AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD9773
Study Code	D0620C00004
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A Placebo-controlled, Double-blind, Dose-escalation Study to Assess the Safety, Tolerability, and Pharmacokinetics and Pharmacodynamics of Single and Multiple Intravenous Infusions of CytoFab™ (AZD9773) in Patients With Severe Sepsis

Study dates: First patient enrolled: 18 January 2008
Last patient last visit: 30 July 2009

Phase of development: IIa

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

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Study centres

The study was conducted at 27 centres in the United States of America. Seventeen centres treated patients. The first patient was enrolled on 18 January 2008 and the last patient had their last visit on 30 July 2009.

Publications

None at the time of writing this report.

Objectives

The primary objective of this study was to characterise the safety and tolerability of AZD9773 in patients with severe sepsis.

The secondary objectives of the study were:

To determine the range of acceptable and tolerable infusion rate regimens for use in subsequent studies

To make a preliminary assessment of the pharmacokinetics (PK) and pharmacodynamics (PD) of AZD9773.

Study design

This was a first-in-man, double-blind, placebo-controlled, multi-centre, dose escalation study to assess the safety, tolerability, PK and PD of single and multiple intravenous (iv) infusions of AZD9773 in patients with severe sepsis. A Safety Review Committee and an Independent Data Monitoring Committee monitored the study.

Target population and sample size

The target population for the study comprised adult patients with severe sepsis who had clinical evidence of infection requiring treatment with parenteral antibiotics, met the criteria for systemic inflammatory response syndrome (SIRS), and had a cardiovascular and/or respiratory dysfunction. The sample size was based on practical requirements rather than any formal sample size justification. The number of patients was chosen so as to obtain sufficient safety and PK data to progress the compound whilst exposing as few patients as possible to AZD9773.

Investigational product and comparator: dosage, mode of administration and batch numbers´

Table S1 Details of investigational product

	Investigational product
Drug product	AZD9773 (CytoFab)
Active component	AZD9773 (rh TNFα immune Fab [ovine] produced using IgG chromatographic isolation, papain digestion, ultrafiltration, and ion exchange chromatography)
Strength, form	5000 units of AZD9773 lyophilised powder/vial for reconstitution in saline and further dilution in saline for iv infusion (dose dependent on cohort)
Dosage	Units AZD9773/dose was dependant on cohort
Excipients	Di-sodium hydrogen phosphate, USP, Ph Eur Sodium chloride, USP, Ph Eur
Manufacturer	Protherics
Manufacturer batch number	CT0713 (2000112812, 2000114963, 2000115379, 2000115565, 2000117281,09-001920AZ) and CT0806 (2000116561)

Abbreviations: Ig = immunoglobulin; iv = intravenous = rh = recombinant human; TNF = tumour necrosis factor.

The study was performed in a double-blind manner. The patient, the investigator and study centre staff were blinded to study drug allocation. Only the study centre pharmacist was unblinded to study drug. The pharmacist prepared AZD9773 or placebo for a patient as specified by the randomisation scheme and the interactive voice recognition system (IVRS) (pharmacists called into the IVRS to obtain the randomisation/treatment allocation details). All samples were blinded using an opaque masking sleeve fastened with tamper-evident tape over the iv bag prior to dispensing to other study personnel to maintain the double-blind conditions.

The placebo was a physiological saline solution (0.9% sodium chloride) administered as an iv infusion in an equivalent volume to the active treatment.

Duration of treatment

Patients were sequentially recruited into 2 single-dose cohorts:

- cohort 1 - single infusion of 50 units AZD9773/kg or placebo
- cohort 2 - single infusion of 250 units AZD9773/kg or placebo

and 3 multiple-dose cohorts:

- cohort 3 - single loading infusion of 250 units AZD9773/kg or placebo followed by 50 units AZD9773/kg or placebo for 9 maintenance doses every 12 hours
- cohort 4 - single loading infusion of 500 units AZD9773/kg or placebo followed by 100 units AZD9773/kg or placebo for 9 maintenance doses every 12 hours
- cohort 5 - single loading infusion of 750 units AZD9773/kg or placebo followed by 250 units AZD9773/kg or placebo for 9 maintenance doses every 12 hours

After a 2-day screen period (-48 to 0 hours), treatment was allocated via the IVRS in a 2:1 ratio (AZD9773:placebo). Patients were followed-up until Day 28.

Criteria for evaluation – efficacy, PD and PK (main variables)

General assessment of sepsis care

- Sequential Organ Failure Assessment (SOFA) score
- Daily volume status
- Ventilator use and pulmonary assessment
- Organ failure assessment
- Infection assessment
- Time to first administration of antibiotics

Criteria for evaluation - safety (main variables)

The following standard assessments were done: adverse events (AEs)/serious AEs (SAEs), laboratory safety data, vital signs, 12-lead electrocardiogram (ECG), physical examination, 28-day mortality, human anti-sheep antibody (HASA) measured as both total HASA and immunoglobulin (Ig) G-specific HASA.

Pharmacokinetics

The PK of both AZD9773 specific Fabs and AZD9773 total Fabs (recombinant human tumour necrosis factor alpha [TNFα] immune Fab and all other non-TNF-directed Fabs present in AZD9773) were assessed by measurement of serum and urine concentrations and derivation, where the data allowed, for standard PK parameters.

Pharmacodynamics

- Serum TNFα, interleukin (IL)-6
- Procalcitonin

- Lactate

Statistical methods

For outcome variables related to PK, PD, general assessment of sepsis and safety, no single variable was considered primary. Standard descriptive statistics and graphs were used to summarise the data. All data were summarised according to treatment received. For placebo patients, data were pooled across the cohorts.

Results

Subject population

Of the 73 patients enrolled into the study, 71 were randomised and 70 received study drug, 47 patients in total in AZD9773 cohorts 1 to 5 and 23 in the placebo group. Overall, 59 patients (83.1%) completed study drug, 39 patients in AZD9773 cohorts 1 to 5 and 20 patients in the placebo group. Four patients (5.6% overall) discontinued study drug prematurely due to an AE and 4 patients (5.6% overall) discontinued study drug prematurely due to death. Three patients overall (4.2%) discontinued study drug for reasons other than death or an AE.

Baseline demographic and disease characteristics were generally well balanced across the cohorts and were representative of patients with sepsis and/or septic shock.

Course of sepsis

The study investigated the course of sepsis in terms of mortality, ventilator-free days (VFDs), number of days alive and shock-free, organ failure assessment, and SOFA score. There are no statistically powered analyses because the study was not sized to detect any differences in these endpoints; consequently, these data should be considered descriptive only.

The incidence of death at Day 28 was 2 patients (25.0%) in AZD9773 cohort 1, 4 patients (44.4%) in AZD9773 cohort 2, 5 patients (41.7%) in AZD9773 cohort 3, 1 patient (10.0%) in AZD9773 cohort 4, 1 patient (12.5%) in AZD9773 cohort 5 and 6 patients (26.1%) in the placebo group.

The median number of VFDs to Day 28 (defined as the number of days from the end of the last period of assisted breathing to Day 28) was 22.5 (range: 0 to 26) in AZD9773 cohort 1, 13.0 (range: 0 to 26) in AZD9773 cohort 2, 8.0 (range: 0 to 28) in AZD9773 cohort 3, 19.0 (range: 0 to 26) in AZD9773 cohort 4, 19.5 (range: 0 to 26) in AZD9773 cohort 5 and 19.0 (range: 0 to 28) in the placebo group.

Median SOFA scores at baseline were similar across cohorts; the highest median score was in AZD9773 cohort 4 (12.5; range: 7 to 14) and the lowest median score was in AZD9773 cohort 3 (10.0; range: 6 to 16). Generally, in each cohort the median score decreased at each timepoint to Day 7 as the number of patients in each cohort decreased. Total organ failure resolution rate was 4 patients (50.0%) in AZD9773 cohort 1, 4 patients (44.4%) in AZD9773 cohort 2, 6 patients (50.0%) in AZD9773 cohort 3, 8 patients (80.0%) in AZD9773

cohort 4, 5 patients (62.5%) in AZD9773 cohort 5 and 14 patients (60.9%) in the placebo group.

Summary of safety results

Median unit compliance (defined as total exposure (units/kg) / planned exposure (units/kg) x 100) was ≥94.7% for all cohorts. An overview of treatment-emergent AEs (TEAEs) during the study is shown in Table S2.

Table S2 Overview of adverse events: Safety analysis set

	AZD9773 cohort 1 (50 units/kg) (N = 8)		AZD9773 cohort 2 (250 units/kg) (N = 9)		AZD9773 cohort 3 (250/50 units/kg) (N = 12)		AZD9773 cohort 4 (500/100 units/kg) (N = 10)		AZD9773 cohort 5 (750/250 units/kg) (N = 8)		Placebo (N = 23)	
	n (%)	**E**	**n (%)**	**E**	**n (%)**	**E**	**n (%)**	**E**	**n (%)**	**E**	**n (%)**	**E**
Any TEAE	8 (100.0)	61	9 (100.0)	67	12 (100.0)	69	8 (80.0)	74	7 (87.5)	67	23 (100.0)	217
Death	2 (25.0)	2	4 (44.4)	5[a]	5 (41.7)	5	1 (10.0)	1	1 (12.5)	1	6 (26.1)	6
At least one severe TEAE	3 (37.5)	3	5 (55.6)	9	6 (50.0)	7	2 (20.0)	3	3 (37.5)	5	14 (60.9)	19
At least one serious TEAE	3 (37.5)	4	6 (66.7)	8	7 (58.3)	9	3 (30.0)	6	4 (50.0)	4	13 (56.5)	18
At least one TEAE possibly related to study drug[b]	0	0	2 (22.2)	3	2 (16.7)	7	3 (30.0)	12	2 (25.0)	4	10 (43.5)	21
At least one TEAE leading to withdrawal from study drug	0	0	1 (11.1)	1	2 (16.7)	2	0	0	0	0	1 (4.3)	1
At least one infusion reaction[c]	1 (12.5)	1	4 (44.4)	8	1 (8.3)	1	2 (20.0)	2	1 (12.5)	1	3 (13.0)	4
At least one hypersensitivity reaction[b]	0	0	1 (11.1)	1	0	0	1 (10.0)	1	1 (12.5)	1	1 (4.3)	1

[a] Patient E0135004 experienced 2 TEAEs where the outcome was given as death.
[b] As determined by the investigator.
[c] As determined by Study Team Physician review prior to database lock.
Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories.
E= episode level; N = number of patients in group; n = number of patients with data; TEAE = treatment-emergent adverse event.

Generally, TEAEs by both system organ class and preferred term were distributed evenly between cohorts with no clear patterns or differences between cohorts.

There was an increased incidence of TEAEs of hypoglycaemia in AZD9773 cohorts 4 (4/10 patients [40%]) and 5 (3/8 patients [37.5%]) compared to the other AZD9773 cohorts (1/8 patients [12.5%], 1/9 patients [11.1%] and 1/12 patients [8.3%] in AZD9773 cohorts 1, 2 and 3, respectively) and placebo (2/23 patients, 8.7%). All reported TEAEs of hypoglycaemia were considered mild or moderate in intensity and all resolved. There was no pattern to the onset of the events. Although there was an increased incidence of reported TEAEs of hypoglycaemia in AZD9773 cohorts 4 and 5, there was no apparent difference in laboratory assessments of glucose levels. The percentage of patients who experienced hypoglycaemia of Common Terminology Criteria (CTC) grade 1 or 2 in AZD9773 cohorts 1, 2, 3, 4, 5 and the placebo group was 28.6%, 22.2%, 18.2%, 22.2%, 14.3% and 36.4% respectively. There were no patients who had glucose laboratory values of CTC grade 3 or 4. Although there was an increased incidence of reported hypoglycaemic TEAEs in AZD9773 cohorts 4 and 5, the events were heavily confounded by the patients' medical histories, underlying disease processes and concomitant medications and therefore at this time hypoglycaemia is not considered to be associated with AZD9773 treatment.

There was also an increased incidence of TEAEs of generalised oedema. Nine cases occurred in patients on AZD9773 and 3 cases occurred in placebo group patients. These patients were characterised by having a significantly positive fluid balance; many had concomitant renal or cardiac disease; and all had a low serum albumin around the time of the AE.

Hypernatraemia was identified as occurring more frequently in patients who received AZD9773. Sodium counts of >150 mmol/L were confined to AZD9773 cohorts 3 and 4 and the placebo group. In all cases, elevated counts were short-lived and occurred at varying times from pre-first dose to Day 7. Except for 1 patient, who died on Day 4, the sodium values all normalised while drug administration was continued. Excluding 1 patient, whose value was high pre-dose, there were 4 patients on AZD9773 with values >150 mmol/L and 2 patients on placebo. All patients had confounding factors that could contribute to hypernatraemia. It is not apparent that there is a causal association with AZD9773 administration.

There were a number of potential safety concerns identified prior to the start of the study based on the administration of an exogenous protein and based on safety concerns associated with other anti-TNFα agents. These potential concerns include hypersensitivity, immunogenicity and secondary infection. Significant AEs including AEs suggestive of congestive cardiac failure, worsening or secondary infections, demyeliniation events, development of auto-antibodies, renal events of significance, skin events of significance and events related to bleeding or a risk of bleeding were reviewed by a minimum of 2 Study Team Physicians, prior to database lock and formal unblinding of the study, and were included if they were biologically plausible events related to the above categories. These events were included for particular review because, either they have been seen with the use of other anti-TNFα agents, they are associated with the infusion of heterologous proteins or, in the case

of bleeding, because it was expected a that number of patients would be co-administered anti-coagulants, heparins and Xigris. The incidence, severity and seriousness of such events were comparable across all of the cohorts.

Overall in the study the number, type, onset and severity of TEAEs of infection was comparable between the AZD9773 cohorts and the pooled placebo group: 50.0%, 33.3%, 50.0%, 20.0%, 50.0% and 43.5% of patients in the AZD9773 cohorts 1, 2, 3, 4 and 5 and the pooled placebo group respectively experienced at least 1 TEAE of infection.

A review of the individual patient profiles for vital signs and each laboratory parameter was undertaken. For vital signs and most laboratory parameters the majority of patients were outside the reference range (of healthy patients), both at baseline and throughout the course of the study. An assessment of the data showed changes within many individual patients for many parameters. However, there was no clear evidence that the pattern of results differed in the AZD9773 cohorts compared to the placebo group (changes within the AZD9773 cohorts generally fell within the range of changes seen in the placebo group) and there was a general trend of an improvement over time in vital signs and the laboratory parameters. Furthermore, there was no apparent effect of increasing exposure to AZD9773 on laboratory parameters. Consequently it is felt that the changes seen may be consistent with the disease under study.

Total HASA, as measured by the bridging assay, was found to be positive post-exposure to AZD9773 in 1 patient in cohort 3 and 5 patients in cohort 4, and undetected in the remainder of the cohorts. HASA IgG was measured and found to be positive post-dosing with AZD9773 in 2 patients in cohort 3, 3 patients in cohort 4 and 2 patients in cohort 5.

Many of the patients included in this study had labile cardiovascular parameters as a result of sepsis, and a number of patients had underlying cardiac disease. Patients with QT with Fredericia correction (QTcF) prolongation, or those receiving medication that could affect the QT interval corrected for heart rate (QTc), were not excluded from enrolment. As a result the data were highly variable and this was likely due to the clinical instability of the underlying disease process or concomitant medications and the small sample size of patients in this study. There was a lack of an apparent dose response relationship or an observed QTcF effect both with single or multiple dosing, and no discernible effect of AZD9773 on QTcF evaluation.

Summary of pharmacokinetic results

Exposure to AZD9773 total and specific Fabs was demonstrated in all patients after dosing at 50 to 750 units/kg. Overall exposure in terms of area under the curve increased with increasing dose in an approximately dose proportional manner for both total and specific Fabs.

The shapes of the plasma concentration-time curves for AZD9773 were similar for both the total and specific Fabs and for each of the dose levels. Apparent clearance (mean: 6 mL/min/kg to 8 mL/min/kg), apparent volume of distribution (mean: 90 mL/kg to 150 mL/kg) and half-life (approximately 20 hours) were similar for total and specific Fabs in the 2 single dose AZD9773 cohorts.

The use of loading doses followed by 12-hourly maintenance doses resulted in steady state being reached after 4 maintenance doses for both total and specific Fabs.

AZD9773 total and specific Fabs were excreted in the urine. The urinary clearance accounted for 1/4 to 1/3 of the total clearance.

Summary of pharmacodynamic results

A single administration of 50 units/kg of AZD9773 had barely discernible effects on circulating levels of TNFα. A single dose of 250 units/kg of AZD9773 rapidly (within 2 hours) reduced circulating TNFα levels where they were raised at baseline to levels that were close to the limit of quantification of the assay. TNFα levels began to rise after about 12 hours by about which time, circulating AZD9773 concentrations were approximately 10-20% of the maximum concentration achieved at the end of infusion. In multiple-dose cohorts, a loading dose (250 units/kg in cohort 3, 500 units/kg in cohort 4 and 750 units/kg in cohort 5) followed by 9 injections every 12 hours (50 units/kg in cohort 3, 100 units/kg in cohort 4 and 250 units/kg in cohort 5) resulted in the immediate suppression of TNFα levels by the loading dose and, during the period of multiple injections, circulating TNFα was maintained at low levels in the majority of patients. Following cessation of treatment, TNFα levels began to rise in most patients in the multiple-dose cohorts. In AZD9773 cohort 5, TNFα levels remained low in 2 patients after treatment was stopped. The variability of TNFα levels out to Day 5 was observed to be less than in the placebo-treated patients, further evidence that the effect of AZD9773 on circulating TNFα was real.

IL-6 levels were higher than TNFα, were even more variable, and declined over the course of a severe sepsis episode in all cohorts. There were no obvious differences between individual AZD9773 cohorts and placebo.