AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD9773
Study Code	D0620C00003
Edition Number	1
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A Multicentre, Randomised, Double Blind, Placebo controlled Phase IIb Study to Compare the Efficacy and Safety of Two Dosing Regimens of Intravenous Infusions of CytoFab™ (AZD9773) in Adult Patients With Severe Sepsis and/or Septic Shock

Study dates: First patient enrolled: 21 October 2010
Last patient last visit: 23 May 2012

Phase of development: IIb

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	Efficacy	To evaluate the effect of 2 different doses of AZD9773 versus placebo on VFDs over 28 days	Number of VFDs over a 28-day period
Secondary	Efficacy	To evaluate the effect of 2 different doses of AZD9773 versus placebo on mortality and morbidity, as well as the HRQoL of sepsis survivors	Mortality at Day 7, 29, and 90; VFDs over 14 days, shock-free days through Day 14, organ failure-free days through Day 14, hospitalisation length of stay at Day 29, ICU length of stay at Day 29, ICU free days through Day 14, Modified SOFA scores (including Glasgow Coma Score); APACHE II score; ventilator use and pulmonary assessment; organ failure assessment; SF-36v2 - Physical Component Score, Mental Component Score, and Item 2 responses for the SF-36 questionnaire at Day 29 and Day 90.
Secondary	PK	To determine the population PK of AZD9773 via sparse sampling and to assess the relationship between PK and measures of PD response, efficacy, and AEs	Serum concentrations of AZD9773 specific Fabs and total Fabs
Secondary	PD	To evaluate the effect of 2 different doses of AZD9773 versus placebo on the biological effect on plasma TNFα levels and relevant cytokines and chemokines	Cytokines: serum TNFα, IL-6, and IL-8
Secondary	Safety	To evaluate the effect of 2 different doses of AZD9773 versus placebo on safety and tolerability	TEAEs, deaths, serious TEAEs, permanent discontinuation of study treatment due to TEAE, other significant TEAEs; clinical laboratory tests; vital signs, physical examination, and ECG; and other safety monitoring (ADAs and, nABs)

ADA antidrug antibody; AE adverse event; APACHE Acute Physiology and Chronic Health Evaluation; ECG electrocardiogram; Fab fragment of immunoglobulin produced by papain treatment; HRQoL health-related quality of life; ICU intensive care unit; IL interleukin; nAB neutralising antibody; PD pharmacodynamics; PK pharmacokinetics;

SF-36v2 Short Form – 36, version 2; SOFA Sequential Organ Failure Assessment; TEAE treatment-emergent adverse event; TNFα tumour necrosis factor alpha; VFD ventilator-free day.

Study design

This was a randomised, double blind, placebo controlled, international, multicentre, Phase IIb study evaluating the efficacy and safety of multiple IV infusions of AZD9773 in patients with acute severe sepsis and/or septic shock.

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 in a 1:1:1 ratio to receive AZD9773 250/50 units/kg, AZD9773 500/100 units/kg, or placebo.

An Independent Data Monitoring Committee was convened when 100 patients reached Day 29 to review safety assessments and make recommendations to continue or stop the study on the basis of safety findings.

Target subject population and sample size

The target population was adult patients with severe sepsis and/or septic shock who had objective clinical evidence of infection, met the criteria for systemic inflammatory response syndrome (SIRS), and had cardiovascular and/or respiratory failure. Approximately 300 patients were to be entered into the study.

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 IV infusion) + 50 units/kg (9 IV infusions) once every 12±2 hours (AZD9773 Dose 1)
- AZD9773 500 units/kg (1 IV infusion) + 100 units/kg (9 IV infusions) once every 12±2 hours (AZD9773 Dose 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 Doses 1 and 2.

The manufacturer batch numbers for AZD9773 IP used in this study were 10-004645AZ, WK90553.003, WK90553.007, 10-004895AZ, WK90553.006, 10-004895AZ, WK90553.002, 10-004846AZ, and WK90553.009.

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

The following efficacy endpoints were subject to formal statistical analysis: VFDs over 28 days, VFDs at Day 15, mortality at Day 7, mortality at Day 29, mortality at Day 90, organ failure-free days at Day 15, shock-free days at Day 15, and ICU-free days at Day 15. All other data were summarised.

For each of the efficacy endpoints that were subject to formal analyses the following statistical comparisons were performed: AZD9773 dose 1 versus placebo, AZD9773 dose 2 versus placebo, and combined AZD9773 dose arms 1 and 2 versus placebo. All patients taking AZD9773 dose 1 or dose 2 were included in the combined AZD9773 dose group. Although there were 3 primary comparisons, this was an exploratory Phase IIb study and consequently no adjustment for multiple comparisons was made.

For the formal statistical analysis, between-treatment comparisons of the number of VFDs (over 28 days) were performed using an analysis of covariance with treatment as a fixed effect and adjusting for the following baseline covariates: APACHE II score, age, geographic region and mechanical ventilation at baseline.

The analysis of the primary endpoint was performed using both the intention-to-treat (ITT) analysis set and the per protocol (PP) analysis set as co-primary analyses. A sensitivity analysis was performed using a modified ITT analysis set. An additional sensitivity analysis based on a modified definition of the primary endpoint was performed using the ITT analysis set. For the secondary efficacy endpoints, analyses were performed using both the ITT and PP analysis sets.

When a substantial deviation from normality was detected, non-parametric analysis techniques were used in addition to the ANCOVA analysis.

Subject population

Table S2 presents a summary of the study patient population.

Table S2 Patient population

	AZD9773				
	Dose 1	**Dose 2**	**Combined**	**Placebo**	**Total**
Disposition					
Patients enrolled n					307
Patients randomised n (%)	100 (33.3)	100 (33.3)	200 (66.7)	100 (33.3)	300 (97.7)
Patients not randomised n					7
Patients who received treatment n (%)	99 (99.0)	98 (98.0)	197 (98.5)	99 (99.0)	296 (98.7)
Patients who completed treatment n (%)	69 (69.0)	85 (85.0)	154 (77.0)	78 (78.0)	232 (77.3)

Table S2 Patient population

		AZD9773				
		Dose 1	**Dose 2**	**Combined**	**Placebo**	**Total**
Analysis sets						
Patients in ITT analysis set n		100	100	200	100	300
Patients included PP analysis set n		92	89	181	94	275
Patients in safety analysis set n		100	97	197	99	296
Demographic characteristics						
Age at screening (years)	Mean	64.4	66.6	65.5	64.1	65.0
	Range	21-88	28-88	21-88	21-87	21-88
Sex n (%)	Male	60 (60.0)	60 (60.0)	120 (60.0)	68 (68.0)	188 (62.7)
	Female	40 (40.0)	40 (40.0)	80 (40.0)	32 (32.0)	112 (37.3)
Race n (%)	Caucasian/White	96 (96.0)	93 (93.0)	189 (94.5)	97 (97.0)	286 (95.3)
	Black/African American	0	1 (1.0)	1 (0.5)	3 (3.0)	4 (1.3)
	Asian	2 (2.0)	3 (3.0)	5 (2.5)	0	5 (1.7)
	Native Hawaiian/Pacific Islander	1 (1.0)	1 (1.0)	2 (1.0)	0	2 (0.7)
	American Indian/Alaska Native	0	0	0	0	0
	Other	1 (1.0)	2 (2.0)	3 (1.5)	0	3 (1.0)

ITT intention to treat; n number of patients with data; PP per protocol

Summary of efficacy results

Primary endpoint

The mean number of VFDs over 28 days was similar across the treatment groups (16.2 for AZD9773 Dose 1 (250/50) group, 14.0 for AZD9773 Dose 2 (500/100) group, and 14.6 for the placebo group. There was no statistically significant difference in the primary endpoint of VFDs over 28 days for either of the AZD9773 doses studies versus placebo.

The results of the adjusted analysis of VFDs over 28 days for patients in the ITT analysis set, performed using ANCOVA with baseline APACHE II score, age at informed consent, geographic region, and baseline mechanical ventilation as covariates and treatment as a fixed effect, showed a difference in LSMeans (SE) of 1.4 (1.51) (80% CI of difference in LSMean of -0.5, 3.30), with a 1-sided p-value of 0.178 for the comparison of AZD9773 Dose 1 (250/50) vs placebo. For the comparison between AZD9773 Dose 2 (500/100) vs placebo, the difference in LSMeans (SE) was -1.0 (1.50) (80% CI of -2.9, 0.9), with a 1-sided p-value of

0.744. The results of the analysis for the PP analysis set are consistent with the results for the ITT analysis set.

Because a substantial deviation from normality was detected, non-parametric analysis techniques were used as a sensitivity analysis in addition to the ANCOVA analysis. Results of the non-parametric analysis of VFDs over 28 days using median values were consistent with the results using the ANCOVA analysis.

Secondary endpoints

For the secondary endpoint of 28-day all-cause mortality (versus placebo), there was a numerical difference of -5% for AZD9773 Dose 1 (250/50), +7% for AZD9773 Dose 2 (500/100), and +1% for the AZD9773 combined doses.

For the secondary endpoints of VFDs, shock-free days, ICU-free days, and organ-failure-free days measured over 14 days there were small numerical increases in the number of days in the AZD9773 Dose 1 (250/50) treatment group when compared with the placebo group, and small numerical decreases in the number of days were observed in the AZD9773 Dose 2 (500/100) treatment group when compared with the placebo group.

Subgroup analyses

Exploratory subgroup analyses were performed to investigate the effect that the baseline covariates and other potential prognostic factors had on the treatment effect. Small numerical differences were observed and considered to be chance findings given the number of tests performed, the small patient numbers, and the low mortality rate. For the primary endpoint of VFDs over 28 days there was no evidence of a subgroup effect, as all 80% confidence interval (CIs) included 0 days. For the secondary endpoint of mortality, the 80% CIs did not include a relative risk of 1 in a small number of baseline subgroups tested (ie, in the quartile of patients with the lowest APACHE II scores, in the quartile of patients with the lowest TNFα levels; in patients with both cardiovascular and pulmonary organ failure, and male gender). For all cases, the observed effect favoured placebo and not AZD9773. However, many subgroup analyses were performed without any adjustments for multiplicity, and the observed effects for APACHE II and TNFα were not consistent across the quartiles.

Summary of pharmacokinetic results

There was a clear increase in exposure with AZD9773 Dose 2 (500/100) compared with AZD9773 Dose 1 (250/50), with the geometric mean for concentration data approximately double with the higher AZD9773 dose at each timepoint. The percentage of specific Fabs exposure as a ratio to total Fabs appeared to be consistent with the batches of investigational product (IP) used for in study (~5%).

Summary of pharmacodynamic results

Treatment with AZD9773 appears to reduce circulating TNFα. The difference in TNF-α AUC_{0-120} hours between the AZD9773 treatment groups and placebo group was statistically significant (P<0.001).

There was no indication of a dose-response in terms of TNFα pharmacodynamics between the AZD9773 Dose 1 (250/50) and Dose 2 (500/100) treatment groups.

Summary of pharmacokinetic/pharmacodynamic relationships

Not applicable.

Summary of pharmacogenetic results

Not applicable

Summary of patient-reported outcomes

Patients treated with AZD9773 had comparable health-related quality of life results to placebo, as measured by the Physical Component Score, Mental Component Score, and Item 2 responses for the SF-36 questionnaire at Day 29 and Day 90. Small numerical improvements in these scores were observed at Day 90 compared to Day 29 in all 3 treatment groups.

Summary of safety results

Exposure for AZD9773 was in proportion to the dose administered. Compliance with study treatments and the number of infusions administered was comparable across the treatment groups.

Table S3 provides an overview of TEAEs during the study.

Table S3 Overview of TEAEs: Safety analysis set

	AZD9773							
	Dose 1 (N=100)		Dose 2 (N=97)		Combined (N=197)		Placebo (N=99)	
	n (%)	E	n (%)	E	n (%)	E	n (%)	E
Any TEAE	86 (86.0)	469	87 (89.7)	410	173 (87.8)	879	92 (92.9)	491
Any TEAE possibly related to IP	16 (16.0)	26	12 (12.4)	22	28 (14.2)	48	14 (14.1)	30
TEAE with outcome of death	9 (9.0)	9	15 (15.5)	16	24 (12.2)	25	12 (12.1)	14
TEAE with outcome of death possibly related to IP	3 (3.0)	3	1 (1.0)	1	4 (2.0)	4	2 (2.0)	2
At least 1 severe TEAE	31 (31.0)	45	25 (25.8)	53	56 (28.4)	98	36 (36.4)	67
At least 1 severe TEAE possibly related to IP	6 (6.0)	7	2 (2.1)	4	8 (4.1)	11	5 (5.1)	7
At least 1 serious TEAE	28 (28.0)	30	27 (27.8)	42	55 (27.9)	72	31 (31.3)	42

Table S3 Overview of TEAEs: Safety analysis set

	AZD9773							
	Dose 1 (N=100)		Dose 2 (N=97)		Combined (N=197)		Placebo (N=99)	
	n (%)	E	n (%)	E	n (%)	E	n (%)	E
At least 1 serious TEAE possibly related to IP	6 (6.0)	7	2 (2.1)	2	8 (4.1)	9	4 (4.0)	4
At least 1 TEAE leading to permanent discontinuation from IP	0	0	0	0	0	0	1 (1.0)	1
At least 1 TEAE leading to permanent discontinuation from investigational product possibly related to IP	0	0	0	0	0	0	0	0
At least 1 other significant TEAE	46 (46.0)	100	49 (50.5)	91	95 (48.2)	191	44 (44.4)	88
At least 1 investigator reported infusion reaction	1 (1.0)	1	3 (3.1)	4	4 (2.0)	5	2 (2.0)	2
At least 1 investigator reported hypersensitivity reaction	0	0	2 (2.1)	2	2 (1.0)	2	1 (1.0)	1

Patients with multiple events in the same category are counted only once in that category. Multiple events in the same category are counted multiple times in that category.
TEAEs are adverse events that were not present at baseline or worsened in severity following the start of treatment.
E number of events; IP Investigational Product; N number of patients in group; n number of patients with data; MedDRA Medical Dictionary for Regulatory Activities; TEAE treatment-emergent adverse event.
Dose 1 = AZD9773 250/50 units/kg and Dose 2 = AZD9773 500/100 units/kg.

AZD9773 appeared to be well-tolerated with a low frequency of hypersensitivity and/or infusion reaction events. This study also included immunogenicity assessments by measuring for ADAs to determine the potential of AZD9773 to provoke an immune response in patients and the degree and nature of the immune response elicited. Overall, the immunogenicity potential of AZD9773 appears to be low, and there was no apparent association with the development of ADAs and hypersensitivity-type events.

There was no evidence of any dose-related safety observations for patients receiving AZD9773. There were no apparent trends with regards to change from baseline for laboratory or vital sign parameters over time between the AZD9773 treatment groups compared with the placebo group. Consistent with previous preclinical and clinical studies with AZD9773, there was no indication of drug-induced liver injury and no apparent association with QT prolongation or ECG abnormalities.