AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD9773
Study Code	D0620C00005
Edition Number	1
Date	10 September 2012

A Phase II, Multicentre, Randomised, Double-Blind, Placebo-Controlled, Dose Escalation Study to Assess the Safety, Tolerability and Pharmacokinetics of Intravenous Infusions of AZD9773 in Japanese Patients with Severe Sepsis and/or Septic Shock

Study dates: First patient enrolled: 25 July 2010
Last patient last visit: 22 August 2011

Phase of development: II

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

Publications

None at the time of writing of this report.

Objectives and criteria for evaluation

Table S1 shows the study objectives and variables.

Table S1 Study objectives and variables

Objective			Variable
Priority	**Type**	**Description**	**Description**
Primary	Safety	To assess the safety and tolerability of AZD9773 in Japanese patients with severe sepsis and/or septic shock	Incidence and nature of TEAEs, incidence and nature of serious TEAEs, TEAEs leading to discontinuation of study treatment, and deaths; 12-lead ECG; vital signs (blood pressure, pulse, body temperature, respiratory rate); oximetry; laboratory variables (haematology, clinical chemistry, coagulation, urinalysis); physical examination; and other safety monitoring (ADA IgG, ADA bridging assay, and nAB)
Primary	PK	To assess the PK of AZD9773 in Japanese patients with severe sepsis and/or septic shock	Blood and urine samples: AZD9773 serum concentrations, AZD9773 total and specific Fabs serum concentrations; AZD9773 total and specific Fabs concentrations in urine. PK parameters for AZD9773 total and specific Fabs: AUC_{0-t}, AUC_{τ}, C_{max}, $C_{max, ss}$, $C_{min,ss}$ accumulation ratio, CL_R, and percentage of drug recovered in urine.
Secondary	PD	To make a preliminary assessment of the PD of 2 different doses of AZD9773 in Japanese patients with severe sepsis and/or septic shock	TNFα, IL-6, and IL-8
Exploratory	General assessment of sepsis care	To obtain a preliminary information on clinical outcomes in Japanese patients with severe sepsis and/or septic shock	28-day mortality, APACHE II scores, Glasgow Coma Score, SOFA score, pulmonary assessment and ventilator use, organ failure assessment, lactate; septic shock, infection assessment, antibiotic use, assessment of ICU-free days, and daily volume status

ADA antidrug antibody; APACHE Acute Physiology and Chronic Health Evaluation; AUC_{0-t} area under serum concentration-time curve; AUC_{τ} AUC during a dosing interval; CL_R renal clearance, C_{max} maximum serum concentration; $C_{max, ss}$ maximum serum concentration at steady state; $C_{mi, ss}$ minimum concentration at steady state; ECG electrocardiogram; ICU intensive care unit; Ig immunoglobulin; IL interleukin; nAB neutralising antibody; PD pharmacodynamics; PK pharmacokinetics; TEAE treatment-emergent adverse event; TNFα tumour necrosis factor alpha; SOFA Sequential Organ Failure Assessment.

.

Study design

This was a Phase II, multicentre, randomised, double-blind, placebo-controlled, dose escalation study to assess the safety, tolerability, PK, and PD of multiple IV infusions of 2 different doses of AZD9773 in Japanese patients with severe sepsis and/or septic shock.

The study consisted of 2 successive cohorts, with a total of 20 patients planned (10 patients per cohort). Prior to enrolment, patients were evaluated by the Clinical Co-ordinating Centre to ensure the study entry criteria were met. Central randomisation was by an interactive voice response system to allocate patients to treatment groups within each cohort (AZD9773: 7 patients, placebo: 3 patients).

To allow evaluation of data by a Safety Review Committee and an Independent Data Monitoring Committee, a minimum of 4:1 (AZD9773: placebo) completers who received at least 6 doses and who were alive for at least 7 days after their last dose, for each cohort, was required. If the number of cohort-completers did not reach the criteria after the originally planned 10 patients were enrolled in a cohort, additional patients were enrolled until at least 4 AZZD9773 patients and at least 1 placebo patient had completed the cohort.

Target subject population and sample size

The target population for the study was adult Japanese patients with objective clinical evidence of infection requiring administration of parenteral antibiotics and with severe sepsis and/or septic shock. Patients had to meet the criteria for systemic inflammatory response syndrome and have cardiovascular and/or respiratory failure. The number of patients was chosen to obtain sufficient safety and PK data while exposing as few patients as possible to AZD9773.

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

Study treatments, in masked administration bags to maintain the blind, were as follows:

- AZD9773 250 units/kg (1 infusion) + 50 units/kg (9 infusions) once every 12±2 hours (AZD9773 Cohort 1)
- AZD9773 500 units/kg (1 infusion) + 100 units/kg (9 infusions) once every 12±2 hours (AZD9773 Cohort 2)
- Placebo as saline solution (0.9% sodium chloride) administered as IV infusions in an equivalent volume to the active treatment with the same regimen and at the same times as noted for AZD9773 Dose Cohorts 1 and 2.

The manufacturer batch numbers for investigational product used in this study were BN200829E and BN200829E-2.

Duration of treatment

A total of 10 doses (loading dose followed by 9 maintenance doses) of AZD9773 or placebo was administered, 1 dose every 12 hours (+/- 2 hours) over 30 minutes. Depending on the start day and time of the first dose, dosing was continued until Day 5 or Day 6.

Statistical methods

Outcome variables for clinical outcomes (general assessment of sepsis) and safety were summarised by cohort and treatment using descriptive statistics, as appropriate. PK parameters were derived using non-compartmental methods. Both serum concentration data and PK parameters were summarised using descriptive statistics for each analyte. PD data were summarised by cohort and treatment using descriptive statistics.

Subject population

A total of 20 Japanese patients with severe sepsis and/or septic shock (9 males and 11 females who ranged from 58 to 98 years of age [mean age 75.4 years]) were enrolled in the study and randomised to treatment. There were 14 patients in total in AZD9773 Cohort 1 and Cohort 2 (7 in each) and 6 in the placebo group. The demographic and baseline disease characteristics of patients were generally well balanced across the treatment cohorts.

Summary of efficacy results

Patients in the AZD9773 and placebo cohorts had similar clinical outcomes in terms of ventilator-free days (VFDs) over 28 days, SOFA score to Day 5/6, the proportion of patients with resolution of organ failure and the rate of resolution of organ failure over 28 days, the number of patients with septic shock over 28 days, and the number of ICU-free days to Day 15. There was a small numerical difference across the cohorts for 28-day mortality in favour of the AZD9773 cohort (1 of 7 patients died in AZD9773 Cohort 1, no patient died in AZD9773 Cohort 2, and 2 of 6 patients died in the placebo cohort).

Summary of pharmacokinetic results

Overall exposure in terms of C_{max} and AUC increased with increasing dose in an approximately dose-proportional manner for both total and specific Fabs, although there was large inter-patient variability.

Since serum PK samples were taken up to 12 hours post-dose, it was not possible to accurately calculate the terminal half-life from this PK dataset. However, following multiple dosing, the mean dose-normalised accumulation ratio ranged from 1.91 to 1.96 across the AZD9773 cohorts, and the mean half-life calculated from the accumulation ratio for total Fabs was approximately 22.5 hours for AZD9773 Cohort 1 and 23.5 hours for AZD9773 Cohort 2. There was no evidence of a change in half-life with dose.

Across the dose levels there appeared to be no change in the percentage of dose excreted (23.8% to 31.6%) with dose, or a change between single and multiple dosing. These findings indicate that renal elimination did play an important role in the clearance of AZD9773, although the majority of AZD9773 is likely cleared through the reticuloendothelial system. In

urine, the percentage of dose excreted for total and specific Fabs after the loading dose ranged from 26.3% to 28.6% for AZD9773 Cohort 1 and 25.6% to 29.5% for AZD9773 Cohort 2.

In AZD9773 Cohort 2, patient E0004002, no increase in serum concentrations of AZD9773 was observed after the final maintenance dose. In this patient, dialysis was instituted from 13:30 on 9 March 2011 to 18:10 on 15 March 2011. The loading infusion was given from 19:30 to 20:00 on 9 March 2011, and the last maintenance infusion was given from 10:00 to 10:30 on 14 March 2011. Therefore, all infusion of AZD9773 occurred during dialysis. However, serum AZD9773 concentrations were increased after the loading infusion, but were not increased after the last maintenance infusion. The reason for this difference in serum AZD9773 concentrations between the loading infusion and the maintenance infusion is unknown. This patient was excluded from the PK analysis summaries as no PK parameters could be calculated.

Summary of pharmacodynamic results

A general trend for a decrease in TNFα levels with time was observed in all 3 cohorts.

TNFα appeared to be more suppressed following dosing with the higher dose of AZD9773 (500 units single dose followed by 100 units/kg) compared to patients receiving the lower dose of AZD9773 (250 units single dose followed by 50 units/kg) or those receiving placebo.

IL-6 and IL-8 levels were variable throughout the study period, with a general decrease observed over time in all cohorts.

Summary of pharmacokinetic/pharmacodynamic relationships

Not applicable.

Summary of pharmacogenetic results

Not applicable

Summary of safety results

The median duration of exposure to study treatment was similar across the cohorts. Median unit compliance was 100% for the AZD9773 cohorts. No overdoses were reported.

Table S2 provides an overview of TEAEs during the study.

Table S2 Overview of TEAEs: Safety analysis set

	Number (%) of patients							
	AZD9773							
	Cohort 1 (N=7)		Cohort 2 (N=7)		Combined (N=14)		Placebo (N=6)	
	n (%)	E	n (%)	E	n (%)	E	n (%)	E
Any TEAE	7 (100.0)	83	7 (100.0)	82	14 (100.0)	165	6 (100.0)	36
Any TEAE possibly related to investigational product	5 (71.4)	8	0	0	5 (35.7)	8	2 (33.3)	2
TEAE with outcome of death	1 (14.3)	1	0	0	1 (7.1)	1	0	0
TEAE with outcome of death possibly related to investigational product[a]	0	0	0	0	0	0	0	0
At least 1 severe TEAE	3 (42.9)	3	5 (71.4)	16	8 (57.1)	19	1 (16.7)	2
At least 1 severe TEAE possibly related to investigational product[a]	1 (14.3)	1	0	0	1 (7.1)	1	0	0
At least 1 serious TEAE	4 (57.1)	4	1 (14.3)	2	5 (35.7)	6	1 (16.7)	1
At least 1 serious TEAE possibly related to investigational product[a]	1 (14.3)	1	0	0	1 (7.1)	1	0	0
At least 1 TEAE leading to permanent discontinuation from investigational product	0	0	0	0	0	0	0	0
At least 1 TEAE leading to permanent discontinuation from investigational product possibly related to investigational product[a]	0	0	0	0	0	0	0	0
At least 1 other significant TEAE	7 (100.0)	21	5 (71.4)	24	12 (85.7)	45	6 (100.0)	13
At least 1 investigator reported infusion reaction[b]	1 (14.3)	1	0	0	1 (7.1)	1	1 (16.7)	1
At least 1 investigator reported hypersensitivity reaction[a]	2 (28.6)	2	0	0	2 (14.3)	2	1 (16.7)	1

[a] As determined by the investigator
[b] As determined by Study Team Physician review before database lock.
AZD9773 Cohort 1 received 250 units/kg (1 infusion) + 50 units/kg (9 infusions) once every 12±2 hours.
AZD9773 Cohort 2 received 500 units/kg (1 infusion) + 100 units/kg (9 infusions) once every 12±2 hours.
E episode level, (total number of TEAEs); N number of patients in group; n number of patients with data; TEAE treatment-emergent adverse event.

The most frequently reported TEAEs in the combined AZD9773 cohorts by PT were ‘pleural effusion’ (9 patients, 64.3%) and oedema-related TEAEs (9 patients, 64.3%), which included preferred terms of 'generalised oedema', 'peripheral oedema' and 'oedema'. The majority of these events were reported in patients with pre-existing underlying disease, which could provide an alternative explanation for the events. In the placebo group, ‘diarrhoea’ was the most frequently reported TEAE (3 patients, 50%). No patient in the placebo group had a TEAE of ’pleural effusion’ or an oedema-related event. There was no apparent increase in the incidence of TEAEs with increasing dose of AZD9773.

A number of potential safety concerns for AZD9773 were defined as 'other significant TEAEs' prior to the start of the study. These included risks associated with the target (ie, suppression of TNFα), including secondary infections, malignancies, demyelination, and congestive heart failure, as well as potential risks associated with infusion of a heterologous sheep protein, including hypersensitivity reactions, secondary infection, and the occurrence of any ovine zoonoses. There was no evidence to support an association with these types of events and AZD9773 in this study. There was no difference in trends between the AZD9773 cohorts and the placebo group with regards to the laboratory results, vital signs, or ECGs.