AstraZeneca

Clinical Study Report Synopsis

Drug Substance	Ceftazidime NXL104 (CAZ104)
Study Code	D4280C00010
Edition Number	1
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A Phase I, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Assess the Safety, Tolerability and Pharmacokinetics of NXL104 Alone and in Combination with Ceftazidime Administered as Single and Repeated Intravenous Doses in Healthy Japanese Subjects

Study dates: First subject enrolled: 17 February 2011
Last subject last visit: 08 April 2011

Phase of development: Clinical Pharmacology (1)

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

Study centre(s)

The study was conducted at a single site. In total, 16 healthy Japanese male subjects from ≥ 20 to ≤ 45 years of age were randomized into the study.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Primary and secondary objectives and outcome variables

Objective			Variable
Priority	**Type**	**Description**	**Description**
Primary	Safety	To investigate the safety and tolerability of single and repeated IV doses of NXL104 and NXL104 with ceftazidime in Japanese subjects.	Adverse events Laboratory variables: chemistry, hematology, and urinalysis Vital signs: Blood pressure (supine and standing), Pulse (supine and standing), Body temperature dECG/ECG: RR, PR, QRS, and QT intervals Physical examination including height and weight
Secondary	PK	To investigate the PK of single and repeated doses of NXL104 and NXL104 with ceftazidime in Japanese subjects.	Blood PK parameters: Days 1 and 7: maximum plasma concentration (C_{max}), time at maximum plasma concentration (t_{max}), plasma concentration at the last quantifiable time point (C_{last}), time at last quantifiable concentration (t_{last}), area under the concentration-time curve from predose (time 0) to t_{last} (AUC_{0-t}), area under the concentration-time curve from predose (time 0) extrapolated to infinite time (AUC), AUC from time 0 extrapolated to infinite time at steady state (AUC_{ss}), percentage of AUC extrapolated ($AUC_{\%extrap}$), AUC over the dosing interval (AUC_{tau}), the terminal elimination rate constant (λz), terminal elimination half-life ($t_{1/2}$), volume of distribution at steady state (V_{ss}), clearance (CL), mean residence time (MRT) Day 7: minimum plasma concentration during the dosing interval (C_{min}), average concentration (C_{av}), steady state clearance (CL_{ss}), accumulation ratio ($RacC_{max}$ and RacAUC) Urine PK: cumulative amount excreted into urine (Ae), percentage of cumulated urinary recovery (Fe), renal clearance (CL_R), non renal clearance (CLnr)

Table S1 Primary and secondary objectives and outcome variables

Objective			Variable
Priority	**Type**	**Description**	**Description**
	Safety	To investigate the influence of NXL104 alone or in combination with ceftazidime on intestinal bacterial flora in Japanese subjects.	Intestinal bacterial flora

Study design

This was a double-blind, placebo-controlled, parallel-group study conducted to evaluate the safety, tolerability, and pharmacokinetics (PK) of single and repeated intravenous (IV) doses of NXL104, NXL104 with ceftazidime (ie, CAZ104), or placebo to healthy male and female (non-child bearing potential) Japanese subjects.

Target subject population and sample size

Healthy male and female (of non-child bearing potential) Japanese subjects, aged 20 to 45 years, inclusive.

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

- NXL104: manufactured by MP5 supplied as a lyophilisate for concentrate for solution for infusion, 1 g vial
- Ceftazidime: manufactured by GlaxoSmithKline supplied as a sterile crystalline powder, 2 g vial
- Placebo: normal saline

Duration of treatment

Each subject was to receive a single dose of NXL104 alone, NXL104 in combination with ceftazidime, or placebo on Day 1. Repeated dosing started on Day 3 with NXL104 alone, NXL104 in combination with ceftazidime, or placebo administered every 8 hours (tid) for 4 days (Day 3 to Day 6) and a final single dose was administered on Day 7.

The total length of the study for each volunteer was approximately 42 days, including up to 28 days for screening, 9 days of in-house treatment, and the follow-up visit 3 to 5 days after the last dosing day.

Statistical methods

Descriptive summary statistics were provided for safety and PK variables. For continuous variables, the number of subjects (n), arithmetic mean, standard deviation (SD), minimum, median, and maximum were calculated (geometric mean and coefficient of variance will also be calculated for PK variables). All safety variables were listed and, as applicable, presented graphically or summarized for the observed value at each scheduled assessment and for the corresponding change from baseline.

For categorical variables, frequency distributions, including percent values, were provided. Graphical presentations were generated, where appropriate.

Subject population

In total, 16 Japanese male subjects were randomised into the study at a single site and received at least 1 administration of IP during the planned treatment visit. Although female subjects of non-child bearing potential were eligible, no females screened for the study.

All subjects completed the study with one exception; one subject (randomized to CAZ104) withdrew consent for personal reasons after receiving the morning dose of CAZ104 on Day 3. Data for this subject were used in the safety analyses and PK analyses up to the point at which he discontinued. The discontinued subject was replaced, resulting in seven subjects in the CAZ104 treatment group. There were no protocol deviations that led to exclusion of data from the PK or safety analyses. The safety and PK analyses included all randomised subjects.

Subjects in the placebo group were older than subjects in the NXL104 and CAZ104 treatment groups, and weight and BMI varied somewhat across the treatment groups. None of these differences was expected to impact the overall interpretation of safety and PK data.

Summary of pharmacokinetic results

Following a single IV administration of 500 mg NXL104 alone (Table S2), NXL104 geometric mean C_{max} was 15100 ng/mL and was achieved at the end of infusion (median 1.97 h). NXL104 geometric mean AUC was 43100 ng.h/mL. The mean half-life of NXL104, determined up to the intended administration interval for NXL104 in clinical practice (8 hours), was approximately 1.4 hours. NXL104 has a low volume of distribution (V_{ss}) with the geometric mean of 19.7 L, and the geometric mean clearance (CL) of NXL104 was 11.6 L/h after single dose (Table S2).

PK parameters after multiple dose administration of NXL104 alone were very similar to those after single dose administration of NXL104 alone. NXL104 geometric mean $C_{max\ ss}$ was 14800 ng/mL and was achieved at the end of infusion (median 1.97 h). NXL104 geometric mean AUC_{ss} was 43500 ng.hr/mL (Table S3). The mean half-life of NXL104, determined up to the intended administration interval for NXL104 in clinical practice (8 hours), was approximately 1.4 hours. The mean V_{ss} and CL of NXL104 were comparable between single and multiple doses of NXL104, with a geometric mean of 21.3 L and 12.1 L/h for multiple doses, respectively (Table S3).

Administration of a single dose of NXL104 500 mg and ceftazidime (2000 mg) did not modify the PK of NXL104 (500 mg). NXL104 geometric mean C_{max} was 15900 ng/mL and was achieved at the end of infusion (median 1.97 h) of CAZ104. NXL104 geometric mean AUC was 45500 ng.h/mL (Table S2). The mean half-life of NXL104, determined up to the intended administration interval for NXL104 in clinical practice (8 hours) was approximately 1.4 hours. Following the single dose of CAZ104, the geometric mean V_{ss} and CL of NXL104 were 18.3 L and 11.0 L/h, respectively (Table S2).

NXL104 PK parameters after multiple dose administration of NXL104 and ceftazidime were very similar to those after single or multiple dose administration of NXL104 alone. NXL104 geometric mean $C_{max\ ss}$ was 15000 ng/mL and was achieved at the end of CAZ104 infusion (median 1.97 h). NXL104 geometric mean AUC_{ss} was 43900 ng.hr/mL (Table S3). The mean half-life of NXL104, determined up to the intended administration interval for NXL104 in clinical practice (8 hours), was approximately 1.4 hours and resulted in no accumulation upon repeated administration of NXL104 alone or with ceftazidime. Following multiple doses of CAZ104, the geometric mean V_{ss} and CL of NXL104 were 19.9 L and 11.9 L/h, respectively (Table S3).

Ceftazidime administered as a single dose in combination with NXL104 or as multiple doses (every 8 hours for 5 days) did not alter the PK of ceftazidime (Table S2 and Table S3). Ceftazidime geometric mean C_{max} was 126000 ng/mL for single dose CAZ104 and ceftazidime geometric mean $C_{max\ ss}$ was 129000 ng/mL for multiple dose CAZ104. Ceftazidime geometric mean AUC was 405000 ng.h/mL for single dose CAZ104 and ceftazidime geometric mean AUC_{ss} was 431000 ng.h/mL for multiple dose CAZ104. The mean half-life of ceftazidime, determined up to the intended administration interval for CAZ104 in clinical practice (8 hours) was approximately 1.7 hours after single and multiple dose of CAZ104. Ceftazidime geometric mean volume of distribution was 10.8 L for single dose of CAZ104 and 11.6 L for multiple doses of CAZ104. Clearance of ceftazidime was comparable between single and multiple doses of CAZ104, with a geometric mean of 4.94 L/h for single dose of CAZ104 and 5.02 L/h for multiple doses of CAZ104.

The majority of NXL104 was excreted unchanged in the urine within 24 hours, following a single administration on Day 1 of NXL104 alone (mean percentage excreted: 73.2%) or in combination with ceftazidime (86.5%) (Table S4). Following multiple dose administration (Day 7), the NXL104 mean percentage excreted was 99.5% for NXL104 alone and 95.8% for CAZ104 (Table S4).

Ceftazidime 2000 mg administered by IV was extensively excreted unchanged in urine within 24 hours (mean: 103%), following a single administration of CAZ104 on Day 1 and following multiple dose administration of CAZ104 (mean Day 7: 110%) (Table S4).

Table S2 Summary of Single Dose NXL104 and Ceftazidime Plasma Pharmacokinetic Parameters from Day 1 (Pharmacokinetic Population)

Analyte	Treatment Group	Statistic	C_{max} (ng/mL)	t_{max}* (h)	AUC (ng.h/mL)	AUC_{0-t} (ng.h/mL)	$t_{1/2}$ (h)	V_{ss} (L)	CL (L/h)
NXL104	NXL104	n	6	6	6	6	6	6	6
		Geo Mean	15100	1.97	43100	42900	1.36	19.7	11.6
		GCV (%)	9.19	(1.97-1.97)	12.3	12.5	8.22	16.2	12.3
NXL104	CAZ104	n	7	7	7	7	7	7	7
		Geo Mean	15900	1.97	45500	45300	1.35	18.3	11.0
		GCV (%)	13.6	(1.97-1.97)	12.2	12.2	8.68	15.3	12.2
CEFTAZIDIME	CAZ104	n	7	7	7	7	7	7	7
		Geo Mean	126000	1.97	405000	405000	1.68	10.8	4.94
		GCV (%)	13.9	(1.97-2.25)	13.0	13.0	9.43	14.0	13.0

SD = standard deviation, Geo Mean = geometric mean.
GCV (%) = 100 x [exp (s^2)-1] $^{1/2}$, where s is the standard deviation of the data on a log scale.
* t_{max} reported as median (minimum-maximum)

Table S3 Summary of Multiple Dose NXL104 and Ceftazidime Plasma Pharmacokinetic Parameters from Day 7 (Pharmacokinetic Population)

Analyte	Treatment Group	Statistic	$C_{max\ ss}$ (ng/mL)	$t_{max\ ss}$ * (h)	AUC_{ss} (ng.h/mL)	$AUC_{0\text{-}t\ ss}$ (ng.h/mL)	$t_{1/2\ ss}$ (h)	V_{ss} (L)	CL_{ss} (L/h)	$Rac_{(Cmax)}$ [a]	$Rac_{(Auc)}$ [b]
NXL104	NXL104	n	6	6	6	6	6	6	6	6	6
		Geo Mean	14800	1.97	43500	43500	1.36	21.3	12.1	0.979	1.01
		GCV (%)	11.8	(1.97-1.97)	9.60	9.60	12.5	13.4	9.56	8.27	7.24
NXL104	CAZ104	n	6	6	6	6	6	6	6	6	6
		Geo Mean	15000	1.97	43900	43800	1.37	19.9	11.9	0.916	0.953
		GCV (%)	20.6	(1.00-1.97)	14.9	15.1	8.58	13.1	14.4	12.4	7.97
CEFTAZIDIME	CAZ104	n	6	6	6	6	6	6	6	6	6
		Geo Mean	129000	1.97	431000	431000	1.68	11.6	5.02	0.995	1.05
		GCV (%)	15.3	(1.97-1.97)	17.0	17.0	4.93	20.1	17.2	12.5	9.01
								6	6		

Day 7 data were not available for Subject 0001016 as he discontinued after Day 3 dosing.
* $t_{max\ ss}$ reported as median (minimum-maximum)
SD = standard deviation, Geo Mean = geometric mean,
GCV (%) = 100 x $[\exp(s^2)-1]^{1/2}$, where s is the SD of the data on a log scale.
Extent of accumulation on multiple dosing:
[a] $C_{max\ ss}$ Day 7 / C_{max} Day 1
[b] $AUC_{(0\text{-}24)}$ Day 7 / $AUC_{(0\text{-}24)}$ Day 1

Table S4 Summary of cumulative amount excreted (Ae), percentage of cumulated urinary recovery (Fe) and renal clearance (CL_R) for NXL104 and ceftazidime in urine (ng/mL) by cumulative interval for each treatment (Pharmacokinetic population)

Treatment Group	Analyte	Statistics	Day	Cumulative Interval (h)	Ae (mg)	Fe (%)	CL_R (L/h)
NXL104	NXL104	n	1	0 to 24	6	6	6
		Geo Mean			319	63.8	7.41
		GCV (%)			77.5	77.5	91.5
		Mean			366	73.2	8.82
		SD			147	29.5	4.03
NXL104	NXL104	n	3	0 to 24	6	6	
		Geo Mean			1190	79.5	
		GCV (%)			24.2	24.2	
		Mean			1220	81.4	
		SD			287	19.1	
NXL104	NXL104	n	7	0 to 24	6	6	
		Geo Mean			497	99.4	
		GCV (%)			5.42	5.42	
		Mean			498	99.5	
		SD			27.1	5.42	
CAZ104	NXL104	n	1	0 to 24	7	7	7
		Geo Mean			428	85.5	9.41
		GCV (%)			16.3	16.3	17.5
		Mean			432	86.5	9.53
		SD			65.4	13.1	1.58
CAZ104	NXL104	n	3	0 to 24	6	6	
		Geo Mean			1180	78.5	
		GCV (%)			11.2	11.2	
		Mean			1180	78.9	
		SD			132	8.81	
CAZ104	NXL104	n	7	0 to 24	6	6	
		Geo Mean			475	95.0	
		GCV (%)			14.4	14.4	
		Mean			479	95.8	
		SD			64.5	12.9	
CAZ104	CEFTAZIDIME	n	1	0 to 24	7	7	7
		Geo Mean			2050	102	5.05
		GCV (%)			14.1	14.1	14.0
		Mean			2060	103	5.09
		SD			280	14.0	0.717
CAZ104	CEFTAZIDIME	n	3	0 to 24	6	6	
		Geo Mean			5170	86.2	
		GCV (%)			8.42	8.42	
		Mean			5190	86.5	
		SD			449	7.48	
CAZ104	CEFTAZIDIME	n	7	0 to 24	6	6	
		Geo Mean			2210	110	
		GCV (%)			4.39	4.39	
		Mean			2210	110	
		SD			96.2	4.81	

SD = standard deviation, Geo Mean = geometric mean.
GCV (%) = 100 x $[\exp(s^2)-1]^{1/2}$, where s is the standard deviation of the data on a log scale.

Pre-dose geometric mean NXL104 concentrations on Day 5 and 7 following TID dosing (Day 3 to 6) were 614 and 616 ng/mL, respectively, for NXL104 administered alone, and 544 and 461 ng/mL, respectively, for NXL104 following administration of CAZ104. By 8 hours following the last dose on Day 7, geometric mean concentrations were 482 and 466 ng/mL for NXL104 administered alone and NXL104 following administration of CAZ104, respectively.

Overall, the observed trough or similar trough concentrations are comparable across study days. The NXL104 and ceftazidime concentrations at 2 and 4 hours post dose on Day 1, 3, 5, and 7 are also in general comparable, indicating no time influence on PK of CAZ104 and ceftazidime.

Summary of safety results

There were no AEs with an outcome of death, SAEs, AEs that led to withdrawal from the study, or other significant AEs (OAEs) during the single dose period. One AE of orthostatic tachycardia was experienced by a single subject in the NXL104 treatment group during the single dose period of the study. The event, which was considered mild in severity and related to the IP, started approximately 8 hours after the start of dosing on Day 1 and resolved spontaneously by Day 10.

Three subjects experienced a total of eight AEs during the multiple dose period. All were considered mild in severity, and all but one AE of contact dermatitis were considered related to the IP.

Two subjects (33.3%) who received NXL104 alone experienced a total of seven AEs, including transaminases increased, infusion site extravasation, infusion site thrombosis, chest discomfort, dyspnoea, and palpitations. The AE of chest discomfort was not associated with an abnormal ECG or significant vital signs changes. One subject (14.3%) who received CAZ104 experienced a single AE of orthostatic hypotension.

No deaths, SAEs, or AEs leading to discontinuation from the study occurred during the multiple dose period of the study. Only the AE of increase in transaminases for one subject was identified as an OAE. One subject randomized to NXL104 exhibited elevated transaminases, alkaline phosphatase and total bilirubin on Day 5, Day 7, and/or Day 8 of the study. At the scheduled Follow-up Visit (3 days after the last dose of IP), the subject's transaminase levels had trended lower but were not yet normalized. The subject was asymptomatic during the time period of liver function test elevations, and no concomitant medications were taken during the study. All other laboratory test results for this subject were within clinically acceptable limits. The transaminases increased was considered mild in severity and related to the IP.

The events of transaminases increased and infusion site thrombosis, experienced by the same subject had not resolved by the end of the study; however, there was substantial decrease in the extent of transaminase elevation. The subject was lost to follow-up as he did not return to the clinical unit for further evaluation. All other AEs experienced by subjects resolved spontaneously by the end of the study.

No other clinically significant individual chemistry, hematology or urinalysis laboratory values were identified for any of the subjects. Mean chemistry and hematology laboratory values occasionally fell slightly outside of the reference ranges but remained within acceptable limits during the study. Increases in mean ALT, AST, and GGT values were seen for the NXL104 group beginning on Day 5 and were attributable to values measured in a single subject. No other differences in mean chemistry and hematology values were identified across treatment groups over time.

Variations in mean supine and standing vital signs were similar across the treatment groups. Two subjects (one subject in the NXL104 treatment group and one subject in the CAZ104 treatment group) experienced a total of three AEs related to vital signs including orthostatic tachycardia, palpitations, and orthostatic hypotension. All events were considered mild in severity and resolved spontaneously by the end of the study.

None of the subjects experienced clinically significant abnormalities in resting ECG data at any time point. There were no AEs related to ECG measurements. A summary of mean change from baseline values for ECG parameters (RR, PR, QRS, QT, and QTcF) showed comparable values for all treatments. There were no clinically relevant changes over time. None of the subjects had a QTcF greater than 450 ms or a change from baseline > 30 ms.

There were no clinically significant findings on physical examinations.

There were no clinically relevant trends observed for mean log ratio scores for aerobic and anaerobic bacterial flora for NXL104.