Two Cohort, Open label, Single and Multiple Dose Pharmacokinetic Study of 4mg/Kg and 6mg/Kg Doses of Daptomycin in Healthy Chinese Subjects Living in China

Study dates: First subject enrolled: 20 Feb 2009
Last subject last visit: 14 March 2009

Phase of development: Clinical pharmacology (I)

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

Study centre(s)

24 subjects were recruited from one institution in China

Publications

No publication 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 characterise the pharmacokinetics and dose proportionality of daptomycin after single and multiple (once daily) 4mg/kg and 6 mg/kg doses of daptomycin in healthy Chinese volunteers	**Primary** All plasma daptomycin concentration data collected will be analysed by non-compartmental PK analysis. For each of the PK parameters, namely (but not limited to) single- and multiple-dose C_{max}, C_{min}, T_{max}, AUC, $t_{1/2}$, Vd_{ss}, Fe, CL DF, Rac and CL_r, descriptive statistics will be tabulated and presented for review and interpretation.	
Secondary To evaluate the safety and tolerability of daptomycin in healthy Chinese volunteers living in China.	**Secondary** Descriptive statistics for the safety data will be presented for collected safety parameters (incidence of AEs and SAEs, Deaths, Premature discontinuation from the study due to an AE, regardless of relationship to study medication; Vital signs).	

Study design

This is an open label, non-randomised, single and multiple dose pharmacokinetic study in healthy subjects of Chinese ethnicity. Subjects will be allocated into Cohort A and followed by Cohort B to receive daptomycin 4mg/Kg or 6 mg/Kg dissolved in 0.9% sodium chloride for injection, USP (normal saline [NS]) administered intravenously over 30 minutes on day 1 and day 4-8. An estimated 10 healthy subjects with adequate PK data will be required for analysis; any subjects with incomplete PK data will be replaced.

For Cohort A (n=12), the subjects will receive a single 4mg/Kg dose of daptomycin -on Day1. On Days 4-8 subjects receive 4mg/Kg daptomycin qd.

For Cohort B (n=12), the subjects will receive a single 6mg/Kg dose of daptomycin -on Day1. On Days 4-8 subjects receive 6mg/Kg daptomycin qd.

The investigational products will be administered over a 30-minute period by IV infusion once on Day 1 and once every 24 hours on Days 4-8.

Target subject population and sample size

Target population: healthy Chinese male or female volunteers living in China, with an age between 18 and 45 inclusive;

A sample size of 24 subjects, based on Chinese SFDA technical guideline on the pharmacokinetics study for chemical products, in which 12 subjects are required for each dosing group.

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

Daptomycin 500 mg vial; Daptomycin 4mg/kg and 6 mg/kg dissolved in 0.9% sodium chloride for injection（dose based on body weight at base-line）, administered intravenously over 30 minutes.

Batch Number: H2008-01-01-01

Duration of treatment

9 days

Statistical methods

Statistical summaries will be carried out by the bio statistical group at AstraZeneca.

All pharmacokinetic parameters, except t_{max}, will be summarized by treatment group using descriptive statistics (number [n], mean, standard deviation, minimum, median, maximum, geometric mean, and coefficient of variation [CV] percentages); t_{max} will be summarized using n, minimum, median, and maximum.

Dose proportionality will be assessed by summarizing dose-adjusted PK parameters (i.e. Cmax/dose, AUC/dose and $AUC_{(0-t)}$/dose) for each treatment group. The ratio of geometric mean PK parameters between the two dose groups will also be calculated.

Plasma concentrations of daptomycin will be summarized at each scheduled sampling time point for each treatment group. Geometric mean (+/- SD) plasma concentration vs. time plots of daptomycin will be produced for each treatment group.

AEs will be summarized at the MedDRA Preferred Term level and organized by System Organ Class. The number and percent of subjects with AEs will be displayed. SAEs will be tabulated and reviewed. AEs will be summarized also by severity and relationship to study medication.

Listings of clinical laboratory data per time point, ECG, and vital signs will be provided and values outside the normal ranges will be flagged.

Subject population

A total of 24 subjects were enrolled in the study, and all the subjects finished the study. The number of subjects in each analysis set are summarised in the **Error! Reference source not found.**. The demographic and key baseline characteristics of study subjects are summarised in the **Error! Reference source not found.**. There were no clinically important differences in the composition of the populations between the 4mg and 6mg dose groups.

Table S2 Analysis sets

	4mg/kg (N=12)	6mg/kg (N=12)	Total (N=24)
Safety Population	12(100.0%)	12(100.0%)	24(100.0%)
PK population	12(100.0%)	12(100.0%)	24(100.0%)
PK evaluable population	12(100.0%)	12(100.0%)	24(100.0%)

There is no major deviation in the study, no subjects were excluded from analysis set due to deviation, and the data from all treated subjects are included in listings and summary tables.

Summary of efficacy results

Not Applicable

Summary of pharmacokinetic results

Table S3 Summary Statistics for Pharmacokinetic Parameter Estimates for Daptomycin Analysis (Day 1) – PK Population

PK Parameter	Summary Statistics	4mg/kg	6mg/kg
Cmax	N	12	12
	GMEAN	46.66	79.67
	CV(%)	14.520	11.248
	Mean	47.10	80.10
	SD	6.697	8.047
	Median	47.10	80.60
	Min	36.8	57.6
	Max	57.5	89.1

Table S3 Summary Statistics for Pharmacokinetic Parameter Estimates for Daptomycin Analysis (Day 1) – PK Population

PK Parameter	Summary Statistics	4mg/kg	6mg/kg
AUC	N	12	12
	GMEAN	349.31	542.66
	CV(%)	20.244	11.402
	Mean	355.75	545.93
	SD	70.734	63.583
	Median	347.16	552.39
	Min	255.9	464.7
	Max	478.9	683.6
t1/2	N	12	12
	GMEAN	7.74	7.60
	CV(%)	16.774	12.924
	Mean	7.84	7.65
	SD	1.265	0.952
	Median	7.71	7.65
	Min	5.8	5.8
	Max	9.5	9.0
AUC(0-t)	N	12	12
	GMEAN	293.64	484.75
	CV(%)	25.487	10.119
	Mean	301.73	487.03
	SD	69.507	49.748
	Median	307.05	493.85
	Min	183.1	417.6
	Max	405.4	589.6
AUC(0-24)	N	12	12
	GMEAN	309.75	484.61
	CV(%)	16.911	10.141
	Mean	313.75	486.91
	SD	52.192	49.828
	Median	307.05	493.85
	Min	231.9	416.8
	Max	405.4	589.6

Table S4 Summary Statistics for Pharmacokinetic Parameter Estimates for Daptomycin Analysis (Day 8) – PK Population

PK Parameter	Summary Statistics	4mg/kg	6mg/kg
Css,max	N	12	12
	GMEAN	51.16	75.17
	CV(%)	10.510	10.408
	Mean	51.42	75.53
	SD	5.333	7.618
	Median	51.40	77.00
	Min	42.4	60.7
	Max	59.4	87.8
AUC(0-24)ss	N	12	12
	GMEAN	344.51	494.79
	CV(%)	18.135	12.269
	Mean	349.43	498.23
	SD	58.938	62.133
	Median	365.95	489.25
	Min	232.7	415.6
	Max	422.5	605.6
DF	N	12	12
	GMEAN	323.91	336.44
	CV(%)	11.198	12.062
	Mean	325.73	338.64
	SD	35.275	39.677
	Median	333.55	341.04
	Min	258.9	268.7
	Max	376.5	395.7
Rac	N	12	12
	GMEAN	1.11	1.02
	CV(%)	11.750	7.773
	Mean	1.12	1.02
	SD	0.130	0.080
	Median	1.10	1.03
	Min	0.9	0.9
	Max	1.3	1.2

The increase in the gmean C_{max} and $AUC_{(0-24)}$ following the first dose of 6mg/kg from the values for 4mg/kg was approximately 1.5-fold, this being in reasonable proportion to the 1.5-fold increase in dose.

T1/2, Tmax, CL, CLr, and Vdss of C are independent of C dose over the course of 5-day of daily dosing. The mean daily accumulation ratios at 4 and 6 mg/kg doses are 1.12 and 1.02, respectively. These results indicate that the pharmacokinetics of C are linear and stationary throughout the course of multiples dosing at both dose levels in healthy Chinese volunteers.

Summary of pharmacodynamic results

Not Applicable

Summary of pharmacokinetic/pharmacodynamic relationships

Not Applicable

Summary of pharmacogenetic results

Not Applicable

Summary of safety results

The numbers of subjects with adverse event by category are summarized in **Error! Reference source not found.**3. In total, 17 out of 24 subjects experienced a total of 28 AEs during the study. No subjects experienced SAEs. 16 subjects experienced at least an AE which were considered by the investigator to be drug-related. There was no occurrence of AEs leading to fatal outcome. The most commonly (>5%) reported drug-related AEs were abnormal pain(2 subjects, 8.3%), constipation(3 subjects, 12.5%), diarrhoea (5 subjects, 20.8%), alanine aminotransferase increased(4 subjects, 16.7%), aspartate aminotransferase increased(3 subjects, 12.5), and anorexia(2 subjects, 8.3%). The frequency of drug-related AEs did not show an increasing trends at higher doses of Cubicin. No drug-related death occurred. There were no clinically important trends found regarding vital signs and physical findings, haematology, clinical laboratory assessment and urinalysis. Only 1 subject had clinically relevant ALT elevation (above 3 X ULN) in all clinical chemistry reported as AE. Diarrhoea were reported as AEs in 5 subjects. There were no AEs reports related to ECG, including QTc prolongation according to definition in this study.

Table S5 Overview of Adverse Events
Safety Population

Variables	4mg/kg (N=12)	6mg/kg (N=12)	Total (N=24)
Number of Adverse Events	16	12	28
Number of subjects with any AE	9 (75.0)	8 (66.7)	17 (70.8)
Number of subjects with treatment related AE	9 (75.0)	7 (58.3)	16 (66.7)

Table S5 Overview of Adverse Events
Safety Population

Variables	4mg/kg (N=12)	6mg/kg (N=12)	Total (N=24)
Number of subjects with SAE (outcome=death)	0 (0.0)	0 (0.0)	0 (0.0)
Number of subjects with SAE	0 (0.0)	0 (0.0)	0 (0.0)
Number of subjects with study treatment related SAE	0 (0.0)	0 (0.0)	0 (0.0)
Number of subjects with AE leading to discontinuation	0 (0.0)	0 (0.0)	0 (0.0)