AstraZeneca

Revised Clinical Study Protocol	
Drug Substance	AZD9773
Study Code	D0620C00003
Edition Number	1
Date	[redacted]

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

Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden.

AstraZeneca Research and Development site representative

[redacted]

The following Amendment(s) and Administrative Changes are included in this revised protocol:

Amendment No.	Date of Amendment	Local Amendment No.	Date of local Amendment
1	[redacted]		

Administrative change No.	Date of Administrative Change	Local Administrative change No.	Date of local Administrative Change
1	[redacted]		

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AstraZeneca

PROTOCOL SYNOPSIS

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

Details of all sites, investigators and related study personnel will be documented in the study central files.

[redacted]

PAREXEL is responsible for all aspects of study management, monitoring, medical monitoring, data management, statistical analysis and report writing under supervision of AstraZeneca as documented in the relevant agreements between PAREXEL and AstraZeneca.

International Co-ordinating Investigator

The signatory co-ordinating investigator for the Clinical Study Report will be designated by AstraZeneca.

[redacted]

Study period

Estimated date of first patient enrolled

Estimated date of last patient completed

[redacted]

Phase of development

Phase IIb

[redacted]

Objectives

The primary objective is to evaluate the effect of two different doses of AZD9773 (CytoFab™) versus placebo on ventilator-free days (VFDs) over 28 days in patients with severe sepsis and/or septic shock, who are receiving appropriate standard of care.

The secondary objectives are to evaluate the effect of two different doses of AZD9773 versus placebo in patients with severe sepsis and/or septic shock on the following:

1. 7-day and 28-day mortality.
2. Safety and tolerability.
3. Morbidity (VFDs at Day 15 [over 14 days]), organ function, shock, intensive care unit (ICU) – length of stay, ICU-free days, hospitalisation.
4. Mortality at Day 90.
5. Health-related Quality of Life (HRQoL) of sepsis survivors at Day 29 and Day 90.
6. The biological effect on plasma tumour necrosis factor alfa (TNFα) levels and relevant cytokines and chemokines.
7. To explore the predictive characteristics of selected biomarkers on outcome parameters.
8. To determine the population pharmacokinetics (PK) of AZD9773 via sparse sampling and to assess the relationship between PK and measures of pharmacodynamic (PD) response, efficacy and adverse events (AEs) in patients with severe sepsis and/or septic shock.

Study design

This is a randomised, double-blind, placebo-controlled, international multicentre Phase IIb study evaluating the efficacy and safety of multiple intravenous (iv) infusions of AZD9773 in patients with acute severe sepsis and/or septic shock (within 24 hours of an organ failure).

The study will randomise approximately 300 patients (100 patients per treatment arm).

Blood samples for genetic and/or biomarker research will be collected in those patients who provide written informed consent for this purpose.

Target patient population

The target population for the study comprises adult patients with severe sepsis and/or septic shock (within 24 hours of an organ failure) who have objective clinical evidence of infection. They must meet the criteria for systemic inflammatory response syndrome (SIRS), and have cardiovascular and/or respiratory failure (see Table 2).

Investigational product, dosage and mode of administration and duration of treatment

AZD9773: lyophilised powder for solution for iv infusion containing a specified number of units of AZD9773. AZD9773 is reconstituted with saline and diluted in saline solution to the required volume for administration.

AZD9773 is a [redacted]

AZD9773 is [redacted]

Study drug (blinded using an opaque sleeve, fastened with tamper-evident tape over the iv bag prior to dispensing) is administered by iv infusion as:

AZD9773 250/50 units/kg (Dose arm 1):

Single iv loading infusion of 250 units AZD9773 per kg body weight (maximum 25000 units) diluted to a volume of 250 mL over 30 minutes followed by 50 units AZD9773 per kg body weight (as measured as close as possible to the first dose but within 24 hours before the first dose) diluted to a volume of 100 mL over 30 minutes once every 12±2 hours for up to a maximum of 9 iv maintenance doses (maximum 5000 units each).

AZD9773 500/100 units/kg (Dose arm 2):

Single iv loading infusion of 500 units AZD9773 per kg body weight (maximum 50000 units) diluted to a volume of 250 mL over 30 minutes followed by 100 units AZD9773 per kg body weight (as measured as close as possible to the first dose but within 24 hours before the first dose) diluted to a volume of 100 mL over 30 minutes once every 12±2 hours for up to a maximum of 9 iv maintenance doses (maximum 10000 units each).

Placebo:

Placebo will be saline solution (0.9% sodium chloride) administered as iv infusions in an equivalent volume to the active treatment (volume of 250 mL for the loading dose and 100 mL for maintenance doses) with the same regimen and at the same times as noted for Dose arms 1 and 2.

Duration of treatment

Up to a maximum of 10 doses (a loading dose followed by up to a maximum of 9 maintenance doses) of blinded study drug will be administered, one dose every 12±2 hours.

For details on monitoring requirements during dosing, dosing interval adjustments, and procedures in case of missed doses, see Section 4.1.

Safety Review and Independent Data Monitoring Committee

An Independent Data Monitoring Committee (IDMC) will be convened and will meet once 100 patients have reached Day 29 to review safety assessments and make recommendations to continue or stop the study based on safety findings. Serious Adverse Events (SAEs), AEs and mortality rates will be reviewed and individual and aggregated safety data will be evaluated by the IDMC. Full details of the IDMC procedures and processes can be found in the IDMC Charter.

Efficacy

- Primary outcome variable:
  - VFDs over 28 days.
- Secondary outcome variables:
  - 7-day mortality.
  - 28-day mortality.
  - Time to death.
  - Mortality at Day 90.
  - VFDs at Day 15 (over 14 days).
  - Shock-free days at Day 15 (over 14 days).
  - Organ failure-free days at Day 15 (over 14 days).
  - Hospitalisation.
  - ICU - length of stay at Day 29.
  - ICU-free days at Day 15 (over 14 days) and at Day 29.
  - Short Form - 36 Health Survey, version 2 Acute (SF-36v2 Acute) - Domain score summaries (Physical Health and Mental Health) plus individual scales Physical Functioning and Bodily Pain measured at Day 29 and Day 90.

Pharmacokinetic

- Sampling will be done for PK assessments in this study. Full details of the population PK and PK-PD analysis will be given in the Pharmacokinetic Analysis Plan. Results will be reported in a separate report.

[redacted]

Pharmacodynamic

- Cytokines: serum TNFα, interleukin (IL)-6, and IL-8, multiplex assay for exploratory chemokines, neutralising antibody assay.

General assessment of sepsis, organ function and sepsis care

- Modified Sequential Organ Failure Assessment (SOFA) score.
- Glasgow Coma Score.
- Volume of iv fluids in the 24 hours prior to randomisation.
- Assessment of renal function and injury by plasma renal panel for exploratory analysis.
- Procalcitonin.
- Lactate.
- Infection assessment at study entry and any subsequent infection during the study. (The site of infection at screening should be noted. All patients must have a blood culture prior to randomisation. The blood culture result does NOT have to be known prior to randomisation.)
- Time to study drug administration (relative to qualifying organ failure).
- Time of initial antibiotic dose relative to the qualifying organ failure.
- Time of initial antibiotic dose from point of care for infection causing the septic episode.

Safety

- AEs, SAEs, deaths.
- Laboratory safety assessments: haematology, clinical chemistry, coagulation parameters, and safety monitoring (troponin I, protein C activity, human anti-sheep antibody [HASA] IgG, total HASA bridging assay and IgE); urinalysis.
- Vitals signs and oximetry.
- 12-lead electrocardiogram (ECG).

Timing of analysis

All study data will be analysed after the 28-day follow up is complete for all patients. A further analysis will be performed using the Day 90 assessment to understand longer-term patient outcomes (survival and HRQoL).

Statistical methods

The sample size has been based on the primary outcome variable of VFDs over 28 days. The Phase IIb study in 81 patients with D-CytoFab has been used as an estimate of the between patient standard deviation (SD) (11.380). Assuming this SD holds for the current study, then 100 patients per group will provide 90% power to detect an underlying true difference in means between a dose of AZD9773 and placebo of 4.2 VFDs using a 10% one-sided significance level. Given this is an exploratory Phase IIb study, a 10% one-sided significance level is considered appropriate as this implies a 1 in 10 chance of a false positive finding which is consistent with the aim in Phase II of identifying a promising therapy.

The following efficacy endpoints will be subjected to formal statistical analysis: VFDs over 28 days and at Day 15 (over 14 days), 7-day mortality, 28-day mortality, mortality at Day 90, organ failure-free days at Day 15 (over 14 days), shock-free days at Day 15 (over 14 days) and ICU-free days at Day 15 (over 14 days). All other data will only be summarised.

All efficacy data will be summarised and analysed using the per protocol (PP) population (including only patients without important detected protocol deviations affecting the efficacy endpoints; data will be considered according to the actual treatment first received). Additionally, an intention-to-treat (ITT) analysis of the endpoints listed above for formal analysis will also be undertaken using the ITT population (all randomised patients will be included and data will be considered according to the randomised treatment).

For each of the endpoints subject to statistical analysis the following statistical comparisons will be performed: AZD9773 dose arm 1 versus placebo, AZD9773 dose arm 2 versus placebo, and combined AZD9773 dose arms 1 and 2 versus placebo. Although there are three primary comparisons, this is an exploratory Phase II study and consequently no adjustment for multiple comparisons will be made. The nominal significance level used will be 10% one-sided. However, it is important to note that the study has only been sized based on VFDs over 28 days; this study is not powered to detect a statistically significant difference in 7-day mortality, 28-day mortality or mortality at Day 90. In this case the confidence intervals (CIs) will provide a guide to the possible range of the true treatment effect. This may also be the case for the other secondary endpoints.

For the formal statistical analysis of all endpoints apart from mortality, an analysis of covariance model will be fitted allowing for treatment group and the following baseline covariates: Acute Physiology and Chronic Health Evaluation (APACHE) II score (4 categories based on the quartiles of the baseline score), age (2 categories: <60, ≥ 60), region (3 categories: Australia, North America [Canada & USA] and All Other) and an indicator variable if the patient was on mechanical ventilation at baseline (2 categories: yes or no). The

difference for each of the comparisons will be presented in terms of the difference in the Least Square Means (LSMeans) and the associated two-sided 80% CI and one-sided p-value. Additionally, a two-sided 95% CI and two-sided p-value will be presented.

In terms of these endpoints for the PP population, the effect of other baseline variables (examples include baseline TNFα, Xigris use prior to study treatment and presence of shock at baseline) on the treatment comparisons will also be explored via a series of analyses including the covariates as specified above for each of the levels of these baseline variables separately. The difference in the treatment LSMeans and the associated two-sided 80% CIs estimated for each level of the covariates will be presented graphically on the same plot. Additionally, an analysis of variance will also be performed for the PP and ITT populations (with no covariates and only treatment as a factor).

The formal analysis of 7-day mortality, 28-day mortality and mortality at Day 90 will be undertaken for each of the treatment comparisons separately using a Cochran-Mantel-Haenszel test in which the test will be stratified on the basis of the same covariates as for VFDs. The corresponding relative risk, the associated two-sided 80% CIs and one-sided p-value will be calculated using the procedure PROC FREQ in SAS. Additionally, a two-sided 95% CI and two-sided p-value will be presented. An unstratified analysis will also be performed for the PP and ITT populations. Additionally, for the PP population the impact of other baseline variables (examples include baseline TNFα, Xigris® use prior to study treatment and presence of shock at baseline) on the treatment comparisons will also be explored by undertaking a series of analyses for each of the levels of these baseline variables separately. The relative risks for the treatment comparisons along with the associated two-sided 80% CIs from these analyses will be presented graphically. A Kaplan-Meier curve of time to death will also be produced and both a stratified (using the same covariates as for the analysis of 28-day mortality) and unstratified log rank test will be undertaken.

Demography data will be summarised using the PP and ITT populations while safety data will be summarised using the safety population (all patients who start an infusion of study drug will be included and summarised according to the actual treatment first received). Safety and tolerability will be assessed in terms of AEs, SAEs, deaths, laboratory data, vital signs data and ECG data. AEs will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent AEs (events which were not present at baseline or worsened in severity following the start of treatment) will be summarised.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study protocol.

Abbreviation or special term	Explanation
AE	Adverse Event (see definition in Section 7.3.1)
APACHE	Acute Physiology and Chronic Health Evaluation
apTT	Activated Partial Thromboplastin Time
AZD9773	AZD9773 refers to the active constituent of CytoFab™, ie, rhTNFα immune Fab (ovine) produced using[redacted] It does not refer to any rhTNFα immune Fab (ovine), but only that produced by the manufacturing process outlined above.
AZD9773 Total Fabs	Rh TNFα immune Fab and all other non-TNF-directed Fabs present in CytoFab™
BP	Blood Pressure
CCC	Clinical Co-ordinating Centre
CI	Confidence Interval
CRO	Contract Research Organisation
CSA	Clinical Study Agreement
CytoFab™	Medicinal product to be used in this study and planned for use in future studies and commercial supply. CytoFab™ is a sterile lyophilised powder for solution for intravenous infusion containing a specified number of units of AZD9773
D-CytoFab	Development-CytoFab. Material used in previously conducted Phase I and II studies in sepsis ([redacted]
DNA	Deoxyribonucleic Acid
ECG	Electrocardiogram
ELISA	Enzyme-linked Immunosorbent Assay
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
ECRF	Electronic Case Report Form
ERT	eResearch Technology
Fab	Fragment of immunoglobulin produced by papain treatment
FiO_2	Fraction of Inspired Oxygen
GCP	Good Clinical Practice

[redacted]

Abbreviation or special term	Explanation
GMP	Good Manufacturing Practice
HASA	Human Anti-Sheep Antibody
HCG	Human Chorionic Gonadotropin
HIV	Human immunodeficiency virus
HR	Heart Rate
HRQoL	Health-related Quality of Life
IB	Investigator Brochure
ICH	International Conference on Harmonisation
ICU	Intensive Care Unit
IDMC	Independent Data Monitoring Committee
Ig	Immunoglobulin
IL	Interleukin
International Co-ordinating investigator	If a study is conducted in several countries the International Co-ordinating Investigator is the Investigator co-ordinating the investigators and/or activities internationally.
IP	Investigational Product
ITT	Intention-to-treat
IU	International Unit
iv	Intravenous(ly)
IVRS	Interactive Voice Response System
LIMS	Laboratory Information Management System
LOCF	Last Observation Carried Forward
LSMeans	Least Square Means
MedDRA	Medical Dictionary for Regulatory Activities
Neutralising antibody (NAB) assay	Determination of NABs to TNFα in the presence of diluted human serum from patients previously dosed with AZD9773, by reference to a standard curve of AZD9773
OAE	Other Significant Adverse Event (ie, adverse events of particular clinical importance, other than SAEs and those AEs leading to discontinuation of the patient from study treatment; see definition in Section 12.1.1
$PaCO_2$	Partial Pressure of Arterial Carbon Dioxide
PaO_2	Partial Pressure of Arterial Oxygen
PD	Pharmacodynamic
PGx	Pharmacogenetics

Abbreviation or special term	Explanation
PK	Pharmacokinetic
PR	Pulse Rate
PRO	Patient Reported Outcome
PP	Per Protocol
PT	Prothrombin Time
QTcB	QT with Bazett correction
QTcF	QT with Fridericia correction
rh	Recombinant Human
RR	Respiratory Rate
SAE	Serious Adverse Event (see definition in Section 7.3.2).
SAP	Statistical Analysis Plan
SD	Standard Deviation
SF-36v2 Acute	Short Form 36 Health Survey, Version 2 Acute
SIRS	Systemic Inflammatory Response Syndrome
SOC	System Organ Class
SOFA	Sequential Organ Failure Assessment
SpO_2	Oxygen Saturation by Pulse Oximetry
TEAE	Treatment-Emergent Adverse Event
TNFα	Tumour Necrosis Factor alfa
USA	United States of America
VFD	Ventilator-Free Day
WBC	White Blood Cell
WBDC	Web Based Data Capture
WD	Withdrawal

1. IMPORTANT MEDICAL PROCEDURES TO BE FOLLOWED BY THE INVESTIGATOR

1.1 Medical emergencies and AstraZeneca contacts

The international co-ordinating investigator is responsible for ensuring that procedures and expertise are available to handle medical emergencies during the study. **A medical emergency usually constitutes a serious adverse event (SAE) and is to be reported as detailed in Section 7.3.4.**

Procedures for managing infusion reactions are described in Appendix D.

In the case of a medical emergency the investigator may contact the Medical Monitor. If the Medical Monitor is not available, contact the Study Delivery Team Physician at AstraZeneca Research and Development.

Name	Role in the study	Address & telephone number
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Name	Role in the study	Address & telephone number
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

1.2 Overdose

The definition of overdose for study drug in this study is a dose equal to or exceeding 750 units/kg body weight. **NOTE:** There is no known antidote to AZD9773 and the Clinical Co-ordinating Center (CCC) or the Medical Monitor should be contacted with any concerns. In the event of an overdose, the following reporting requirements should be adhered to and sent to PAREXEL:

- An overdose with associated SAEs should be recorded as the SAE diagnosis/symptoms on the relevant adverse event (AE) forms in the electronic case report form (eCRF) and on the Overdose eCRF module.
- An overdose with associated non-serious AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the eCRF and on the Overdose eCRF module.
- An overdose without associated symptoms should only be reported on the Overdose eCRF module.

Symptoms resulting from an overdose should be treated as the patient's medical condition indicates.

1.3 Pregnancy

The outcomes of any conception occurring from the date of the first dose until 90 days after the last dose and must be followed-up and documented.

All outcomes of pregnancy must be reported to PAREXEL.

1.3.1 Maternal exposure

Patients with a positive pregnancy test (except for post-partum) will be discontinued from study treatment (see Section 5.4.1).

Pregnancy itself is not regarded as an AE unless there is a suspicion that the investigational product (IP) under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be reported as AEs. The outcome of all pregnancies (spontaneous miscarriage, ectopic pregnancy, elective termination, normal birth or congenital abnormality) must be followed up and documented even if the patient was discontinued from the study.

Female patients must refrain from becoming pregnant during the study treatment period and **three** months following the last dose, since the potential effects on the developing foetus are unknown.

If any pregnancy occurs in the course of the study, then investigators or other site personnel will inform appropriate AstraZeneca representatives immediately but no later than the end of the next business day. The designated AstraZeneca representative, together with the investigator, will ensure that all relevant information is provided to the appropriate AstraZeneca Clinical Patient Safety data entry site within 30 calendar days.

The PREGREP module in the eCRF will be used to report the pregnancy and related information, including expected delivery date and details of previous pregnancies. Information relating to the pregnancy outcome will be reported on the "AstraZeneca Pregnancy Outcome Report" via fax.

1.3.2 Paternal exposure

Male patients must refrain from fathering a child during the study and **three** months following the last dose, since the potential for chromosomal aberrations in male gametes, and possible teratogenic effects thereof, are unknown.

Pregnancy of the patient's partner is not considered to be an AE. However, if possible, the outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) will be followed-up and documented as per International Conference on Harmonisation (ICH)/Good Clinical Practice (GCP) guidance (see Section 1.3.1 above).

2. INTRODUCTION

2.1 Background

2.1.1 Sepsis

Sepsis is a life-threatening disorder that arises through the body's response to infection. It is a complex clinical syndrome that may occur in any age group, and in response to a multitude of microbial pathogens or inflammatory conditions, from multiple different anatomical sites within the body. According to current understanding, the critical pathophysiological trigger is a disturbance in the equilibrium between the pro-inflammatory and anti-inflammatory responses to infection (Marshall 2003).

Severe sepsis and/or septic shock is an important cause of morbidity and mortality in hospitalised patients despite the establishment of specialised critical care units, the availability of broad-spectrum antimicrobial agents, and advancement in the management of inter-current conditions that put patients at risk for the development of severe sepsis and/or septic shock. Indeed, the incidence of severe sepsis and/or septic shock continues to increase, probably due to the overall aging of the general population, the increasing use of invasive procedures and aggressive cancer chemotherapies, and the increase in antibiotic resistance. Despite medical progress, mortality rates remain unacceptably high, and consequently there is an urgent medical need to develop an efficacious treatment in sepsis.

Current therapy for sepsis includes eradication of the infection (eg, using antibiotics and, where appropriate, surgical intervention), resuscitation and restoration of tissue perfusion, restoration of adequate oxygen delivery, and renal replacement therapy. Drotrecogin alfa (activated) recombinant human (rh) activated protein C (Xigris®, Eli Lilly and Company) has been approved in the USA and European Union (EU) for the treatment of adult patients with severe sepsis and at a high risk of death.

The release of cytokines into the circulation is an essential part of the inflammatory cascade that underlies sepsis. Experimental and clinical data have shown that the pro-inflammatory cytokine tumour necrosis factor-α (TNFα) is a principal initiator of this cascade (Balk and Bone 1989, Bone et al 1989). TNFα is the first cytokine to be released by macrophages in response to infection (van der Poll and van Deventer 1999), and once in the circulation, it causes systemic inflammation through stimulating the widespread release of "downstream" cytokines such as interleukin (IL)-6 and IL-8 in uninfected tissues (Thijs and Hack 1995). Given its important role as an early mediator in the inflammatory response, TNFα is an appropriate target for the treatment of sepsis.

2.1.2 AZD9773 (CytoFab™)

AZD9773 (CytoFab™) is a [redacted]

[redacted]

AZD9773 is [redacted]

Other anti-TNF approaches have been evaluated in sepsis. The potential advantages of AZD9773 over previously tested agents designed to neutralise TNFα are:

- Unlike monoclonal antibodies, AZD9773 is a polyclonal product that can bind to more than one domain of TNFα (Nelson et al 2000) to enhance TNF neutralisation.
- Being an antibody Fab fragment rather than an intact antibody, AZD9773 is small and may penetrate into tissues (eg, in the lung) where TNFα can reside and mediate an inflammatory response (Covell et al 1986, Schaumann et al 1986, Rice et al 2006)
- In contrast to intact antibodies against TNFα that are cleared over days to weeks, AZD9773 is cleared more rapidly and has a shorter half-life (approximately 20 hours).
- Unlike TNF-soluble receptors, AZD9773 has a high affinity for TNFα.

Prior to the development of AZD9773, a related form of this drug product (D-CytoFab) has been investigated in clinical studies. Phase I and II studies using D-CytoFab have indicated a potential therapeutic benefit of treating patients with severe sepsis with polyclonal ovine Fab fragments targeted against TNFα (see Section 2.1.4). Since the conduct of these studies with D-CytoFab, significant manufacturing changes have been introduced in order to ensure quality and to enable increased production for further study and commercialisation of the drug product. The key modification has been [redacted] s not believed to present an increased safety concern. This view is based upon long history of safe use of many antisera derived from animals, eg, Crofab, and the nonclinical assessment of AZD9773 (see Section 2.1.3). Most importantly, the safety and tolerability of AZD9773 has been evaluated in patients with severe sepsis over a wide range of doses in a recent IIa study (D0620C00004).

Further information on AZD9773 and D-CytoFab is provided in the current investigator brochure (IB).

2.1.3 Nonclinical studies

For information regarding the nonclinical studies conducted with AZD9773, refer to the current IB.

2.1.4 Clinical studies

Data from Phase I and II clinical studies with D-CytoFab have demonstrated a potential therapeutic benefit of treating patients with severe sepsis with polyclonal ovine Fab fragments targeted against TNFα. A trend towards improved all-cause 28-day mortality was seen compared to placebo (37% versus 26%) (Rice et al 2006). The number of serious and non-serious AEs was comparable between placebo and D-CytoFab groups.

An ascending-dose single- and multiple-dose Phase IIa study, D0620C00004, has been completed with AZD9773 in a similar population. At entry to the study, the median Acute Physiology and Chronic Health Evaluation (APACHE) II score was 27. The highest dose studied was a single loading infusion of 750 units AZD9773/kg followed by 9 maintenance doses of 250 units AZD9773/kg. The overall findings were that the infusion rate and dose were well tolerated without significant safety concerns. The administration of AZD9773 resulted in sustained reduction of serum levels of TNFα close to the limit of quantification of the assay for the duration of the dosing period. The overall mortality rate in this study was 28% in single- and multiple-dose cohorts of AZD9773 (n=47) and 26% on the placebo arm (n=23). The number of serious and non-serious AEs was comparable between AZD9773 and placebo groups. During the course of the study, unblinded safety data were reviewed by an Independent Data Monitoring Committee (IDMC) on 10 occasions. There were no recommendations to modify or stop the study for safety reasons based on these multiple unblinded reviews.

Further information regarding the Phase IIa clinical study (D0620C00004) conducted with AZD9733 is provided in the current IB.

2.1.5 Pharmacogenetics

AstraZeneca intends to perform genetic research (pharmacogenetics [PGx]) in the AZD9773 clinical development programme to explore how genetic variations may affect the clinical parameters associated with AZD9773. Collection of deoxyribonucleic acid (DNA) samples from populations with well-described clinical characteristics may aid in the identification of future drug targets and projects to validate identified targets.

Future research may suggest other genes or gene categories as candidates for influencing not only response to AZD9773 but also susceptibility to sepsis for which AZD9773 may be evaluated. Thus, this genetic research may involve study of additional un-named genes or gene categories, but only as related to acute sepsis.

2.2 Research hypothesis

The research hypothesis to be tested in this study is that TNF neutralisation by AZD9773 results in clinically meaningful benefit to severe sepsis and/or septic shock patients as reflected in ventilator-free days (VFDs), mortality and organ dysfunction.

2.3 Rationale for conducting this study

There is a medical need for a safe and efficacious treatment of severe sepsis and/or septic shock. Phase I and II studies with D-CytoFab have indicated a potential therapeutic benefit of treating patients with severe sepsis with polyclonal ovine Fab fragments targeted against TNFα. The safety profile of AZD9773 has been evaluated in a Phase IIa study (D0620C00004) in patients with severe sepsis; AZD9773 was well tolerated in this study and had an acceptable safety profile. Data from that Phase IIa (D0620C00004) study have been used to determine the doses and infusion rates for use in this study.

This study is being conducted to assess the effect of AZD9773 in a larger population of severe sepsis and/or septic shock patients. It is intended to further substantiate the biological and clinical effects of AZD9773 across doses. A Phase IIb study of D-CytoFab in severe sepsis patients showed significant improvement in VFDs and intensive care unit (ICU)-free days along with a trend toward improved survival in the AZD9773 group. The current Phase IIb study is designed to evaluate the effect of AZD9773 in a similar setting. Thus VFD over 28 days is the primary endpoint and mortality, shock-free days, Health-related Quality of Life (HRQoL) and other organ failure assessments are important secondary endpoints. This Phase IIb study may or may not be large enough to show definitive effects on these endpoints (sepsis outcomes) but trends are expected. Effects across the doses will help to characterise AZD9773.

In a Phase IIb study conducted with D-CytoFab, a loading dose of 250 units/kg followed by 9 doses of 50 units/kg every 12 hours infused over 30 minutes was associated with a significant, prompt and sustained suppression of plasma TNFα during treatment such that TNFα was undetectable in plasma during the entire 5 days of active treatment (Rice et al 2006). This dosing regimen was found to significantly improve clinical outcomes for the D-CytoFab-treated group with no adverse safety findings. The optimal duration of therapy with an anti-TNFα agent is a balance between intervening to suppress TNFα bursts while not inhibiting the host inflammatory response for too long. A treatment period of 5 days was chosen for the Phase IIb study of D-CytoFab and for the recently completed Phase IIa study (D0620C00004) conducted withAZD9773. In this Phase IIb study the maximum treatment period will also be 5 days

In a recently completed Phase IIa study (D0620C00004) conducted with AZD9773, similar effects on plasma TNFα were seen. This particular study was not powered to detect efficacy, but did demonstrate that loading doses of up to 750 units/kg and maintenance doses of up to 250 units/kg every 12 hours were well tolerated in patients with severe sepsis.

[redacted]

At the present time, there are no commercially available and approved prognostic assays for sepsis mediators measured in the blood. Several biomarker assay systems are in development (not by AstraZeneca) and may become available in the near future. One blood sample is being drawn prior to dosing from patients who provide consent for their sample to be held for analysis. It is unlikely that the result of this testing will be reported in time for the Clinical Study Report.

AZD9773 neutralises released TNFα and through this effect can decrease the production of other cytokines. This effect of AZD9773 will be assessed by measuring serum levels of TNFα, IL-6, IL-8, and multiplex assay for exploratory chemokines. The analysis of the multiplex assay for exploratory chemokines is not planned to be included in the Clinical Study Report for this study. Procalcitonin will be explored as an infection and prognostic marker.

The purpose of the genetic research is to generate data for use in future retrospective analyses. Future genotyping could be correlated with pharmacokinetic (PK) profiles or markers of AZD9773 response and/or susceptibility to or prognosis of sepsis. The results of the genetic research will not form part of the Clinical Study Report for this study. The results may be pooled with genetic data from other studies on AZD9773 to generate hypotheses to be tested in future studies.

2.4 Benefit/risk and ethical assessment

Data from Phase I and II clinical studies with D-CytoFab have demonstrated a potential therapeutic benefit of treating patients with severe sepsis with polyclonal ovine Fab fragments targeted against TNFα (see Section 2.1.2). The Phase IIb study in 81 patients also indicated a benefit in increased mean VFDs for D-CytoFab versus placebo (15.0 versus 9.8 VFDs, respectively), as well as a trend towards improved all-cause 28-day mortality compared to placebo (37% versus 26%). The number of AEs and SAEs was comparable between placebo and D-CytoFab groups. The overall mortality rate in the Phase IIa study (D0620C00004) was 28% in single- and multiple-dose cohorts of AZD9773 (n=47) and 26% on the placebo arm (n=23). The mortality rate in the multiple-dose AZD9773 cohorts was 23%. The number of serious and non-serious AEs was comparable between AZD9773 and placebo groups. Based on data available to date, the TNF neutralising capabilities and the tolerability profile of AZD9773 appear to be similar to D-CytoFab. Thus, AZD9773 has a potentially favourable risk/benefit profile.

Treatment with AZD9773 initial infusion will be given within a monitored setting (ie, ICU or Emergency Department, with a nurse to patient ratio of at least 1:2 and with physiological monitoring [vital signs and cardiac]). These are closely monitored environments equipped to deal with adverse reactions. Investigators will be capable of assessing and treating immediate hypersensitivity reactions and medications required will be ready to use if required. The safety and tolerability of the dose regimen and rate of infusion in this study have been established from the Phase 2a study (D0620C00004). The doses selected for this study were considered well tolerated in the Phase 2a study (D0620C00004) and produced detectable suppression of circulating TNFα for the duration of dosing.

For further details on the overall risk and benefits of AZD9773, see the current IB.

3. STUDY OBJECTIVES

3.1 Primary objective

The primary objective is to evaluate the effect of two different doses of AZD9773 versus placebo on VFDs over 28 days in patients with severe sepsis and/or septic shock, who are receiving appropriate standard of care.

3.2 Secondary objectives

The secondary objectives are to evaluate the effect of two different doses of AZD9773 versus placebo in patients with severe sepsis and/or septic shock on the following:

1. 7-day and 28-day mortality.
2. Safety and tolerability.
3. Morbidity (VFDs at Day 15 [over 14 days]), organ function, shock, ICU – length of stay, ICU-free days, hospitalisation.
4. Mortality at Day 90.
5. HRQoL of sepsis survivors at Day 29 and Day 90.
6. The biological effect on plasma tumour necrosis factor alfa (TNFα) levels and relevant cytokines and chemokines.
7. To explore the predictive characteristics of selected biomarkers on outcome parameters.
8. To determine the population PK of AZD9773 via sparse sampling and to assess the relationship between PK and measures of pharmacodynamic (PD) response, efficacy and adverse events (AEs) in patients with severe sepsis and/or septic shock.

3.3 Other objectives

Optional blood samples will be collected in this study for genetic (PGx) and future biomarker research. No planned number of patients is required for this genetic and biomarker research. The samples will be stored and may be analysed in future research. All patients meeting the study eligibility criteria may participate in the genetic and/or biomarker research.

4. STUDY PLAN AND PROCEDURES

4.1 Overall study design and flow chart

This Clinical Study Protocol has been subject to a peer review according to AstraZeneca standard procedures.

This is 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 (within 24 hours of organ failure).

The target population for the study comprises adult patients with severe sepsis and/or septic shock who have objective clinical evidence of infection, meet the criteria for systemic inflammatory response syndrome (SIRS), and have cardiovascular and/or respiratory failure according to the definitions in Section 5.1. Written informed consent for participation in the study is required from the patient (or his/her legally authorised representative) before any study-specific procedures are conducted.

Approximately 300 patients will be entered into the study (ie, allocated to study treatment) from approximately 100 centres. The maximum duration that a patient is expected to remain in the study including screening and the follow-up phone contact is approximately 91 days (about 13 weeks). An IDMC will be convened and will meet once 100 patients have reached Day 29 to review safety assessments and make recommendations to continue or stop the study based on safety findings (see Section 13.6).

The study design is presented in Figure 1 and the study plan is presented in Table 1. Day 1 is defined as time 0 hours (start of first infusion of study drug) to the end of that calendar day. The study comprises the following three periods:

Screening period

During the screening period, patients will be entered into the study on the basis of inclusion and exclusion criteria. Patients will have the option to provide a blood sample for biomarker research within 3 hours prior to the first dose (preferably at the same time as the first pre-study drug infusion cytokine blood sample) and a blood sample for genotyping. Patients (or their legally authorised representative) who agree to take part in the genetic research will be asked to sign a separate informed consent form to confirm their willingness to have this sample taken. Patients (or their legally authorised representative) who agree to take part in the biomarker research will be asked to sign either a separate informed consent form or note consent in a specific section of the general informed consent form to confirm their willingness to have this sample taken. The samples will be stored and may be analysed in future research.

Eligible patients (ie, those who have met the study inclusion and exclusion criteria) will be randomised in a 1:1:1 ratio to receive either AZD9773 250/50 units/kg or AZD9773 500/100 units/kg or placebo (saline). Dosing will be determined by body weight (taken at screening as close as possible to the first dose but within 24 hours before the first dose) up to 100 kg. Patients with a body weight >100 kg will receive doses corresponding to 100 kg.

Treatment period (Day 1 up to Day 5)

Day 1 begins at the start of the first dose (within 24 hours of qualifying organ failure) and continues until the end of that calendar day.

AZD9773 250/50 units/kg (Dose arm 1):

Single iv loading infusion of 250 units AZD9773 per kg body weight (maximum 25000 units) in a volume of 250 mL over 30 minutes followed by 50 units AZD9773 per kg body weight in a volume of 100 mL over 30 minutes once every 12±2 hours for up to a maximum of 9 iv maintenance doses (maximum 5000 units each) or until the patient no longer requires haemodynamic or ventilatory support and ICU care and there is no evidence of worsening organ failure (see below for duration of treatment).

AZD9773 500/100 units/kg (Dose arm 2):

Single iv loading infusion of 500 units AZD9773 per kg body weight (maximum 50000 units) in a volume of 250 mL over 30 minutes followed by 100 units AZD9773 per kg body weight in a volume of 100 mL over 30 minutes once every 12±2 hours for up to a maximum of 9 iv maintenance doses (maximum 10000 units each) or until the patient no longer requires haemodynamic or ventilatory support and ICU care and there is no evidence of worsening organ failure (see below for duration of treatment).

Placebo:

Placebo will be saline solution (0.9% sodium chloride) administered as iv infusions in an equivalent volume to the active treatment (in a volume of 250 mL for the loading dose and 100 mL for maintenance doses) with the same regimen and at the same times as noted for Dose arms 1 and 2 or until the patient no longer requires haemodynamic or ventilatory support and ICU care and there is no evidence of worsening organ failure (see below for duration of treatment). The pharmacy at each study centre will supply saline for the study.

Duration of treatment

Up to a maximum of 10 doses (a loading dose followed by up to a maximum of 9 maintenance doses) of AZD9773 will be administered, one dose every 12±2 hours until the patient no longer requires haemodynamic or ventilatory support, no longer requires ICU admission and there is no evidence of worsening organ failure for at least 24 hours. Maximum duration of study drug treatment will be up to approximately 5 days for all patients.

Location of treatment

The initial infusion of study drug will be given to patients in a monitored setting (ie, ICU or emergency department, with a nurse to patient ratio of at least 1:2 and with physiological monitoring [vital signs and cardiac]). Another location in the hospital may be acceptable if it meets these criteria and is approved by the CCC. Subsequent doses will be given to patients in a monitored setting as above.

Timing of treatment

If necessary, a one-time dosing interval adjustment can be made after the loading dose to create a suitable morning/evening schedule 12 hours apart. The dosing interval adjustment must be such that the first maintenance dose is given a minimum of 6 hours and a maximum of 15 hours after the loading dose. Dosing can be discontinued before all 10 doses are administered if the patient improves and maintains improvement for 24 hours. Improvement is defined as a patient no longer requiring haemodynamic or ventilatory support, no longer requiring ICU admission and there is no evidence of worsening organ failure for at least 24 hours. This may require laboratory confirmation for liver and/or renal function or platelets.

Dosing should not continue past Day 6. During the treatment period, the patient will be given supportive care for the management of severe sepsis and/or septic shock as well as any treatment required for inter-current disease.

Missed and late doses

Time windows for dosing of ±2 hours have been factored into the study but it is possible that these windows may be missed or doses given late due to such factors as patient in surgery or X-ray suite, etc. If a dose is late by 2 to 5 hours, the CCC should be contacted first and then the dose should be given immediately. The next scheduled dose should be given at the scheduled time. If a dose is late by over 5 hours, it should be missed and the next scheduled dose should be given at the scheduled time. Below are two example scenarios where the previous dose was given on time but the next dose, dose 6, is late.

Dose No.	Scheduled dose time	Scenario 1	Scenario 2
5	Day 3, 06:00 (given at scheduled time)		
6	Day 3, 18:00	**Dose 6 is late and the time is between 20:00 and 23:00** Contact the CCC first and then give this dose immediately	**Dose 6 is late and the time is after 23:00** Miss this dose
7	Day 4, 06:00	Give this dose at scheduled time	Give this dose at scheduled time

If a PK sample was scheduled for the missed dose, the PK sample should be taken at the next dose and the actual time that the dose was given and the actual sample time and date should be recorded.

Missed doses will not be replaced.

[redacted]

In the case where a patient stops study drug early because of improvement, protocol assessments including PK should be continued.

Follow-Up Period (Day 7-10, Day 15, Day 29, Day 90)

Ventilator use will be assessed during the first complete 28 days of the study period. After completing the treatment period, patients will be followed-up for 28 **FULL CALENDAR** days after start of study drug administration, with a post-study follow up at Day 90 to further understand longer-term patient outcomes. Follow-up assessments in surviving patients are scheduled for Days 7-10, Day 15, Day 29 and Day 90 (see Table 1 for time windows for these assessments). At Day 15 and Day 29, every effort will be made to obtain a blood sample for safety laboratory assessments. These assessments may occur in the hospital for those remaining hospitalised, as a follow-up visit if a patient is able to attend after hospital discharge, or study centre personnel or a third party vendor may visit the patient. A medically qualified physician will conduct an examination of patients at Day 29 or at discharge from hospital, whichever occurs first. In the event a patient is discharged before Day 29, a telephone contact is planned at Day 29 for assessment of AEs, survival, and assessment of secondary infections or other AEs (if these have occurred, details will be obtained from patients' medical records). It is planned that patients (or a designate) will also complete a HRQoL assessment at Day 29. Additionally, a second post-study follow-up by telephone contact will be undertaken at Day 90 to assess longer-term outcomes (SAEs considered related to study drug, survival, presence of secondary infections, follow-up of AEs ongoing at Day 29 and HRQoL information).

Independent Data Monitoring Committee

An IDMC will be convened and will meet once 100 patients have reached Day 29 to review safety assessments and make recommendations to continue or stop the study based on safety findings. All patients who receive a dose of study drug will be evaluated for safety and tolerability. Enrolment will continue unless there is an unexpected safety concern. The treatment regimens may be adjusted or suspended depending on the IDMC review outcome.

Details on the IDMC are provided in Section 13.6 and full details of the IDMC procedures and processes can be found in the IDMC Charter.

[redacted]

Figure 1 Study flow chart

	Treatment: AZD9773 250/50 units/kg or AZD9773 500/100 units/kg or placebo		Follow-up		
Up to 0 hours	D1[c]-6[d]	D7-10	D15±1[e]	D29[f]+2 (phone contact)	D90+14 phone contact[g]
Screening[a]				D29[g]-6/+14 blood sample	Final Follow-up visit or Withdrawal[h]
↑ Randomisation[b]					

Abbreviations: AE = adverse event; CCC=Clinical Coordinating Centre; HRQoL= Health-related Quality of Life; ICU=intensive care unit; PK=pharmacokinetic; VFD=ventilator-free day.

a Informed consent must be obtained prior to any study-specific procedure.

b Randomisation prior to dosing.

c Day 1 begins at the start of the first dose (within 24 hours of qualifying organ failure) and continues until the end of that calendar day. The initial dose must be administered in a monitored setting (ie, ICU or emergency department, with a nurse to patient ratio of at least 1:2 and with physiological monitoring [vital signs and cardiac]). Another location in the hospital may be acceptable if it meets these criteria and is approved by the CCC.

d In the case where a patient stops study drug early because of improvement, protocol assessments including PK should be continued.

e At Day 15 (±1 day), every effort will be made to obtain a blood sample for safety assessments (if no longer hospitalised, the patient may visit the study centre, or study centre personnel or a blood draw vendor may visit the patient).

f At Day 29+2 the patient will be assessed for AEs, survival, ventilator use for assessment of VFDs, presence of secondary infections or other AEs, and HRQoL. If the patient is discharged, telephone contact is planned. A medically qualified physician will conduct an examination of patients at Day 29 or at discharge from hospital, whichever occurs first. **28-day survival assessment must take place after a minimum of 28 FULL CALENDAR days has elapsed since start of study.**

g At Day 29 (-6 days/+14 days), every effort will be made to obtain a blood sample for safety assessments (if no longer hospitalised, the patient may visit the study centre, or study centre personnel or a blood draw vendor may visit the patient).

h A telephone contact is planned at Day 90 (+14 days) for assessment of SAEs considered related to study drug, survival, presence of secondary infections, follow-up of AEs ongoing at Day 29 and HRQoL information.

[redacted]

Table 1 Study plan

Assessments	Screening	Treatment period[b]						Follow-up							
	Up to 0 h	D1[a]	D2	D3	D4	D5	D6	D7	D8	D9	D10	D15±1[c]	D29+2[c] or WD	D29[c] -6/+14	D90+14[d] or WD
Admission to ICU (date/time)[e]	X														
Informed consent; assignment of E-code	X														
Inclusion/exclusion criteria	X														
Adverse events	X[f]	X	X	X	X	X	X	X	X	X	X	X	X[g]		X[g]
Pregnancy test (serum and urine)	X[h]														
Demographics, Charlson Comorbidity Scale, APACHE II (all questions)[i]; medical/ surgical history	X														
Optional blood sample for biomarker research	X[j]														
Optional blood sample for genetic research	X[k]														
24-hour volume status	X														
Physical examination; Lung auscultation, dermal examination	X[l]	(X)[m]	(X)[m]	(X)[m]	(X)[m]	(X)[m]	(X)[m]						X[n]		
Blood sample: clinical chemistry, haematology	X[o]	X[p]	X[q]	X[p]	X[q]	X[p]	X[q]	X[p]				X[q]		X	
Blood sample: coagulation parameters	X[o]	X[p]	X[q]	X[p]	X[q]	X[p]	X[q]	X[p]				X[q]		X	

Table 1 Study plan

Assessments	Screening	Treatment period[b]						Follow-up							
	Up to 0 h	D1[a]	D2	D3	D4	D5	D6	D7	D8	D9	D10	D15±1[c]	D29+2[c] or WD	D29[c] -6/+14	D90+14[d] or WD
Urine sample: urinalysis	X[o]	X[q]		X[q]				X[q]				X[q]			
Protein C activity	X[o]														
Troponin I	X[o]		X[q]					X[q]							
HASA IgG and total HASA bridging assay	X[o]											X[q]		X[q]	
NAB assay	X[o]											X[q]		X[q]	
IgE	X[o]													(X[q,r])	
Procalcitonin	X[o,s]	X[q,s]	X[q]		X[q]			X[q]							
Lactate	X[o,s]	X[s]	X												
12-lead ECG		X[t]		X[t]		4-6 hours after last dose[t]					X		X[t]		
BP, PR, RR, temperature, blood O_2[u]	X	X	X	X	X	X	X	X	X	X	X	X			
PK[v]	X	X	X	X	X	12 hours after last dose					X				
Height	X														
Weight	X[w]						X[w]								
Modified SOFA Score[x]	X	X	X	X	X	X	X	X	X	X	X	X			
Glasgow Coma Score	X						X					X			
Pre-study and concomitant medication[y]	X	X	X	X	X	X	X	X	X	X	X	X			
Infection assessment	X[z]	X	X	X	X	X	X	X	X	X	X	X	X		

Table 1 Study plan

Assessments	Screening	Treatment period[b]						Follow-up							
	Up to 0 h	D1[a]	D2	D3	D4	D5	D6	D7	D8	D9	D10	D15±1[c]	D29+2[c] or WD	D29[c] -6/+14	D90+14[d] or WD
Randomisation	X														
Study drug administration[a]		X	X	X	X	X	X								
Pulmonary assessment	X	X	X	X	X	X	X	X							
Ventilator use	X	X	X	X	X	X	X	X	X	X	X	X			
Cytokines blood sample TNFα[aa]	X	X	X		X		X	X			X	X			
Cytokines blood sample IL-6, IL-8[ab]	X	X	X		X		X								
Multiplex assay[ac]	X	X	X		X		X	X			X	X			
Plasma renal panel[ac]	X	X	X		X		X	X			X	X			
7-day mortality, **28-day mortality**[ad], and mortality at Day 90									X				X[ad]		X
HRQoL[ae]													X[ae]		X[ae]

Abbreviations: AE = adverse event; APACHE=acute physiology and chronic health evaluation; BP=blood pressure; D=day; ECG=electrocardiogram; eCRF = electronic Case Report Form; HRQoL=Health-related Quality of Life; ICU=intensive care unit; Ig=immunoglobulin; HASA=human anti-sheep antibody; IL=interleukin; NAB=neutralising antibody assay; PK=pharmacokinetics; PR=pulse rate; RR=respiratory rate; SAE = serious adverse event; SF-36v2 Acute=Short Form-36 Health Survey, version 2 Acute; SOFA=sequential organ failure assessment; TNF=tumour necrosis factor; WD=withdrawal.

a Day 1 starts at first administration of study drug (within 24 hours of qualifying organ failure) and finishes at the end of that calendar day.

b In the case where a patient stops study drug early because of improvement, protocol assessments including PK should be continued.

c Every effort should be made to obtain a blood sample for safety assessments at this visit (if no longer hospitalised, the patient may visit the study centre, or study centre personnel or a third party vendor may visit the patient). At Day 29 or at discharge from hospital, whichever occurs first, a medically qualified physician will conduct an examination of patients. If the patient has been discharged then telephone contact will be made. The window for the Day 29 blood sample is –6 to +14 days.

d Phone call only. Visit window is +14 days.

e Or monitored setting (ie, ICU, hospital ward or emergency department with a nurse to patient ratio of at least 1:2 and with physiological monitoring [vital signs and cardiac]).

f AEs and SAEs will be collected from the provision of written informed consent for the study to Day 29.

g SAEs and AEs ongoing at Day 29 will be followed up until they resolve. SAEs and AEs ongoing at Day 90 will be considered to be ongoing at end of study. An SAE beginning after Day 29 need only be reported at the investigator's discretion if considered related to study drug.

h Patients may be entered into the study on the basis of a negative urine pregnancy test, pending the results of a serum pregnancy test. If the serum pregnancy test is positive, the patient must be discontinued from study treatment unless the patient is felt to have a post-partum elevation of β human chorionic gonadotropin.

i The APACHE II score will be calculated using completed standard of care laboratory assessments from the 24 hours preceding randomisation.

j Within 3 hours prior to the first dose (preferably at the same time as the first pre-study drug infusion cytokine blood sample).

k At screening but may be taken at any time during the study.

l The baseline physical examination (including lung auscultation and dermal examination) should be done within 4 hours before dose administration.

m A minimum of a lung auscultation and dermal examination must be performed after each dose. In the event of an infusion reaction (as evidenced by a causal change in BP, skin or lung examination), an additional full physical examination should be performed and changes (skin, lung, physical examination and BP) should be recorded in the eCRF.

n Physical examination should be done at discharge if discharge is before Day 29.

o One sample should be collected within 12 hours before dose administration (6 hours for lactate).

p Record only if available and do not draw these laboratory blood samples if not available or required for other purposes.

q Collect the sample at the routine collection time closest to 8 a.m.

r In the event a patient experiences a hypersensitivity reaction, a blood sample for tryptase, IgE and quantitative eosinophil count should be obtained at 20 to 60 minutes post suspected infusion or hypersensitivity reaction and at Day 29.

s There must be an interval of at least 6 hours between the lactate screening samples and the samples at Day 1. To preserve this minimum 6-hour window, the Day 1 samples may in fact need to be taken on Day 2.

t ECG should be recorded as follows: baseline (pre-infusion Day 1; Day 1 end of infusion; Day 3 before first dose and end of infusion; Day 5 before first dose and end of infusion; Day 5 ECG 4-6 hrs after last dose; Day 10 at the same time as the PK sample; and Day 29 or at discharge. All ECGs will be obtained in triplicate within approximately 1 to 2 minutes, ensuring that the 3rd reading is prior to infusion start for pre-infusion measurements.

u Collect only those values closest to 8 a.m.

v PK blood samples should be taken as described in Section 7.7.1. Note: Some PK samples may need to be taken on the following day depending on the time of first dose administration.

w Weight will be measured at screening as close as possible to the first dose but within 24 hours before the first dose. If the patient is discharged prior to Day 6, weight should be measured at discharge.

x Modified SOFA scores: the worst BP and saturation values of the day should be used, and if no value is collected, the last assessment performed should be the value for that day. On days when laboratory results are unavailable, values will be extrapolated from the previous available values (Section 13.3.5).

y Investigators will record all pre-study concomitant medications taken by patients in the 2 weeks prior to written informed consent and all on-study concomitant medication taken during the study until Day 29. They will record medications (name of drug, route of administration, start date, stop date). If vasopressors are required during the loading dose, the following should be recorded from 2 hours before the loading dose, during the loading dose and until 30 minutes after completion of the loading dose: name of drug, start date and time, dose, all interim rate changes during administration, route of administration, stop date and time. This applies only to the loading dose. Additional information (as above but also including start time and stop time) will be recorded for the following medications/therapies: antibiotics, steroids, Xigris, blood products, immunosuppressants, anti-TNFs (see

[redacted]

Sections 5.4.1, bullet point 9, 6.1 and 6.5.2). Oral nutrition supplements and total parenteral nutrition, with and without lipids, will be recorded in the eCRF from randomisation end of treatment.

z The site of infection at screening should be noted. All patients must have a blood culture prior to randomisation. The blood culture result does **NOT** have to be known prior to randomisation. Positive culture results defining the index infection will also be recorded. Any subsequent positive culture will also be recorded. The site of infection, associated pathogen(s) and antimicrobial susceptibility for the associated pathogens will be recorded.

aa TNFα samples should be taken as follows: screening - pre-infusion; Day 1 at 1-2 hours after the end of infusion; before the morning dose on Day 2 and 1-2 hours after the end of infusion on Day 2, before the morning dose on 4, and 6; and on Days 7, 10 and 15.

ab IL-6 and IL-8 samples should be taken as follows: screening - pre-infusion; Day 1 at 1-2 hours after the end of infusion; before the morning dose on Days 2, 4, and 6.

ac Samples for multiplex assay for exploratory chemokines and for exploratory plasma renal panel should be taken at the same time as samples for cytokines or other blood samples and the date and time should be noted.

ad 28-day survival assessment must take place after a minimum 28 FULL CALENDAR days have elapsed since start of study and within 2 days after Day 29.

ae HRQoL will be assessed via completion of the SF-36v2 Acute questionnaire by the patient or designate at Days 29 and 90.

4.2 Rationale for study design, doses and control groups

In a Phase IIb study conducted with D-CytoFab employing a loading dose of 250 units/kg followed by 9 doses of 50 units/kg every 12 hours, there was a significant, prompt and sustained suppression of plasma TNFα during treatment such that TNFα was undetectable in nearly all plasma samples obtained during the entire 5 days of active treatment. Modest and transient rises of TNFα in the treated group occurred in only 2 patients. These 2 patients had the highest baseline TNFα levels of the group, suggesting that dosing was in the optimal region. This dosing regimen was found to significantly improve clinical outcomes for the D-CytoFab-treated group with no adverse safety findings.

In a recently completed Phase IIa study (D0620C00004) conducted withAZD9773, similar effects on plasma TNFα were seen. This particular study was not powered to detect efficacy, but did demonstrate that loading doses of up to 750 units/kg and maintenance doses of up to 250 units/kg every 12 hours were well tolerated in patients with severe sepsis.

In this Phase IIb study, which is powered to detect an effect on the parameter of VFD as a measure of efficacy, both the 250/50 units/kg regimen and the 500/100 units/kg regimen will be evaluated to determine which dose regimen should be employed in further clinical studies to evaluate an effect of AZD9773 on 28-day mortality. Both of these dose regimens were well tolerated in the Phase IIa (D0620C00004) study and the 250 units/kg dose was also well tolerated in the earlier D-CytoFab study. A dose regimen lower than 250/50 units/kg was not included in this Phase IIb study because 250/50 units/kg produced significant clinical benefit with D-CytoFab and there is currently no tolerability concern with the doses chosen for this study. The higher dose will explore the possibility of increased benefit with more TNFα suppression and help define the therapeutic dose-response.

The optimal duration of therapy with an anti-TNFα agent is a balance between intervening to suppress TNFα bursts while not inhibiting the host inflammatory response for too long. A treatment period of 5 days was chosen for the Phase IIb study of D-CytoFab and for the recently completed Phase IIa study (D0620C00004) conducted withAZD9773. In this Phase IIb study the maximum treatment period will also be 5 days.

In the D-CytoFab Phase IIb study, and the AZD9773 Phase IIa study (D0620C00004), nearly all patients receiving study drug treatment had undetectable TNFα during dosing, but within 48 hours after the last dose, mean plasma TNFα levels rose to those comparable to placebo recipients, consistent with the plasma half-life of both D-CytoFab and AZD9773 (18-20 hours in AZD9773 Phase IIa study).

The inclusion of a placebo control will enable an evaluation of efficacy and help to identify drug-related AEs from those due to the disease under study. All patients will receive current standard of care for severe sepsis and/or septic shock in addition to AZD9773 or placebo.

Safety laboratory monitoring will include markers for potential cardiac, coagulation, renal, liver, hypersensitivity and immunological events. The measurement of HASA will be performed to determine if exposure to AZD9773 induces HASA formation. Tryptase is a

protease released by mast cells. It is found in all human mast cells but in few other cells and thus is a good marker of mast cell activation. This may be helpful in the assessment of hypersensitivity or infusion reactions should they occur.

5. PATIENT SELECTION CRITERIA

Patient population should be selected without bias.

Investigators must keep a record of patients who entered pre-study screening by meeting inclusion/exclusion criteria but were never enrolled, eg, a patient screening log. To enter the study, each patient must meet all of the inclusion criteria and none of the exclusion criteria for this study. Under no circumstances can there be exceptions to this rule.

Patients will be recruited from health care-related institutions or facilities.

Summary of inclusion criteria (complete details are listed in section 5.1)

1. Adults with a first episode of sepsis during this hospitalisation (including transfer from another hospital) (Inclusion criterion 1).

2. Objective evidence of infection that requires parenteral antibiotics (Inclusion criteria 2 and 5).

3. At least 2 of 4 SIRS criteria in the 24 hours before organ dysfunction (must include either fever OR elevated white blood cells [WBC]) (Inclusion criterion 3).

4. Cardiovascular or respiratory dysfunction (Inclusion criteria 4 and 5).

Overview of exclusion criteria (complete details are listed in section 5.2)

1. Moribund (not likely to survive 24 hours) or significant comorbidities making survival for 3 months unlikely (Exclusion criterion 5).

2. Immunocompromising comorbidities or concomitant medications.

   - Advanced human immunodeficiency virus (HIV) infection (CD4 $\leq 50/mm^3$) (Exclusion criterion 4).
   - Stage III or IV cancer (see Appendix J) (Exclusion criterion 7).
   - Haemopoietic or lymphoreticular malignancies not in remission (Exclusion criterion 9).
   - Receiving radiation therapy or chemotherapy (Exclusion criterion 10).
   - Stem cell, organ or bone marrow transplant in the past 6 months (Exclusion criterion 11).

- High dose steroids or other immunocompromising drugs (Exclusion criterion 12).
- Absolute neutrophil count <500 per µL not due to sepsis (Exclusion criterion 13).

3. Concomitant diseases:

- Cirrhosis with portal hypertension or Childs-Pugh Class C (Exclusion criterion 14).
- Burns over > 30% of body surface area (Exclusion criterion 15).
- New York Heart Association functional Class IV due to heart failure or any disorder (Exclusion criterion 16).
- Deep seated fungal infection or active tuberculosis (Exclusion criterion 21).
- History of chronic hypercarbia, respiratory failure in past 6 months or use of home oxygen in the setting of severe chronic respiratory disease (Exclusion criterion 23).
- Neuromuscular disorders that impact breathing/spontaneous ventilation (Exclusion criterion 24).
- Quadriplegia (Exclusion criterion 25).
- Cardiac arrest in the past 30 days (Exclusion criterion 26).

4. Medication and allergy disqualifications.

- Previously received ovine derived products (CroFab™, DigiFab™) (Exclusion criterion 18).
- Sheep product allergy or allergy to latex, papain, chymopapain (Exclusion criterion 18).
- Treatment with anti-TNF agents within the last 8 weeks (Exclusion criterion 19).

5. Pregnancy or plans to breast feed upon resolution of sepsis (Exclusion criterion 17).

5.1 Inclusion criteria

For inclusion in the study patients must fulfil the following criteria.

1. Patients undergoing a first episode of sepsis during this hospitalisation (including transfer from another hospital).

2. Objective clinical evidence of infection; at least 1 of the following (see also inclusion criterion 5). Including:

   - Perforated viscus.
   - WBC and/or pathogens in a normally sterile body fluid.
   - Radiographic evidence of pneumonia.
   - Signs of a local source of infection such as cellulitis.
   - A syndrome associated with a high risk of infection (eg, ascending cholangitis).
   - Positive culture from blood or from another normally sterile body fluid prior to study drug administration.
   - Evidence of an infecting organism such as pneumococcal antigen or Legionella antigen.

3. Patients must meet at least **2** of the following **4** SIRS criteria at least one of which must be the core temperature criterion or the WBC criterion (see also inclusion criterion 5); these criteria do not have to be met simultaneously; the actual values and the date and time that the criteria were met will be collected.

   - Hypothermia by core temperature <36ºC, or hyperthermia >38ºC measured via any means.
   - Heart rate (HR)>90 beats per minute.
   - Respiratory rate (RR) >20 breaths/minute related to septic event or partial pressure of arterial carbon dioxide (PaCO2) <32 mmHg related to septic event or requiring mechanical ventilation related to septic event.
   - Total WBC absolute count >12000 cells/mm^3 or <4000 cells/mm^3. In the presence of granulocyte-stimulating factor, for those patients whose WBC absolute count is >12000 cells/mm^3, they must have a fever and at least one other criterion (RR or HR).

4. Patients must meet criteria for cardiovascular and/or respiratory dysfunction (see also inclusion criterion 5). Newly developed organ failures must be due to the acute

septic process and not be explained by a chronic condition or by effects of concomitant therapy. Time of onset of the protocol qualifying organ dysfunction/failure will be recorded. For cardiovascular dysfunction, the time of organ dysfunction/failure is defined as the time of initiation of vasopressors. The time of pulmonary dysfunction/failure is defined as the time that the patient meets the appropriate PaO_2/FiO_2 (or SpO_2/FiO_2 ratio) ratio while on mechanical ventilation (for organ dysfunction/failure definitions, see Table 2). An arterial blood gas or recording of the patient's SpO_2 value within 2 hours of intubation will be required otherwise the 24 hour clock will begin at the time of intubation. Patients who have been on mechanical ventilation for more than 48 hours prior to the CCC call cannot use pulmonary dysfunction as the qualifying organ failure. These patients can be enrolled if they meet criteria for cardiovascular dysfunction.

Table 2 Organ dysfunction/failure definitions

System / organ	Definition
Cardiovascular System	Hypotension, as defined as a systolic blood pressure <90 mmHg, or a mean arterial blood pressure ≤65 mmHg requiring vasopressors despite a) a volume infusion of 20 mL/kg crystalloid or colloid equivalent over 4-6 hours before randomisation or b) 30mL/kg crystalloid or colloid equivalent in the 24 hours prior to randomisation after consultation with the CCC. NOTE 1: If hypotension and vasopressor requirement is in the setting of intubation, the patient must still be vasopressor-dependent 1 hour after intubation. Patients requiring vasopressors prior to intubation are eligible for the study. NOTE 2: 10 mL/kg of colloids = 20 mL/kg crystalloids.
Pulmonary Dysfunction	Pulmonary dysfunction is defined as the patient requiring mechanical ventilation related to the septic process and having a $PaO_2/FiO_2 \leq 300$ (or $SpO_2/FiO_2 < 357$). However, if lung is the primary site of infection then PaO_2/FiO_2 must be <200 (or $SpO_2/FiO_2 < 214$). Arterial blood gas measurements are preferred but if unobtainable, SpO_2 will be sufficient. SpO_2 should be obtained for all patients. If SpO_2/FiO_2 is being used, saturation must be ≤ 97%. Otherwise, SpO_2 should be measured at a different FiO_2 if clinically appropriate, or arterial blood gases should be obtained and PaO_2/FiO_2 used instead. Patients who have been on mechanical ventilation for more than 48 hours prior to the CCC call cannot use pulmonary dysfunction as the qualifying organ failure. These patients can be enrolled if they meet criteria for cardiovascular dysfunction.

Abbreviations: CCC = Clinical Co-ordinating Centre; FiO_2 = fraction of inspired oxygen; PaO_2 = partial pressure of arterial oxygen.; SpO_2 = Oxygen saturation by pulse oximetry.

5. Sepsis (infection + SIRS criteria) must be present prior to cardiovascular and/or respiratory failure. SIRS criteria and cardiovascular and/or respiratory failure do not need to be present simultaneously but SIRS criteria must have been demonstrated at some time within the 24 hours preceding the initial cardiovascular and/or respiratory failure, even if SIRS criteria have been present for more than 24 hours. In the case where the patient first presents with cardiovascular and/or

respiratory dysfunction due to infectious process (eg, a new hospital admission), SIRS criteria must be met prior to study drug administration.

Study drug administration must occur within 24 hours after the onset of qualifying cardiovascular and/or respiratory failure.

In addition to the above criteria, for inclusion in the genetic and/or biomarker research undertaken in this study, patients must fulfil the following criterion:

1. Provision of informed consent for genetic and/or biomarker research (by the patient or his/her legally authorised representative).

If a patient declines to participate in the genetic and/or biomarker research, there will be no penalty or loss of benefit to the patient. The patient will not be excluded from other aspects of the study described in this Clinical Study Protocol, so long as they consent.

5.2 Exclusion criteria

Patients must not enter the study if any of the following exclusion criteria are fulfilled:

1. Age <18 years of age.

2. Failure to obtain informed consent.

3. Clinical judgment by the investigator that the patient should not participate in the study (reasons will be recorded in the screening log).

4. HIV infection in association with a last known CD4 count of $\leq 50/mm^3$, cytomegalovirus, disseminated mycobacterium avium complex disease, toxoplasmosis, or progressive multifocal leukoencephalopathy.

5. Moribund, and death is considered imminent within 24 hours.

6. Inability to maintain a mean arterial pressure ≥50 mmHg when measured via an arterial line and/or systolic blood pressure (BP) >70 mmHg for at least 1 hour prior to screening despite the presence of vasopressors and iv fluids.

7. Patient is not expected to survive 90 days because of underlying medical condition, such as poorly controlled neoplasm (eg, Stage III or IV cancer). Appendix J contains the specific exclusion criteria for malignancies (contact the CCC for guidance).

8. Patient's family is not committed to aggressive management of the patient's condition, or the combination of sepsis and underlying illness makes it unlikely that life support will be maintained.

9. Haemopoietic and lymphoreticular malignancies, unless in remission (patients in remission must have completed induction and consolidation therapy before provision of written informed consent for the study).

10. Patients undergoing active radiation or chemotherapy treatment for any type of malignancy. Hormonal manipulation therapies for breast and prostate malignancies are permitted.

11. Any stem cell, organ or bone marrow transplant within the past 6 months prior to provision of informed consent for study.

12. High dose steroids (eg, >40 mg or 0.5 mg/kg prednisone or a steroid with equivalent activity, daily for >7 days) within 1 month before provision of written informed consent for the study (See Appendix I).

13. Granulocytopenia, not due to sepsis, as evidenced by leukocyte absolute neutrophil count <500 per μL.

14. Patients with biopsy proven cirrhosis and documented portal hypertension; episodes of past upper gastrointestinal bleeding attributed to portal hypertension; or prior episodes of hepatic failure/encephalopathy/coma or patients who appear to be Childs-Pugh Class C.

15. Second or third degree burns involving more than 30% of body surface within 5 days before provision of written informed consent for the study.

16. Conditions resulting in a New York Heart Association Class IV functional status.

17. Females of child bearing potential who do not have a negative pregnancy test (serum) at screening (patients may be entered into the study on the basis of a negative urine pregnancy test, pending the results of a serum pregnancy test; if the serum pregnancy test is positive, the patient must be discontinued from study treatment). Post-partum patients who have a persistent positive pregnancy test (human chorionic gonadotropin [HCG] values have not had time to decrease) will be allowed in the study. Females who are lactating and insist on breast feeding within 5 days of the last dose of study drug if their sepsis resolves.

18. Potential intolerance to AZD9773 drug product:

- Any history of hypersensitivity reaction to sheep products, latex, papain or papaya, chymopapain, eg, meat tenderisers or contact lens cleaning solution containing papain or chymopapain.

- Previously administered antivenom manufactured using ovine serum, digoxin immune Fab (DigiFab™, DIGIBIND®) crotalidae polyvalent immune Fab (ovine) (CroFab™), or other sheep-derived product.

19. Treatment with anti-TNF antibodies (eg, infliximab [REMICADE®, Centocor], adalimumab [Humira®, Abbott Laboratories], etanercept [Enbrel®, Immunex]) or IL-1 Receptor Antagonist (Kineret) within last 8 weeks.

20. Enrolment in an interventional experimental protocol involving investigational drug or a medical device within 60 days before provision of written informed consent for the study or within five half-lives of the study drug, whichever is longer (Co-enrolment in process of care trials or comparative trials of approved products will be allowed if the protocol has been approved in advance by the sponsor, as long as the co-enrolment does not violate participation in the other protocol).

21. Deep-seated fungal infection (eg, histoplasmosis, cryptococcal meningitis and aspergillosis). Superficial fungal infections are not excluded (eg, tinea pedis, yeast infections [eg, oral thrush, candida dermatitis] limited to skin).

22. Active tuberculosis (documented, or strong clinical suspicion or patients receiving active treatment for tuberculosis).

23. Severe chronic respiratory disease (ie, present before the onset of the current episode of severe sepsis and/or septic shock) that would prevent weaning from mechanical ventilation. Examples of severe disease may include:

    - Chronic hypercarbia ($PaCO_2$ >45 mmHg) and /or chronic hypoxemia (partial pressure of arterial oxygen [PaO_2] <55 mmHg) on fraction of inspired oxygen (FiO_2)=0.21, OR

    - Hospitalisation for respiratory failure ($PaCO_2$ >50 mmHg or PaO_2 <55 mmHg or oxygen saturation [O_2 Sat] <88% on FiO_2 = 0.21) within last 6 months, or chronic use of home ventilation, OR

    - Unable to climb stairs or perform household duties due to chronic restrictive, obstructive, neuromuscular, chest wall or pulmonary vascular disease resulting in severe exercise restriction, OR

    - Use of continuous home oxygen prior to hospital admission. Sleep apnoea treated with continuous positive airway pressure or biphasic positive airway pressure oxygen during sleep is acceptable.

24. End-stage neuromuscular disorders that impair the patient's ability to ventilate spontaneously (eg, amyotrophic lateral sclerosis).

25. Patients with complete quadriplegia (traumatic or otherwise). All other patients not ambulatory (eg, chronically bed-bound, failure to thrive, cachexia) prior to onset of sepsis will need to be reviewed and approved by the CCC prior to enrolment.

26. Patients with cardiac arrest requiring cardiopulmonary resuscitation within the past 30 days. If the patient has documented complete neurological recovery or if the cardiopulmonary resuscitation was brief and associated with intubation the patient will not be excluded. The patient must be able to follow commands post-arrest.

27. Involvement in the planning and/or conduct of the study (applies to AstraZeneca and PAREXEL staff and/or staff at the study site).

28. Previous randomisation of treatment in the present study or any other AZD9773 study.

Patients must not enter the genetic and/or biomarker portion of the study if the following exclusion criterion is fulfilled

1. Patients who have received a whole blood transfusion within 120 days of the date of genetic sample collection.

5.3 Procedures for handling incorrectly included patients

Patients that do not meet the inclusion/exclusion criteria for the study should not, under any circumstances, be randomised into the study - there are no exceptions to this rule.

If any randomised patients are subsequently found to have not met the inclusion/exclusion criteria then a discussion must occur between the CCC, the Medical Monitor, the AstraZeneca Study Team Physician and the investigator regarding whether to continue or discontinue the patient from the study treatment. Such patients should only be discontinued from treatment if there are safety concerns. However, as this study is including an Intention-to-treat (ITT) analysis, any such patient must be followed up according to the study plan. Decisions must be appropriately documented by the CCC.

5.4 Withdrawal of patients

5.4.1 Criteria for discontinuation from the study treatment

Patients may be discontinued from study treatment at any time. Specific reasons for discontinuing a patient from study treatment are:

- Voluntary discontinuation by the patient who is at any time free to discontinue study treatment, without prejudice to further treatment (incapacitated patients may be withdrawn from study treatment by their legally authorised representative).
- AEs (eg, risk to patients as judged by the investigator and/or IDMC, CCC, PAREXEL or AstraZeneca).
- Severe non-compliance to protocol as judged by the investigator and/or CCC, PAREXEL, or AstraZeneca.
- See Section 5.3 for the procedures for handling incorrectly enrolled patients.

- Patient discharged from an adequately monitored setting.
- Positive pregnancy test (except for post-partum).
- Severe reaction to study drug infusion, or progressive, moderate reaction continuing to worsen, or the patient is refractory (eg, moderate reaction which does not respond to treatment) or at the discretion of the investigator (Appendix D) or study drug is not tolerated.
- Treatment is unblinded by the site investigator or designee.
- Need for immunosuppressant drugs and/or anti-TNF antibodies other than study drug. In the event of the need for these medications, the patient will be discontinued from study treatment but details of the medications (drug name, start date and time, dose, route of administration, stop date and time) will be collected for 28 days from the start of study drug (see Section 6.5.2 on concomitant medications).
- Dosing can be discontinued before all 10 doses are administered if the patient improves and maintains improvement for 24 hours (see Section 4.1).

5.4.2 Criteria for discontinuation from the study

Patients may be discontinued from the study at any time. See Section 5.4.4 for the procedures for discontinuing a patient from the study. Specific reasons for discontinuing a patient from this study are:

- Voluntary discontinuation by the patient who is at any time free to discontinue his/her participation in the study, without prejudice to further treatment (incapacitated patients may be withdrawn from the study by their legally authorised representative)
- Patient lost to follow-up
- Screening Failures. Note: This is only applicable as a reason for study discontinuation if the patient has not been randomised.

A discussion between the CCC, the Medical Monitor, the AstraZeneca Study Team Physician and the investigator must take place before a patient is withdrawn from the study for reasons other than those specified above.

All patients who die before Day 90 will be classified as completing the study.

5.4.3 Criteria for discontinuation from genetic and/or biomarker research

Specific reasons for discontinuing a patient from the genetic and/or biomarker research are:

- Withdrawal of consent for genetic and/or biomarker research. A patient may withdraw from either of these research sample populations at any time, independent of any decision concerning participation in other aspects of the main study described in this protocol. These patients may continue in the main study providing they have not also withdrawn consent from participation in the main study, and their data will be used in the analysis of the primary and secondary objectives. Voluntary discontinuation by the patient will not prejudice further treatment.

5.4.4 Procedures for discontinuation of a patient from the study

A patient (or legally authorised representative will be asked in the case of incapacitated patients) that discontinues will always be asked about the reason(s) for discontinuation and the presence of any AE. If possible, they will be seen and assessed by an investigator(s). AEs will be followed up (refer to Sections 7.3.3 and 7.3.4). The reason for discontinuation from study drug or from the study must be recorded in the eCRF.

Patients who discontinue study treatment will be given appropriate treatment in accordance with institutional protocol and best practice. Every effort will be made to collect safety data from patients who discontinue.

Discontinuation of patients will be recorded in the Interactive Voice Response System (IVRS).

Procedures for discontinuation from study treatment

Patients who discontinue study drug should remain in the study and continue to have all scheduled assessments as shown in Table 1 (an assessment of all-cause mortality is required at Day 29 [+2] and Day 90, and a blood sample is required at Day 29 [-6/+14]) unless consent is withdrawn for participation in the study.

Procedures for discontinuation from study

In the case of withdrawal from the study, if possible, patients should be seen and assessed by an investigator. At the time of withdrawal, the procedures scheduled for the Day 29 Follow-up Visit should be performed, or Day 90 if the Day 29 Follow-up Visit has already occurred (see Table 1). AEs should be followed up as described in Sections 5.4.2, 7.3.3 and 7.3.4.

5.4.5 Procedures for discontinuation from genetic and/or biomarker aspects of the study

Patients who discontinue from the study should always be asked specifically whether they are withdrawing or continuing their consent for this genetic research or for future biomarker analysis. It must be established whether the patient:

- Agrees to the sample(s) and any DNA extracted from the sample(s) being kept for genetic and/or biomarker research in the future
- Withdraws consent for the sample(s) to be kept for genetic and/or biomarker research in the future and/or wishes the sample(s) to be destroyed. Destruction of the sample(s) (or the DNA extracted from the sample[s]) will only be possible so long as the particular sample(s) is traceable. In the event that genetic and/or biomarker research has already been performed, AstraZeneca will retain the results and associated data for regulatory reasons but these will not be used in any subsequent analyses.

The international co-ordinating investigator is responsible for providing written notification to AstraZeneca of any patient who has withdrawn consent for the use of the sample(s) taken for genetic and/or biomarker research. AstraZeneca will provide written confirmation to the investigator of the actions taken with the sample(s), which must be filed in the investigator study file.

6. STUDY CONDUCT

6.1 Restrictions during the study

The following are prohibited during the study treatment period:

- Immunosuppressant drugs (eg, methotrexate, cyclosporine, tacrolimus).
- Anti-TNF antibodies (eg, infliximab, adalimumab, etanercept) other than study drug.
- If any of the above criteria are fulfilled, the patient must be withdrawn from study treatment in accordance with Section 5.4.1

Patients of reproductive capability must agree to use one of the following forms of contraception throughout the study period and for 90 days after discontinuation of treatment: abstinence, oral contraceptives or other hormonal therapy (eg, hormone implants), intra-uterine device, diaphragm with spermicide or condom with spermicide. It is not known whether AZD9773 interacts with hormonal contraceptives: if female patients are taking hormonal contraceptives to prevent pregnancy then this should be combined with a barrier method of contraception. For males, in the event that a female partner becomes pregnant, due to the unknown risk for the foetus, male partners have the same responsibility with regard to

contraception.

6.2 Patient enrolment and randomisation

Patient eligibility will be confirmed by the CCC following a telephone interview with the enrolling site. If the patient meets the criteria for participation in the study, the CCC will provide the enrolling site with an enrolment authorisation number. The site will call the IVRS and enter the enrolment authorisation number into the IVRS that will, in turn, enrol the subject. Once enrolled, the pharmacist will be provided with the subject E-code (assigned by the site), the date of birth and the weight. The pharmacist will call the IVRS system that will issue them a randomisation number and allocated treatment for that patient based upon a predetermined randomisation schedule.

The investigative site personnel will:

1. Identify a potential patient and assign a unique screening number.

2. Complete an enrolment authorisation worksheet.

3. Contact the CCC and present the enrolment worksheet information to determine patient eligibility (see Sections 5.1 and 5.2).

4. On obtaining the informed consent, assign an E-code.

   The patient E-code will be assigned in chronological order of receiving informed consent and this number will be used throughout the study. If a patient is subsequently not randomised, his or her patient number will not be re-used. Patient E-codes will be 8-digit identifiers, Exxxxyyy, where xxxx is a 4-digit centre identifier and yyy is a 3-digit patient identifier.

5. Be provided with a 5-digit enrolment authorisation number by the CCC if the patient meets all inclusion criteria and no exclusion criteria, and informed consent has been obtained from the patient or their guardian/legal representative.

6. Study centre pharmacists will be provided with patient demographic data (including E-code, date of birth, weight [as taken at screening measured as close as possible to the first dose but within 24 hours before the first dose]) by the investigator and enter the IVRS to receive the randomisation number and allocated treatment for each eligible patient.

If a patient discontinues participation in the study, then his/her enrolment/randomisation code cannot be re-used.

If patients have discontinued their participation in the study then they cannot re-enter into the study.

6.2.1 Procedures for randomisation

Patients will be randomised to treatment following verification of conformance with eligibility criteria at screening. Central randomisation via IVRS will be used to allocate patients to treatment groups (AZD9773: dose 1, dose 2, placebo) in a 1:1:1 ratio and avoid selection bias.

Randomisation will be performed in blocks based on a computer-generated randomisation scheme provided by AstraZeneca. The size of randomisation blocks will not be disclosed to the study centres. Randomisation will not be stratified. The randomisation scheme will randomly assign the study drug to the randomisation numbers.

Randomisation codes will be assigned strictly sequentially as patients become eligible for randomisation. Randomised patients who terminate their study participation for any reason, regardless of whether the study drug was taken or not, will retain their randomisation number. The next patient will be given the next randomisation number.

Patients who are withdrawn after randomisation will not be replaced.

Sections 6.3.1 and 6.3.2 describes procedures for blinding and breaking the blind.

6.3 Blinding and procedures for unblinding the study

6.3.1 Methods for ensuring blinding

The study will be performed in a double-blind manner. The patient, the investigator and study centre staff will be blinded to study drug allocation. The study centre pharmacist will be unblinded to study drug and will prepare AZD9773 or placebo for a patient as specified by the randomisation scheme and IVRS (pharmacists will call into IVRS to obtain the randomisation/treatment allocation details). All study drug will be blinded using an opaque sleeve, fastened with tamper-evident tape over the iv bag prior to dispensing to other study personnel to maintain the double-blind conditions. Pharmacists will be given specific instructions for study drug preparation and will note if the double-blind conditions have been compromised or the blind broken. All loading doses will be made up to a volume of 250 mL and all maintenance doses will be made up to a volume of 100 mL. Lot numbers of AZD9773 dispensed will be recorded by the pharmacist and monitored by an unblinded monitor. Other study centre staff and monitors will not be given access to lot number information.

Procedures in the case of unblinding by the investigator or designee are described in Section 6.3.2.

6.3.2 Methods for unblinding the study

Individual treatment codes, indicating the treatment randomisation for each randomised patient, will be available to the investigator(s) or pharmacists from the IVRS. The process for unblinding will be described in the IVRS user manual that will be provided to each centre.

The treatment code must not be broken except in medical emergencies when the appropriate management of the patient necessitates knowledge of the treatment randomisation. There is

no known antidote to AZD9773, and CCC or the Medical Monitor should be contacted with any concerns. Hence, overdose will not normally be considered a reason for breaking the blind.

If the treatment code is broken then the investigator(s) must document and report to AstraZeneca. AstraZeneca retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to an IP and that potentially require expedited reporting to regulatory authorities. Treatment codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual patient have been made and documented.

If the blind is broken, the date, time and reason will be recorded in IVRS, and any associated AE report. If a patient's study treatment is unblinded by the investigator or designee, the patient will be withdrawn from study treatment as described in Section 5.4.4.

The IDMC will be provided with unblinded data for their review but AstraZeneca and PAREXEL staff and investigators involved in the study will remain blinded.

6.4 Treatments

6.4.1 Identity of investigational product(s)

Details of the investigational study drug are provided in Table 3. Further information on AZD9773 can be found in the current IB. Doses will be prepared by a pharmacist unblinded to study treatment as specified in the Pharmacist Handling Instructions. All study drug will be blinded using an opaque sleeve, fastened with tamper-evident tape over the iv bag prior to dispensing to other study personnel.

Table 3 Investigational product

Investigational product	Dosage form and strength	Manufacturer	Formulation number
AZD9773	5000 units of AZD9773 lyophilised powder/vial for reconstitution in saline and dilution in saline for iv infusion (dose is dependent on treatment arm)	[redacted]	F13605
Active Component	AZD9773 (rh TNFα immune Fab [ovine][redacted]		
Excipients	Di-sodium hydrogen phosphate, USP, Ph Eur Sodium chloride, USP, Ph Eur		
Placebo	0.9% sodium chloride		Not applicable

Vials of AZD9773 will be supplied by AstraZeneca or an AstraZeneca designee to each centre. Study centres will be supplied with sufficient AZD9773 for the study.

Prior to use, AZD9773 must be reconstituted with saline. For iv loading infusions, the reconstituted solution will be diluted to 250 mL of saline solution. For all iv maintenance doses, the reconstituted solution will be diluted to 100 mL of saline solution.

Placebo

Placebo will be saline solution (0.9% sodium chloride) administered as an iv infusion in an equivalent volume to the active treatment (volume of 250 mL for the loading dose and 100 mL for maintenance doses). The pharmacy at each study centre will supply saline for the study.

6.4.2 Doses and treatment regimens

During the treatment period, patients will receive AZD9773 250/50 units/kg or AZD9773 500/100 units/kg or placebo. The first dose of study drug should be administered within 24 hours after confirmation of the onset of qualifying organ failure resulting in severe sepsis and/or septic shock (see Section 5.1 for further details on inclusion criteria). Study drug will be administered by iv infusion.

Each infusion in all treatment arms will be administered over a 30-minute period. Medical management of infusion reactions is detailed in Appendix D. AZD9773 and placebo will be

administered by the investigator or medically qualified personnel in a medically monitored setting. The dose, infusion time and volume remaining for each dose will be recorded in the eCRF together with the date and time of administration (using 24:00-hour clock).

If vasopressors are required during the loading dose, the following should be recorded from 2 hours before the loading dose, during the loading dose and until 30 minutes after completion of the loading dose: name of drug, start date and time, dose, all interim rate changes during administration, route of administration, stop date and time. This applies only to the loading dose.

The body weight measured at screening, measured as close as possible to the first dose but within 24 hours before the first dose, will be the body weight used for all dose calculations during the study. The maximum dose given is based on a 100 kg body weight. If a patient weighs >100 kg, he or she will be given the maximum dose. See Appendix D for more detailed guidance on handling tolerability.

The last dose may be on Day 5 or Day 6 depending on the start time of the loading dose on Day 1. Dosing should not continue past Day 6.

If necessary, a one-time dosing interval adjustment can be made after the loading dose to create a suitable morning/evening schedule 12 hours apart. The dosing interval adjustment must be such that the first maintenance dose is given a minimum of 6 hours and a maximum of 15 hours after the loading dose. Dosing can be discontinued before all 10 doses are administered if the patient improves and maintains improvement for 24 hours. Improvement is defined as a patient no longer requiring haemodynamic or ventilatory support, no longer requiring ICU admission and there is no evidence of worsening organ failure for at least 24 hours.

Time windows for dosing of ±2 hours have been factored into the study but it is possible that these windows may be missed or doses given late due to such factors as patient in surgery or X-ray suite, etc. If a dose is late by 2 to 5 hours, the CCC should be contacted first and then the dose should be given immediately. The next scheduled dose should be given at the scheduled time. If a dose is late by over 5 hours, it should be missed and the next scheduled dose should be given at the scheduled time. Below are two example scenarios where the previous dose was given on time but the next dose, dose 6, is late.

Dose No.	Scheduled dose time	Scenario 1	Scenario 2
5	Day 3, 06:00 (given at scheduled time)		
6	Day 3, 18:00	**Dose 6 is late and the time is between 20:00 and 23:00** Contact the CCC first and then give this dose immediately	**Dose 6 is late and the time is after 23:00** Miss this dose
7	Day 4, 06:00	Give this dose at scheduled time	Give this dose at scheduled time

If a PK sample was scheduled for the missed dose, the PK sample should be taken at the next dose and the actual time that the dose was given and the actual sample time and date should be recorded.

Missed doses will not be replaced.

In the case where a patient stops study drug early because of improvement, protocol assessments including PK should be continued.

6.4.3 Labelling

Labels will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. The labels will fulfil GMP Annex 13 requirements for labelling. Label text will be translated into local language. Labels will include the following the following information: protocol number, storage conditions, batch identification number, and instructions for dosing; there will be a blank line for the pharmacist to add the patient's enrolment number. The iv bag cover labelling will contain similar information but will exclude the batch number in order to maintain the investigator blinding.

6.4.4 Storage

All study drugs must be kept in a secure place under appropriate storage conditions. The Pharmacist Handling Instructions and the Investigational Product label specify appropriate storage and shelf life.

6.5 Pre-study, concomitant and post-study treatment(s)

6.5.1 Pre-study treatments

Investigators will record all pre-study concomitant medications taken by patients in the 2 weeks prior to patients providing written informed consent for the study. In addition, special attention will be paid to eliciting information about the pre-study therapies listed

[redacted]

below. Patients are not eligible for the study if they have taken any of following within the specified timeframe:

- Immunosuppressants (eg, methotrexate, cyclosporine, tacrolimus) within 2 months before provision of written informed consent for the study.
- High dose steroids (eg, >40 mg or 0.5 mg/kg prednisone or a steroid with equivalent activity, daily for >7 days) within 1 month before provision of written informed consent for the study.
- Currently undergoing active radiation or chemotherapy (including non-cytotoxic) treatment for any type of malignancy (hormonal manipulation therapies for breast and prostate malignancies are permitted).
- Antivenom manufactured using ovine serum, digoxin immune Fab, crotalidae polyvalent immune Fab (ovine), or other parentally-delivered sheep-derived product at any time.
- Anti-TNF antibodies (eg, infliximab, adalimumab, etanercept) within 8 weeks before provision of written informed consent for the study.

6.5.2 Concomitant medications

All medications and aspects of medical management that are standard in the treatment of severe sepsis and/or septic shock as well as any treatment for inter-current diseases will be allowed with the exception of the following during the treatment period (Days 1 to 6):

- Immunosuppressant drugs (eg, methotrexate, cyclosporine, tacrolimus)
- Anti-TNF antibodies (eg, infliximab, adalimumab, etanercept) other than study drug.

Patients requiring immunosuppressant drugs and/or anti-TNF antibodies during the treatment period (Days 1 to 6) will be discontinued from study treatment (see Section 5.4.1). If given during the treatment period or at any time prior to Day 29, the following information should be recorded in the eCRF: name of drug, start date and time, dose, route of administration, stop date and time, from 14 days prior to the loading dose until Day 29.

Drotrecogin alfa (activated) use will be permitted at the discretion of the treating physician. If drotrecogin alfa (activated) is administered, the start date and time, dose, route of administration, stop date and time must be recorded in the eCRF from 14 days prior to the loading dose until Day 29.

For all systemic (parenteral or enteral) antiinfective drugs (antibiotics, antifungals, antivirals, antiparasitics) the following will be recorded: name of drug, start date and time, dose, route of administration, stop date and time, from 14 days prior to the loading dose until Day 29.

If vasopressors are required during the loading dose, the following should be recorded from 2 hours before the loading dose, during the loading dose and until 30 minutes after completion of the loading dose: name of drug, start date and time, dose, all interim rate changes during administration, route of administration, stop date and time. This applies only to the loading dose.

For all other concomitant medications, the following will be recorded: name of drug, start date, route of administration, and stop date from 14 days prior to the loading dose until Day 29.

If the median QTcF is >500 msec at any timepoint, all concomitant medication administered in the 8 hours prior to the ECG will be recorded in the eCRF.

Oral nutrition supplements, total parenteral nutrition, with or without lipids and blood product administration (including whole blood, packed red blood cells, platelets, fresh frozen plasma), will be recorded in the eCRF from randomisation until the end of study treatment.

The administration of all concomitant medication (including IPs) must be recorded in the appropriate sections of the eCRF in accordance with Table 1.

Other medication, which is considered necessary for the patient's safety and well-being, may be given at the discretion of the investigator.

6.5.3 Post-study medications

Post-study treatment will be in accordance with institutional protocol and best practice.

6.6 Treatment compliance

AZD9773 and placebo infusions will be administered by the investigator or medically qualified personnel in a medically monitored setting. The times and dates of the AZD9773 and placebo doses will be recorded in the eCRF.

6.6.1 Accountability

The study drug provided for this study will be used only as directed in the study protocol.

The study personnel will account for all medications dispensed and returned.

It is the study centre's responsibility to establish a system for handling study drugs, including IPs, so as to ensure that:

- Deliveries of such products are correctly received by a responsible person (eg, a pharmacist) and are recorded
- Study drug is handled and stored safely and properly
- Study drug is administered only to study patients in accordance with the protocol

- Unused study drug and empty containers are destroyed at the centre or through a destruction vendor after appropriate monitoring

- Certificates of delivery and return are signed, preferably by the investigator or a pharmacist, and copies retained in the investigator file.

At the end of the study, it must be possible to reconcile delivery records with records of study drug use and destroyed/returned stock.

Study drug will be dispensed to the investigator or medically qualified personnel by the site pharmacist. The IPs will be administered to patients only by the investigator or medically qualified personnel named on the form of the Food and Drug Administration-1572 for sites in the USA, or as documented per local requirements in the clinical study agreement (CSA). Records of study drug usage should include the identification of the person to whom the study treatment was administered, the quantity and date of administration, and a record of unused study drug. The investigator/pharmacist is responsible for maintaining accurate study drug accountability records throughout the study on the relevant forms provided by AstraZeneca or PAREXEL. Each administration of study drug will be documented in the eCRF.

7. COLLECTION OF STUDY VARIABLES

7.1 Recording of data

The investigator will ensure that all data collected in the study are provided to AstraZeneca. He/she ensures the accuracy, completeness, legibility and timeliness of the data recorded in the appropriate sections of the eCRF and according to any instructions provided and of the provision of answers to data queries according to the CSA.

The investigator will provide AstraZeneca with all data produced during the study from the scheduled study assessments. He/she ensures the accuracy, completeness, legibility, and timeliness of the data reported to AstraZeneca in the eCRF and in all required reports.

Data will be entered in the Web Based Data Capture (WBDC) system at the study site. Trained study personnel will be responsible for entering data specified in the protocol into the WBDC system and according to the eCRF instructions. When data have been entered, reviewed, edited and Source Data Verification performed by a PAREXEL representative, the data will be frozen to prevent further editing. The investigator will be notified to sign the eCRF electronically as per the eCRF instructions. A copy of the eCRF data will be archived at the study site.

7.2 Screening and demography procedures

The following screening and demographic data must be collected prior to the first dose of study drug and will be documented in the eCRF (see Table 1 for the timing of these assessments). All times will be recorded using the 24-hour clock.

- Provision of written informed consent by the patient or his/her legally authorised representative. This must be obtained at screening for all patients. Additional written informed consent for participation in the genetic and/or biomarker research is also required for patients willing to participate.
- Confirmation of inclusion and exclusion criteria.
- Date of birth, race/ethnic background, and gender, date and time of admission to ICU, distance of patient's residence from study hospital, details of any transfer from previous hospital to study hospital.
- Medical and surgical history including previous medications (see Section 6.5.1) and concomitant medications, and Charlson Comorbidity Scale (see Section 7.5).
- Physical examination, plus measurement of height, weight (measured as close as possible to the first dose but within 24 hours before the first dose), lung auscultation and a dermal examination (the baseline physical examination at screening must be done within 4 hours before study drug administration) (see Section 7.3.6).
- Blood samples will be collected for:
  - Serum pregnancy test (patients may be entered into the study on the basis of a negative urine pregnancy test, pending the results of a serum pregnancy test; if the serum pregnancy test is positive, the patient must be discontinued from study treatment), unless post-partum.
  - Haematology, clinical chemistry, coagulation parameters, and safety monitoring; samples to be collected within 12 hours prior to start of first infusion (within 6 hours for lactate) (see Section 7.3.5.1).
  - Optional blood sample for biomarker development (see Section 7.8.1). This should be taken at screening within 3 hours prior to the first dose.
  - Optional blood sample for genetic research (see Section 7.8.1). This should be taken at screening but may be taken at any time during the study.
  - Cytokines and chemokines.
  - Plasma renal panel for exploratory analysis.
  - IgE.
- Urine sample (see Section 7.3.5.1):
  - Urinalysis.

- Ventilator use and pulmonary assessment (see Section 7.6.4).
- Vital signs including oximetry (see Section 7.3.8).
- APACHE II score; modified Sequential Organ Failure Assessment (SOFA) score, and Glasgow Coma Score (see Sections 7.6.1 and 7.6.3).
- Daily volume status prior to randomisation.
- AEs.
- Assessment of organ failure (see Section 7.6.5).
- Infection assessment (see Section 7.6.7). The site of infection at screening should be noted. All patients must have a blood culture prior to randomisation. The blood culture result does NOT have to be known prior to randomisation.

7.2.1 Follow-up procedures

The follow-up data will be collected and recorded in the appropriate sections of the eCRF (refer to Study Plan, Table 1). Whether a patient is alive or not at Day 29+2 and Day 90+14, should be recorded in the eCRF (see Table 1). Additionally, the question will be asked "Was aggressive medical care withdrawn?" for those patients who died. For patients discharged from a medical setting, a vendor specialising in home visitation and/or medical aftercare may assist in obtaining follow-up study information according to study procedures.

For HRQoL, the questionnaire may be completed face-to-face or by telephone. Completion of the questionnaire will be interviewer-led.

7.3 Safety

It is of the utmost importance that all staff involved in the study is familiar with the content of this section. The international co-ordinating investigator is responsible for ensuring this.

7.3.1 Definition of adverse events

An adverse event is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (eg, nausea, chest pain), signs (eg, tachycardia, enlarged liver) or the abnormal results of an investigation (eg, laboratory findings, ECG). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

The term AE is used to include both serious and non-serious AEs.

Treatment-emergent AEs (TEAEs) (ie, not present at baseline or worsened in severity following start of treatment), including sepsis-related symptoms should be reported as AEs.

7.3.2 Definitions of serious adverse event

A serious adverse event is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up), and at any dose of the IP or placebo, that fulfils one or more of the following criteria:

- Results in death. All deaths that occur between provision of informed consent and Day 90 must be reported on the statement of death page.
  - Deaths between provision of informed consent and Day 29, if considered unequivocally due to sepsis by the investigator, should **NOT** be reported as a SAE but should be recorded on the statement of death page.
  - Deaths between provision of informed consent and Day 29 if **NOT** considered unequivocally due to sepsis by the investigator should be reported as an SAE as well as on the statement of death page.
  - Deaths between Days 30 and 90 will **ONLY** be reported as a SAE if considered to be related to late-onset toxicity to the study drug by the investigator.
- Is immediately life-threatening.
- Requires in-patient hospitalisation or prolongation of existing hospitalisation.
- Results in persistent or significant disability or incapacity.
- Is a congenital abnormality or birth defect.
- Is an important medical event that may jeopardise the patient or may require medical intervention to prevent one of the outcomes listed above.

For reporting purposes, any suspected transmission via a medicinal product of an infectious agent is also considered an SAE and is reported in an expedited manner. Any organism, virus or infectious particle (for example prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent.

For further guidance on the definition of a SAE, see Appendix B to the Clinical Study Protocol.

Note that SAEs that could be associated with any study procedure should also be reported. For such events the causal relationship is implied as “yes”.

7.3.3 Recording of adverse events

Non-serious AEs and SAEs are collected from the provision of written informed consent and throughout the study until Day 29 (see Section 7.3.4). Any new onset AEs/SAEs beginning

after Day 29 will not be collected unless the investigator deems that such an event is related to late-onset toxicity of the drug or is a pre-specified AE of special interest.

The method of detecting AEs and SAEs in this study will be by:

- Observation by the investigational team, other care providers or relatives.
- Information volunteered by the patient or carer.

Open-ended and non-leading verbal questioning of the patient at every visit (where possible), such as the following: "How are you feeling? Have you had any (other) medical problems since your last visit/check?"

  - If a patient is unable to answer for themselves, his/her carer will be questioned instead of the patient. They will be asked open-ended and non-leading verbal questions at every visit (where possible), such as the following: "How is he/she feeling? Has he/she had any (other) medical problems since his/her last visit/check?".

Variables

The following variables will be recorded in the eCRF for each AE: description of the AE, date and time when the AE started and stopped, maximum intensity, whether the AE is serious, date and time the AE became serious, causality rating to IP (yes or no), action taken with regard to IP (eg, changes to study treatment, other treatment given, follow-up tests), severity and outcome.

AEs will be coded according to the version of the Medical Dictionary for Regulatory Activities (MedDRA) agreed with AstraZeneca.

Severity of adverse events

The severity of AEs will be recorded in the eCRF as follows:

- mild (as judged by the investigator).
- moderate (discomfort sufficient to cause interference with normal activities).
- severe (as judged by the investigator).

Further details on classifying the severity of infusion or hypersensitivity reactions are provided in Appendix D.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 7.3.2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE. On the other hand, a stroke

[redacted]

that results in only a limited degree of disability may be considered a mild stroke but would be a SAE.

Causality of adverse events

The investigator will assess causal relationship between IP and AEs, and answer "yes" or "no" to the question "Do you consider that there is a reasonable possibility that the event may have been caused by the IP.

AEs will be recorded in the eCRF as being related or not-related to study drug. For an AE to be a suspected drug-related event, there should be at least a reasonable possibility of a causal relationship between the study medicinal product and the AE. If an AE is considered to be related to treatment(s) other than the study drug, this treatment must be named in the eCRF.

For SAEs, causal relationship will also be assessed for study procedures.

For SAEs that could be associated with any study procedure, the causal relational is implied as "yes".

A guide to the interpretation of the causality question is found in Appendix B.

Adverse events based on signs and symptoms

All AEs spontaneously reported by the patient or reported in response to the open question from the study personnel: "Have you had any health problems since the previous visit?", or revealed by observation will be collected and recorded in the eCRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

Adverse events based on examinations and tests

The reporting of laboratory/vital signs/ECG abnormalities as both abnormalities and AEs should be avoided.

Deterioration as compared to baseline in protocol-mandated laboratory values, vital signs and other safety variables should only be reported as AEs if they fulfil any of the SAE criteria or are the reason for discontinuation of treatment with the IP. However, the investigator may record such findings as an AE at his/her discretion in addition to completing an unscheduled laboratory/vital signs page with the information on the clinically significant test abnormality. If a deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign/symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Any new or aggravated clinically relevant abnormal medical finding at a physical examination, dermal examination or lung auscultation as compared with the baseline assessment will be reported as an AE. Clinically relevant deterioration in

unscheduled assessments of laboratory/vital signs/ECG parameters should be reported on additional eCRF pages.

Wherever possible, the reporting investigator uses the clinical, rather than the laboratory term (eg, anaemia versus low haemoglobin value).

Overdose

Please refer to Section 1.2.

Pregnancy

Please refer to Section 1.3.

Deaths

All deaths occurring from provision of informed consent until Day 90 must be reported on the statement of death page. The cause of death may be reported as a SAE based on the criteria described in Section 7.3.2.

Follow-up of unresolved adverse events

After the initial AE/SAE report the investigator is required to follow up proactively each patient and provide further information to PAREXEL Clinical Studies Safety Centre on the patient's condition. During the study all AE/SAEs should be followed up to resolution or until the patient completes the study (ie, Day 90 or death) unless the event is considered by the investigator to be unlikely to resolve due to the patient's underlying disease (in these cases, the investigators must record their opinions in the patient's medical records), or the patient is lost to follow-up. Events still present at the time of death, and that were not the cause of death, should be classified as "ongoing". AstraZeneca and/or PAREXEL retain the right to ask for further information on any AE, which may be considered of interest.

Other significant adverse events

During the evaluation of the AE data, medically qualified experts on the study team will review the safety data to select significant AEs of particular clinical importance/special interest, which will be considered other significant AEs (OAEs) / events of special interest and reported as such in the Clinical Study Report.

Infusion reactions

Full details on classifying infusion reactions are provided in Appendix D. In the event a patient experiences a hypersensitivity reaction, a blood sample for tryptase, IgE and quantitative eosinophil count should be obtained at 20 to 60 minutes post suspected infusion or hypersensitivity reaction and at Day 29 (see Table 1).

Worsening adverse events present at baseline

Conditions present at baseline will be recorded. If such a condition worsens or deteriorates, it will be recorded as an AE/SAE with the onset date corresponding to the date that it worsened from its baseline intensity.

7.3.4 Reporting of serious adverse events

All SAEs have to be reported, whether or not considered causally related to the investigational product, or to the study procedure(s). All SAEs will be recorded in the eCRF. Death may be reported as a SAE based on the criteria described in Section 7.3.2.

If any SAE occurs in the course of the study, then investigators or other site personnel inform appropriate PAREXEL representatives within 24 hours of becoming aware of the SAE.

The designated PAREXEL representative works with the investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within one calendar day*** of initial receipt for fatal and life-threatening events and **within five calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform PAREXEL representatives of any follow-up information on a previously reported SAE within 24 hours.

Follow up information should be sent to AstraZeneca Patient Safety within the same timelines as the initial report unless any follow-up information indicates a change in the SAE from serious to fatal or life-threatening: this information needs to be forwarded to AstraZeneca Patient Safety within one calendar day*.

Initial and follow-up SAE information will be reported using paper SAE reporting forms.

* For fatal and life-threatening events the PAREXEL representative sends the report on the day that they first become aware of it. If this is not possible, it can be sent as early as possible on the next business day. If the report is received after normal business hours, for instance during a weekend or public holiday, the information is forwarded as early as possible on the first business day following the weekend or holiday.

Investigators or other site personnel send the relevant SAE report by fax to the designated PAREXEL representative.

[redacted]

The investigator will submit a paper SAE report to:

	Fax number	Hotline number	Emergency contact number
North America **Europe and South Africa** **Australia** **South America**	[redacted]		

SAE information will also be entered and submitted into the WBDC system on the relevant eCRF modules. SAE and AE data entered into the eCRF does not need to meet the same timelines but should be done in a timely manner.

The reference document for definition of expectness/listedness of adverse drug reactions is the IB.

7.3.5 Laboratory safety assessment

7.3.5.1 Methods of assessment

Blood samples will be collected for haematology, clinical chemistry, coagulation parameters, and safety monitoring. Urine samples will be collected for urinalysis. Unscheduled laboratory results, from tests pre-specified in this protocol, that are both abnormal and clinically significant will be recorded on an additional eCRF page(s) and the data will be included in the assessment of out of range parameters. The investigator will decide if the unscheduled laboratory results are "clinically significant".

All blood and urine samples will be collected according to standard procedures at the timepoints scheduled in Table 1 by the investigator or medically qualified personnel. Details on sampling and handling procedures for samples processed centrally will be specified in the study laboratory manual. Samples should be taken before dosing as applicable.

The parameters to be assessed are detailed in Table 4.

For blood volume see Section 8.1

[redacted]

Table 4 Laboratory safety parameters

Haematology[a]	Clinical chemistry[a]	Coagulation[a]	Safety monitoring	Urinalysis[a]
Haemoglobin	ALT	apTT	Troponin I	Protein
Haematocrit	AST	D-dimer	Multiplex renal panel	Blood
WBC with differential	GGT	Fibrinogen	Total HASA bridging assay	Ketones
Platelets	Alkaline phosphatase	International normalised ratio (PT)	HASA IgG	Microscopic analysis
	Serum albumin		Protein C activity	pH
	Creatinine		IgE[c]	Clarity
	Blood urea nitrogen		Tryptase[c]	Colour
	Total protein			Specific gravity
	Total bilirubin			Glucose
	Creatine kinase			
	Calcium[b]			
	Lactate dehydrogenase			
	Lactate			
	Sodium			
	Potassium			
	Chloride			
	Carbon dioxide			
	Glucose			

[a] To be performed at local laboratory.
[b] Calcium (total).
[c] Tryptase and IgE are not routine safety parameters and will only be measured in the event of an infusion or hypersensitivity reaction, although IgE is being done routinely at screening.

Abbreviations: ALT = alanine aminotransferase; apTT = activated partial thromboplastin time; AST = aspartate aminotransferase; GGT = gamma glutamyl transferase; HASA = human anti-sheep antibody; Ig = immunoglobulin; PT = prothrombin time; WBC = white blood cell.

A blood sample for serum pregnancy testing will be taken from all females of child-bearing potential at screening. Patients may be entered into the study on the basis of a negative urine pregnancy test (sensitivity of at least 50 mIU/mL of βHCG), pending results of the serum pregnancy test. If the serum pregnancy test is positive, the patient must be discontinued from study treatment, unless post-partum.

Haematology, clinical chemistry, coagulation and urinalysis parameters will be analysed locally (d-dimer should be analysed using a quantitative assay) with the exception of those specified below.

Each laboratory (local and central) will be required to provide up-to-date reference ranges.

Collection of troponin I, protein C activity, IgE and tryptase

Blood samples for measurement of troponin I, protein C activity, IgE and tryptase will be collected according to standard procedures at timepoints specified in Table 1 (or only in case of infusion or hypersensitivity reactions for tryptase, see Appendix D) by the investigator or medically qualified personnel. Details on sampling and handling procedures for samples processed centrally will be specified in the study laboratory manual.

Blood samples may be taken from a peripheral or central venous source or from an arterial source. The time that each blood sample is taken will be recorded in the eCRF. If a sample is missed, the next sample should be taken as scheduled.

Analysis of troponin I, IgE and protein C activity will be done centrally by Covance Central Laboratory Services, Inc.

Tryptase (if obtained for infusion or hypersensitivity reactions) samples will be analysed by Specialty Laboratories. All laboratory samples will be labelled, stored and shipped according to standard laboratory procedures.

Collection of Human Anti-Sheep Antibody (HASA) IgG and total HASA bridging assay

Blood samples for measurement of HASA IgG and total HASA by bridging assay will be collected according to standard procedures at timepoints specified in Table 1 by the investigator or medically qualified personnel, according to methods specified by Covance or AstraZeneca. In addition, samples may be used for the improvement or development of further analytical assays related to AZD9773 or sepsis. Details on sampling and handling procedures will be specified in the study laboratory manual. Blood samples may be taken from a peripheral or central venous source or from an arterial source. The time that each blood is taken will be recorded in the eCRF. If a sample is missed, the next sample should be taken as scheduled.

[redacted]

Exploratory safety markers

Blood samples for plasma renal panel exploratory analysis will be collected according to standard procedures at timepoints specified in Table 1 by the investigator or medically qualified personnel, according to methods specified by Covance or AstraZeneca. Details on

[redacted]

sampling and handling procedures will be specified in the study laboratory manual. Blood samples may be taken from a peripheral or central venous source or from an arterial source. The time that each blood is taken will be recorded in the eCRF. If a sample is missed, the next sample should be taken as scheduled.

A multiplex panel of established and exploratory markers of renal damage will be assessed. The plasma renal panel will be analysed by a third party vendor. Samples will be labelled, stored and shipped according to AstraZeneca Standard Operating Procedures.

7.3.6 Physical examinations

Physical examinations will be performed at Baseline and Day 29 (or the discharge visit if prior to Day 29) (Table 1) and reported in the physical examination page of the eCRF. The examination should be based on the following body systems: general appearance, skin, head and neck, lymph node, thyroid, musculoskeletal/extremities, cardiovascular, lungs, abdomen, and neurological. A minimum of a lung auscultation and dermal examination must be performed after each dose. Pulmonary auscultation must be performed by a medically qualified staff member who will listen to the patient's lungs to assess whether there is a change from baseline. A dermal examination will also be performed to assess for infusion reactions such as oedema, urticaria and rash. Additional findings of note will be recorded at this time. In the event of an infusion reaction (as evidenced by a change in BP, skin or lung examination), an additional full physical examination should be performed and changes (skin, lung, physical examination and BP) should be recorded in the eCRF.

Height will be recorded at screening. Weight will be recorded at the timepoints specified in Table 1. Screening weight will be measured as close as possible to the first dose but within 24 hours before the first dose.

7.3.7 Electrocardiogram

A digital 12-lead ECG will be recorded, in triplicate within 1 to 2 minutes, at the timepoints specified in Table 1 using equipment provided by the central ECG laboratory eResearch Technology, Inc (eRT). Patients must relax in a recumbent position for at least 10 minutes prior to the ECG reading being recorded. eRT will provide centralised processing of ECGs and data storage. Each ECG will define HR, PR interval, RR interval, QRS duration, QT interval, QTc (QTcF and Bazett [QTcB] corrections), T wave morphology (normal versus abnormal) and overall interpretation. eRT will contact the study centre if alert criteria are found on any ECG. Specific procedures for use of the ECG recorder and transfer process, as well as detailed alert criteria, will be provided in separate study documentation.

Abnormal values should not be recorded as AEs unless they result in discontinuation from the study or they fulfil the criteria for an SAE.

Abnormal QTcF values in relation to concomitant medications will be evaluated.

7.3.8 Vital signs, pulse, blood pressure and oximetry

Vital signs and blood oxygen-haemoglobin saturation will be collected at the timepoints specified in Table 1.

Vital signs measured will include: BP (systolic and diastolic), pulse rate (PR), RR, and body temperature (oral, aural or core). The method of measuring body temperature must be recorded in the eCRF. BP, RR and PR will be measured after the patient has been in the supine position for 5 minutes.

The oxygen-haemoglobin saturation of the blood will be assessed using standard pulse oximetry or by arterial blood gas for those patients who have an arterial blood gas obtained.

Abnormal values should not be recorded as AEs unless they result in discontinuation from the study or they fulfil the criteria for an SAE.

7.4 Efficacy and pharmacodynamic measurements

Objective	Variables
To evaluate the effect of two different doses of AZD9773 versus placebo on ventilator-free days over 28 days and further characterise the safety profile of AZD9773.	TNFα, IL-6, IL-8 Multiplex cytokine assay for exploratory chemokines Neutralising antibody assay Procalcitonin Lactate VFDs 7-day mortality 28-day mortality Mortality at Day 90 Organ failure-free days Shock-free days ICU-free days

7.4.1 Efficacy

Mortality will be assessed at the timepoints specified in Table 1. VFDs, organ failure-free days, shock-free days and ICU-free days will be assessed at the timepoints specified in Table 1. For further details of these parameters, see Section 7.6.

7.4.2 Cytokine serum concentrations

Blood samples for measurement of cytokine serum concentrations will be collected from all patients at the timepoints specified in Table 1 by the investigator or medically qualified personnel, according to methods specified by Covance. Details on sampling and handling procedures will be specified in the study laboratory manual.

Cytokine samples will be taken as follows:

- TNFα for enzyme-linked immunosorbent assay (ELISA) analysis will be taken at screening - pre-infusion; Day 1 at 1-2 hours after the end of infusion; before the morning dose on Day 2, 1-2 hours after the end of infusion on Day 2, before the morning dose on Days 4 and 6; and on Days 7, 10 and 15.

- IL-6, and IL-8 samples for ELISA analysis will be taken at screening - pre-infusion; Day 1 at 1-2 hours after the end of infusion, and before the morning dose on Days 2, 4, and 6.

- Multiplex assay samples for exploratory chemokines will be taken at screening - pre-infusion; Day 1 at 1-2 hours after the end of infusion; before the morning dose on Day 2, 1-2 hours after the end of infusion on Day 2, before the morning dose on Days 4 and 6; and on Days 7, 10 and 15. Samples will be used to evaluate the potential utility of a multiplex chemokine assay.

7.4.3 Neutralising antibody assay

Blood samples for neutralising antibody (NAB) assay will be collected according to standard procedures at timepoints specified in Table 1 by the investigator or medically qualified personnel, according to methods specified by Covance or AstraZeneca. In addition, samples may be used for the improvement or further development of assay methodology. Details on sampling and handling procedures will be specified in the study laboratory manual. Blood samples may be taken from a peripheral or central venous source or from an arterial source. The time that each blood is taken will be recorded in the eCRF. If a sample is missed, the next sample should be taken as scheduled.

The NAB assay will be analysed by Covance Laboratories Ltd., Otley Road, Harrogate, HG3 1PY, United Kingdom. Samples will be labelled, stored and shipped according to AstraZeneca Standard Operating Procedures.

7.4.4 Lactate and procalcitonin

Blood samples for analysis of serum lactate and serum procalcitonin will be collected according to local standard procedures at the timepoints scheduled in Table 1 by the investigator or medically qualified personnel. However, for serum lactate, there must be an interval of at least 6 hours between the screening samples and the samples at Day 1. To preserve this minimum 6-hour window, the Day 1 samples may in fact need to be taken on Day 2.

Blood samples for lactate assessments will be analysed locally. Each laboratory will be required to provide up-to-date reference ranges. See Section 8.1 for the total estimated volume of blood samples to be collected.

7.4.5 Patient reported outcomes (PRO)

7.4.5.1 Short Form 36 Health Survey, version 2 Acute

Assessment of patients' HRQoL will be derived from the Short Form 36 Health Survey, version 2 Acute (SF-36v2 Acute) questionnaire. The SF-36v2 Acute is a multi-purpose, short-form health survey with only 36 questions, which is provided in Appendix K. It yields an 8-scale profile of HRQoL scores (Physical functioning Role-physical, Bodily pain, General health, Vitality, Social functioning, Role-emotional, Mental health) as well as a psychometrically based physical (physical component score) and mental health summary (mental component score) measures and a preference based health utility index.

The SF-36v2 Acute differs from the standard SF-36 in that the recall period for 6 of the 8 scales (Role-physical, Bodily pain, Vitality, Social functioning, Role-emotional and Mental health) changes from "the past 4 weeks" to "the past week". Two scales, Physical functioning and General health do not have a recall period; the items and instructions for these scales are identical across acute and standard forms. This version was chosen for the study as the 1-week recall period seems more appropriate for these scales specifically at Day 29.

Additionally for this study, 1 further change will be made to the SF-36v2 Acute. The original question 2 from the standard version – " Compared to 1 year ago, how would you rate your health in general now?" will replace the question 2 from the acute version – " Compared to 1 week ago, how would you rate your health in general now?". This has been included to allow a better understanding of a patient's return to their pre-sepsis levels of HRQoL. As this question does not form a part of any of the main outcome measures outlined above, this does not affect the validity of these endpoints.

The SF-36v2 Acute will be completed at Day 29+2 and at Day 90+14. The Day 29 value will be the initial measurement and the Day 90 value will be taken as follow-up. The SF-36v2 Acute has been validated for multiple completion methods (face-to-face, telephone, IVRS), and the most appropriate method for the patient will be used in this study, although all assessments will be interviewer-led.

7.4.5.2 Administration of PRO questionnaires

The SF-36v2 Acute will be administered at Day 29+2 and at Day 90+14 follow-up contact as outlined in Figure 1 and Table 1.

7.5 Charlson Comorbidity Scale Assessment

Comorbidity at Screening will be assessed using the Charlson Comorbidity Scale (see Appendix L). Charlson et al (Charlson et al 1987) developed a score for evaluating prognosis based on age and comorbid conditions. With each increased level of the comorbidity index the cumulative mortality attributable to comorbid disease increases in a step-wise fashion.

[redacted]

7.6 General assessment of sepsis care

7.6.1 Acute Physiology and Chronic Health Evaluation (APACHE) II Scores

APACHE II is a point score based upon 12 routine physiological measurements, age and previous health status that provides a general measure of severity of disease. The measurements needed to calculate APACHE II Scores will be recorded at the timepoints scheduled in Appendix E. APACHE II Scores will be calculated using the assessments from the 24 hours preceding randomisation, not the calendar day.

The 12 physiological measurements should be assessed using standard procedures. These are: temperature (°C), mean arterial pressure (mmHg), heart rate (ventricular response), RR (ventilated or non-ventilated), alveolar to arterial oxygen tension difference (if $FiO_2 \geq 0.5$) or PaO_2 (if $FiO_2 < 0.5$), arterial pH (serum bicarbonate if no arterial blood gas for pH [venous mmol/L]), serum sodium (mmol/L), serum potassium (mmol/L), serum creatinine (mg/dL), haematocrit (%), WBC count ($10^3/mm^3$), and Glasgow Coma Score.

If more than one set of results for any parameter is obtained on the scheduled assessment day, the most out-of-range result will be used for the calculation of the score (eg, the worst results from that day).

For further details of the APACHE II Score, see Appendix E.

7.6.2 Glasgow Coma Score

The assessments needed to calculate the Glasgow Coma Score at screening, Day 6 and Day 15 will be performed as part of the APACHE II assessment at screening and at the timepoints shown in Appendix F to assess level of consciousness and degree of dysfunction. Patients will be assessed with regard to their level of eye, verbal and motor responses as described in Appendix F. If it is possible to do so, the score should be obtained prior to administering medications that could alter the Glasgow Coma Score. For subsequent daily assessments, the Glasgow Coma Score should be obtained during sedation holiday periods. If this is not possible, the patient's most likely response should be recorded.

7.6.3 Modified Sequential Organ Failure Assessment (SOFA) Scores

A modified SOFA score (ie, not including Glasgow Coma Score) will be calculated at each of the timepoints shown in Table 1. For each of the following routine assessments, the worst value of the day will be recorded in the eCRF: PaO_2/FiO_2 (mmHg) or oxygen saturation by pulse oximetry (SpO_2)/FiO_2 (mmHg), platelet count, bilirubin, vasopressor use (µg/kg/min, mmHg), and creatinine ([or urine output]). For laboratory values, use last available (if within 48 hours). On days when laboratory results are unavailable, values will be extrapolated from the previous available values. On days when laboratory results are unavailable, values will be extrapolated from the previous available values (Section 13.3.5).

The SOFA score for the cardiovascular component does not account for the use of phenylephrine or vasopressin as vasopressor medications. A cardiovascular component score of 3 will be assigned for phenylephrine doses of ≤ 300 µg/kg/min or vasopressin doses of

< 0.04 units/min. A cardiovascular component score of 4 will be assigned for phenylephrine doses of > 300 µg/kg/min or vasopressin doses of ≥ 0.04 units/min.

7.6.4 Ventilator use and pulmonary assessment

Whether a patient requires mechanical ventilation will be recorded at the timepoints specified in Table 1. If a patient requires mechanical ventilation, data will be recorded regarding whether ventilator weaning was attempted (see Appendix H for recommended procedures for ventilator weaning). The definitions of VFDs and unassisted breathing are provided in Section 12.2.6.

For patients on mechanical ventilation the following ventilator settings will be recorded daily at the timepoints specified in Table 1: tidal volume, FiO_2, peak airway pressure over the last 24 hours, plateau pressure, positive end expiratory pressure, and RR. For patients on mechanical ventilation an arterial blood gas (pH, PaO_2, $PaCO_2$ and FiO_2 at the time the sample was obtained), if available, will be recorded once per day. If more than one value is obtained, the value closest to 08:00 will be used.

Predicted body weight will be recorded on the ventilator eCRF for assessment of tidal volume.

Ventilator-free days

The number of VFDs will be derived. This is a composite endpoint including days free of mechanical ventilation and mortality.

7.6.5 Organ failure assessment

Organ failure developing after study entry, regardless of cause, will be assessed using the modified SOFA score at the timepoints specified in Table 1.

7.6.6 Septic shock

Occurrence of septic shock will be collected as part of organ failure outcome data.

7.6.7 Infection assessment

The presence of infections will be monitored at the timepoints specified in Table 1. At screening, the site of infection should be noted. All patients must have a blood culture prior to randomisation. The blood culture result does NOT have to be known prior to randomisation. The estimated date and time of presentation of all infections will be recorded. The time of all blood cultures will be recorded. Additional information will be collected for positive blood cultures. Positive culture results defining the index infection will also be recorded. Any subsequent positive culture will also be recorded. The site of infection, associated pathogen(s) and antimicrobial susceptibility for the associated pathogens will be recorded. In addition, infections will be classified as community acquired or healthcare associated. Healthcare associated will be defined as a patient meeting one or more of the following (Niederman et al 2005):

1. Hospitalisation for ≥2 days in the preceding 90 days.

2. Residence in a nursing home or extended care facility.

3. Undergoing home infusion therapy (including antibiotics).

4. Chronic dialysis within the preceding 30 days.

5. Home wound care.

6. A family member with a multidrug-resistant pathogen.

7.6.8 Antibiotic use

The use of antibiotics will be recorded as part of concomitant medication monitoring as described in Section 6.5.2.

The time to first administration of antibiotics for a sepsis infection is defined as the time from timepoint of first qualifying organ failure meeting study entry requirements to the timepoint of the first administration of antibiotics. Investigators will be asked to record the time and date of qualifying organ failure and the time and date of the first administration of antibiotics for that infection. Investigators will also be asked to record the time and date of the patient first seeking care for the infection/septic process and the time and date of the first administration of antibiotics for that infection.

7.6.9 Assessment of ICU-free days

Assessment of ICU-free days will be obtained by asking the investigator to determine if the patient is receiving ICU-standard care (or equivalent) on each day up to Day 15 (over 14 days). In the event of an affirmative response, a further question will be asked to determine if this ICU care is considered necessary (rather than being due to logistical reasons). Only days in the ICU (or equivalent), which the investigator considers necessary, will be regarded as ICU days.

7.6.10 Shock-free days

The number of shock-free days will be recorded up to Day 15. Shock-free is defined as a score <2 taken from the cardiovascular component of the modified SOFA score (see Appendix G).

7.7 Pharmacokinetics

Objective	Variables
To further characterise the PK of AZD9773.	AZD9773 Total Fabs serum and AZD9773 specific Fabs concentration AZD9773 serum concentration

AZD9773 refers to the active constituent of CytoFab™ ie, rhTNFα immune Fab (ovine)[redacted]

[redacted]

The methods for collection of biological samples and derivation of PK variables are presented below in Sections 7.7.1 and 7.7.2

7.7.1 Collection of biological samples

Blood samples for measurement of AZD9773 specific and AZD9773 Total Fabs (rhTNFα immune Fab and all other non-TNFα-directed Fabs present in AZD9773) serum concentrations will be collected at the timepoints shown in Table 5 by the investigator or medically qualified personnel according to standard procedures. Blood samples taken during and up to 30 minutes after an infusion may be obtained from either a peripheral venous or arterial source. All other samples may be taken from a central or peripheral venous source or arterial source; the source of the specimen (central or peripheral venous or arterial) should be recorded in the eCRF. If it is not possible to obtain a good peripheral or arterial sample at the timepoints up to 30 minutes post-dose, then the site should record the sample as unobtainable.

The time that each blood sample is taken will be recorded in the eCRF. If a sample is missed, the next sample should be taken as scheduled and the time recorded. If a PK sample was scheduled for a missed dose, the PK sample should be taken at the next dose and the actual time that the dose was given and the actual sample time and date should be recorded.

In the case where a patient stops study drug early because of improvement, PK assessments should be continued.

All blood samples will be taken according to methods specified by Covance and/or AstraZeneca. Details on sampling and handling procedures will be specified in the study laboratory manual.

Table 5 Pharmacokinetic sampling

Blood sampling[a]	Sampling times
All patients	Loading dose, Day 1: pre-dose, 30 minutes (immediately after end of infusion), between 1 to 2 hours post-end of infusion, and between 9 to 12 hours post-end of infusion[b]
	Day 3: pre-infusion sample (preferably before the first dose of the day)
	Day 4: post-infusion sample (preferably following the first dose of the day)
	Day 5/6: sample 12 hours after the last infusion
	Day 10
	Actual times of sampling must be recorded[c].

[a] Blood samples taken during and up to 30 minutes after an infusion must be either peripheral venous or arterial samples. All other samples may be taken from a central or peripheral venous source or arterial source; the source of the specimen (central or peripheral venous or arterial) should be recorded in the eCRF.

[b] The 9-12 hour timepoint may be adjusted to fall between 6-15 hours post-end of infusion if appropriate (eg, a one-time dosing interval adjustment is being incorporated, however, the sample should be collected prior to start of infusion for the first maintenance dose).

[c] If a PK sample was scheduled for a missed dose, the PK sample should be taken at the next dose and the actual time that the dose was given and the actual sample time and date should be recorded.

Samples will be collected, labelled stored and shipped as detailed in the Laboratory Manual. Bioanalytical evaluation of the analyte concentrations will be done by Quotient Bioresearch Ltd. (Newmarket Road, Fordham, Cambridgeshire CB7 5WW, United Kingdom). For transfer to Quotient Bioresearch Ltd., samples will be labelled, stored and shipped according to AstraZeneca or Quotient Bioresearch Ltd. Standard Operating Procedures.

For estimated blood volume see Section 8.1.

7.7.2 Determination of drug concentration in biological samples

Bioanalytical evaluation of the analyte concentrations will be done by Quotient Bioresearch Ltd. using the assay described in the Laboratory Manual. AstraZeneca will perform derivation of PK data. Samples may also be used for evaluation of Incurred Sample Analysis or Incurred Sample Stability.

The relationship between AZD9773 plasma concentration or other parameters of exposure and measures of PD response, efficacy and AEs will be explored. Full details of the population PK and PK-PD analysis will be given in the Pharmacokinetic Analysis Plan approved before the start of analysis and will be reported separately to the Clinical Study Report.

7.8 Pharmacogenetics and Biomarker

7.8.1 Collection of samples

The blood sample for genetic research will be obtained from the patients after randomisation. Samples will be collected, labelled stored and shipped as detailed in the Laboratory Manual.

- Optional blood sample for biomarker development (see Section 7.8.2). This should be taken at screening within 3 hours prior to the first dose

- Optional blood sample for genetic research (see Section 8.2.1). This should be taken at screening but may be taken at any time during the study.

For blood volume see Section 8.1.

7.8.2 Storage and analysis of samples

The biomarker samples will be processed to serum, aliquotted and stored for potential future analysis. Any analysis is likely to be performed retrospectively and only the appropriate subset of samples taken forward to formal analysis. The selection of this subset of samples will be wholly dependent on the outcome data of this study.

Any future analyses will explore factors, which may influence the disposition, efficacy, safety and tolerability to AZD9773 and/or susceptibility to or prognosis of sepsis.

7.8.3 Data analysis of samples:

The results from any exploratory analyses may be pooled with biomarker data from other studies on AZD9773 to generate or validate emerging hypotheses. It is not planned that any exploratory biomarker data will be included in the clinical study report.

Neither the patient's name nor any other personal identifiers will be part of this dataset. Only the date the patient gave consent to participation in the research and the date and time the biological sample were taken from the patient will be recorded on the sample requisition form, eCRF and database. AstraZeneca will not provide optional biomarker research results to patients, their family members, any insurance company, an employer, general physician or any other third party, unless required to do so by law. The patient's samples will not be used for any purpose other than those described in the study protocol.

Individual patients will not be identified in any report or publication resulting from this work. The data and results of this research may be reviewed with collaborators and published, but neither the patient's name nor any other personal identifiers will appear in any publication or report.

7.9 Health economics

Not applicable.

8. BIOLOGICAL SAMPLING PROCEDURES

8.1 Volume of blood

The total volume of blood that will be drawn from each patient in the study will be approximately 272.5 mL over 28 days. Approximately 25% of the scheduled blood samples are considered part of routine clinical care at the hospital laboratory and are not duplicated.

Table 6 Approximate volume of blood to be drawn from each patient over 28 days

Assessment	Sample volume (mL)	Number of samples	Total volume (mL)
Pharmacodynamics:			
IL-6, IL-8[a]	2 x 3	5	30
TNFα[b]	4	9	36
Multiplex assay for exploratory chemokines[c]	2	9	18
Procalcitonin	2.5	5	12.5
Lactate	3	3	9
Neutralising antibody assay	3.5	3	10.5
Pharmacokinetics	3	8	24
Clinical chemistry[d]	5	6	30
Haematology	3	6	18
Coagulation	3	6	18
Safety monitoring			
Troponin I	2.5	3	7.5
Protein C activity	2.5	1	2.5
HASA IgG and total HASA bridging assay	7	3	21
IgE	2.5	1	2.5
Renal panel for exploratory analysis[c]	2	9	18
Genetic research	10	1	10
Biomarker research	5	1	5
Total			**272.5**

[a] IL-6, and IL-8 samples will be taken at screening - pre-infusion; Day 1 at 1-2 hours after the end of infusion, and before the morning dose on Days 2, 4, and 6.

[b] TNFα samples will be taken at screening - pre-infusion; Day 1 at 1-2 hours after the end of infusion; before the morning dose on Day 2, 1-2 hours after the end of infusion on Day 2, before the morning dose on Days 4 and 6; and on Days 7, 10 and 15.

[c] Samples for multiplex assay for exploratory chemokines and for exploratory plasma renal panel should be taken at the same time as samples for cytokines or other blood samples and the date and time should be noted.

[d] Including pregnancy test for the sample at screening.

Abbreviations: Ig = immunoglobulin; IL = interleukin; HASA = human anti-sheep antibody; TNF = tumour necrosis factor.

8.1.1 Clinical samples

All biological samples will be handled and stored as specified in the Laboratory Manual. The analyte stability limits defined by the central and local laboratories will be applied to all analyses performed on behalf of AstraZeneca. The central and local laboratories will not analyse samples that fall outside these stability limits. Analytical data will not be reported if found to have been derived from a sample that fell outside these stability limits. The standards of procedure followed by the central and local laboratories may be amended in accordance with their respective Standard Operating Procedures.

An optional blood sample for future sepsis biomarker research will be collected at screening within 3 hours prior to the first dose (preferably at the same time as the first pre-study drug infusion cytokine blood sample) from patients who provide consent. This blood sample should ideally be drawn through the same cannula used to draw blood samples required for other study laboratory assessments, after the coagulation sample but before the safety monitoring sample. This sample will be stored and used with future sepsis biomarker assays that may become commercially available in the near future. Any analysis is likely to be performed retrospectively and only the appropriate subset of samples taken forward to formal analysis. The selection of this subset of samples will be wholly dependent on the outcome data of this study. Any future analyses will explore factors, which may influence the disposition, efficacy, safety and tolerability to AZD9773 and/or susceptibility to or prognosis of sepsis. Blood samples (4 mL for TNFα samples, 3 mL for IL samples and 2 mL for multiplex assay for exploratory chemokines.) will be collected, according to methods specified in the Laboratory Manual. Tubes will be labelled with the protocol study number, centre number, enrolment code and date of sample collection. A record of the patient consent for this research and the date of the blood sample collection will be recorded in the appropriate section of the eCRF. The analysis of the multiplex assay for exploratory chemokines is not planned to be included in the Clinical Study Report for this study. In addition, the plasma renal panel exploratory analysis is not planned to be included in the Clinical Study Report.

8.1.2 Pharmacokinetic samples

The long-term stability of the analyte(s) should be documented in method validation produced by AstraZeneca. Results from analyses of samples stored longer than the time period for which stability has been demonstrated should not be reported unless complementary analyte(s) stability data is acquired and amended to the relevant method validation report.

8.2 Genetic measurements and co-variables

8.2.1 Collection of samples for genetic research

An optional blood sample for genetic research will be collected at screening (but may be taken at any time during the study) from patients who provide written informed consent to confirm their willingness to take part in genetic research. The genetic blood sample should ideally be drawn through the same cannula used to draw blood samples required for the main study.

A single venous blood sample (10 mL) will be collected, according to methods specified by Covance or AstraZeneca. Details on sampling and handling procedures will be specified in

the Laboratory Manual. Samples will be labelled with the protocol study number, centre number, enrolment code and date of sample collection. No personal identifiers (patient name, initials or date of birth) will be placed on the tube or accompanying documentation. A record of the date of the patient consent to the genetic research and the date of the blood sample collection will be recorded in the appropriate section of the eCRF.

8.2.2 Summary of genetic assessments and analysis

The purpose of the genetic research is to generate data for use in future retrospective analyses. Future genotyping could be correlated with PK profiles or markers of AZD9773 response and/or susceptibility to or prognosis of sepsis. The results of the genetic research will not form part of the Clinical Study Report for this study. The results may be pooled with genetic data from other studies on AZD9773 to generate hypotheses to be tested in future studies.

8.3 Handling, storage and destruction of biological samples

8.3.1 Pharmacogenetic samples, storage and coding of DNA samples

The processes adopted for the coding and storage of samples for genetic analysis are important to maintain patient confidentiality.

For all samples irrespective of the type of coding used the DNA will be extracted from the blood sample. The DNA sample will be assigned a unique number replacing the information on the sample tube. Thereafter, the DNA sample will be identifiable by the unique DNA number only. The DNA number will used to identify the sample and corresponding data at the AstraZeneca genetics laboratories, or at the designated contract laboratory. No personal details identifying the individual will be available to any AstraZeneca employee or designee working with the DNA.

The blood samples and data for genetic analysis in this study will be coded. Each blood sample will be labelled with the study number and patient number. Only the investigator will be able to link the blood sample to the individual patient. The sample and data will not be labelled with a personal identifier. The link between the patient enrolment/randomisation code and the DNA number will be maintained.

This link file and any corresponding genetic data will be stored in a secure environment, with restricted access within the Clinical Genotyping Group Laboratory Information Management System (LIMS) at AstraZeneca, Alderley Park, United Kingdom. The link will be used to identify the relevant DNA samples for analysis, facilitate correlation of genotypic results with clinical data, allow regulatory audit and to trace samples for destruction in the case of withdrawal of consent. Access to the link file will require written authorisation from the Project Team Leader.

All DNA samples will be stored under secure conditions with restricted access at the AstraZeneca laboratory or laboratory contracted by AstraZeneca. The blood, DNA samples or data derived from the samples may be made available to groups or organisations working with AstraZeneca on this study or as part of the development drug project. However, the samples

and any results will remain the property of AstraZeneca at all times. AstraZeneca will not give blood, DNA samples or data derived from the samples to any other parties, except as required by law.

Samples will be stored for a maximum of 25 years from the date of completion of the study, after which they will be destroyed.

8.4 Labelling and shipment of biohazard samples

The investigator ensures that samples are labelled and shipped in accordance with the Laboratory Manual and the Biological Substance, Category B (materials containing or suspected to contain infectious substances that do not meet Category A criteria (see IATA 6.2 Regulations Guidance in Appendix C).

Any samples identified as Infectious Category A materials should not be shipped to a central laboratory for analysis and further samples taken from the same patient should not be shipped for analysis unless agreed with AstraZeneca and appropriate labelling, shipment and containment provisions are approved. Covance will perform all shipping of samples.

Details will be provided in the Laboratory Manual.

8.5 Chain of custody of biological samples

A full chain of custody is maintained for all samples throughout their lifecycle.

The principal investigator at each centre keeps full tractability of collected biological samples from the patients while in storage at the centre until shipment and keeps documentation of receipt of arrival.

The sample receiver keeps full tractability of the samples while in storage and during use until used or disposed.

AstraZeneca keeps oversight of the entire life cycle through internal procedures, monitoring of study sites and auditing of external laboratory providers.

Samples retained for further use are registered in AstraZeneca bio bank system during the entire life cycle.

8.6 Withdrawal of informed consent for donated biological samples

If a patient withdraws consent to the use of biological samples donated the samples will be disposed/destroyed, if not already analysed and documented.

If collection of the biological samples is a voluntary part of the study then the patient may continue in the study.

The investigator:

- Ensures a patient's withdrawal of informed consent is notified immediately to AstraZeneca
- Ensures that biological samples from that patient, if stored at the study site, are immediately identified, disposed/destructed and the action documented
- Ensures the laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed/destructed and the action documented returned to the study site.

AstraZeneca ensures that the central laboratory (ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed/destructed and the action documented returned to the study site.

In the event that analysis/research has already been performed, AstraZeneca will retain the results and associated data for regulatory reasons but these will not be used in any subsequent analyses.

9. ETHICAL AND REGULATORY REQUIREMENTS

Details on financing, insurance and publication policy will be documented in a separate agreement.

9.1 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/GCP, applicable regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples.

9.2 Patient data protection

The Master Informed Consent Form will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation. Pursuant to this wording, patients (or their legally authorised representative) will authorise the collection, use and disclosure of their study data by the investigator and by those persons who need that information for the purposes of the study.

The Master Informed Consent Form will explain that study data will be stored in a computer database, maintaining confidentiality in accordance with national data legislation. All data computer processed by PAREXEL and/or AstraZeneca will be identified by enrolment number and study code.

The Master Informed Consent Form will also explain that for data verification purposes, authorised representatives of AstraZeneca, PAREXEL, a regulatory authority, and/or an Ethics Committee (EC) may require direct access to parts of the hospital or practice records relevant to the study, including patients' medical history.

All data protection and confidentiality principles described in the main study protocol are applicable to the genetic and biomarker research carried out in this study. Reference to participation in this genetic and/or biomarker research should not be recorded into the patients' general medical records. All notes should be kept within the clinical study records. Due to the exploratory nature of this genetic and/or biomarker research, there will be no routine communication of results to patients. AstraZeneca will not provide individual genotype and/or biomarker results to patients, any insurance company, any employer, their family members, general physician or any other third party, unless required to do so by law. Extra precautions are taken to preserve confidentiality and prevent genetic and/or biomarker data being linked to the identity of the patient, however, it must be recognised that there are exceptional circumstances where individuals may see both genetic and/or biomarker data and a patient's personal identifier, for example in the case of a medical emergency, when AstraZeneca Physicians and investigators might know the patients' identity and might have access to the genetic and/or biomarker data, or during regulatory audit where designated authorities must be permitted access to the relevant files. Individual patients will not be identified in any report or publication resulting from this exploratory genetic and/or biomarker research. The data and results of this research may be reviewed with collaborators and published, but neither the patient's name nor any other personal identifiers will appear in any publication or report.

9.3 Ethics and regulatory review

An EC must approve or give a favourable opinion in writing the final study protocol, including the final version of the Informed Consent Form and any other written information to be provided to the patients. The investigator will ensure the distribution of these documents to the applicable EC, and to the study site staff.

The investigator must submit written approval to PAREXEL before he or she can enrol any patient into the study. Following approval, the protocol and amendment(s) will be submitted to the IND under which the study is being conducted, according to local requirements.

The EC must approve all advertising used to recruit patients for the study.

PAREXEL must approve any modifications to the Informed Consent Form that are needed to meet local requirements.

Before enrolment of any patient into the study, the final study protocol, including the final version of the Informed Consent Form, is approved by the national regulatory authority or a notification to the national regulatory authority is done, according to local regulations.

The distribution of any of these documents to the national regulatory authorities will be handled by AstraZeneca or PAREXEL as appropriate.

AstraZeneca will provide ECs and principal investigators with safety updates/reports according to local requirements.

The principal investigator is also responsible for providing the EC with reports of any serious and unexpected adverse drug reactions from any other study conducted with the IP. AstraZeneca will provide this information to the principal investigator.

Progress reports and notifications of serious and unexpected adverse drug reactions will be provided to the EC according to local regulations and guidelines.

Where there is genetic and/or/biomarker research, approval must be obtained for this genetic and/or biomarker research, respectively, and the associated informed consents from the EC. It must be clearly stated in the approval that this genetic and/or biomarker research is approved. The investigator must submit written approval to PAREXEL before any patient participates in this genetic and/or biomarker research.

9.4 Informed consent

The principal investigator(s) at each centre will ensure that the patient or his/her legally authorised representative is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Patients or their legally authorised representative must also be notified that they are free to discontinue from the study at any time. The patient or his/her legally authorised representative should be given the opportunity to ask questions and allowed time to consider the information provided.

The patient's or his/her legally authorised representative's signed and dated informed consent must be obtained before conducting any procedure specifically for the study. Country and/or local EC requirements for acceptable methods of obtaining signed and dated informed consent will be followed (such as acceptability of Fax).

The principal investigator(s) must store the original, signed Informed Consent Form. A copy of the signed Informed Consent Form must be given to the patient or his/her legally authorised representative.

The genetic and biomarker research is optional and the patient may participate in the main study without participating in the genetic and/or biomarker component. Patients (or their legally authorised representative) who agree to take part in this genetic research will be asked to sign a separate Informed Consent Form to confirm their willingness to have this sample taken. Patients (or their legally authorised representative) who agree to take part in the biomarker research will be asked to sign either a separate Informed Consent Form or note consent in a specific section of the general Informed Consent Form to confirm their willingness to have this sample taken.

To participate in the genetic component of the study the patient or his/her legally authorised representative must sign and date both the consent form for the main study (non-genetic/biomarker components of the study) and a consent form for each of the genetic and biomarker components of the study. Copies of all signed and dated consent forms must be given to the patient or his/her legally authorised representative and the original filed at the study centre. The principal investigator(s) is responsible for ensuring that consent is given

freely and that the patient or his/her legally authorised representative understands that they may freely discontinue the genetic and/or biomarker aspects of the study at any time.

If modifications are made according to local requirements, the new version of either consent has to be approved by PAREXEL and the EC.

Those patients who are unconscious or considered by the investigator clinically unable to consent at screening and who are entered into the study by the consent of a legally acceptable representative should provide their own written informed consent for continuing to participate in the study as soon as possible on recovery, as applicable in accordance with local regulations.

9.5 Changes to the protocol and informed consent form

Study procedures will not be changed without the mutual agreement of the co-ordinating investigator and PAREXEL.

If there are any substantial changes to the study protocol, then these changes will be documented in a study protocol amendment and/or a new version of the study protocol (Amended Protocol).

The amendment must be approved by each EC and if applicable, also the national regulatory authority, before implementation. Local requirements must be followed for amended protocols.

AstraZeneca will distribute any subsequent amendments and new versions of the protocol to each principal investigator(s). For distribution to EC see Section 9.3.

If a protocol amendment requires a change to a centre's Informed Consent Form, AstraZeneca and the centre's EC must approve the revised Informed Consent Form before the revised form is used.

If local regulations require, any administrative change will be communicated to or approved by each EC.

9.6 Audits and inspections

Authorised representatives of AstraZeneca, PAREXEL, a regulatory authority, or an EC may perform audits or inspections at the centre, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the protocol, GCP, guidelines of the ICH, and any applicable regulatory requirements. The investigator will contact PAREXEL immediately if contacted by a regulatory agency about an inspection at the centre. Investigators must allow direct access to all source data and source documents in the event of such an inspection.

10. STUDY MANAGEMENT BY ASTRAZENECA

10.1 Pre-study activities

Before the first patient is entered into the study, it is necessary for a representative of PAREXEL to visit the investigational study site to:

- Determine the adequacy of the facilities and to verify qualifications of each investigator and associated staff.
- Discuss with the investigator(s) (and other personnel involved with the study) their responsibilities with regard to protocol adherence, investigator responsibilities, procedures for ensuring adequate and correct documentation, and the responsibilities of AstraZeneca or its representatives, including those from PAREXEL. This will be documented in a CSA between AstraZeneca and the investigator.

10.2 Training of study site personnel

Before the first patient is entered into the study, a PAREXEL representative will review and discuss the requirements of the Clinical Study Protocol and related documents with the investigational staff and also train them in any study specific procedures and the WBDC system utilised.

The principal investigator will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information relevant to the performance of this study is forwarded to the staff involved.

The principal investigator will maintain a record of all individuals involved in the study (medical, nursing and other staff).

10.3 Monitoring of the study

During the study, a PAREXEL representative will have regular contacts with the study site, including visits to:

- Provide information and support to the investigator(s).
- Confirm that facilities remain acceptable.
- Confirm that the investigational team is adhering to the protocol that data are being accurately and timely recorded in the eCRFs, and that IP accountability checks are being performed.
- Perform source data verification (a comparison of the data in the eCRFs with the patient's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating patients.

Investigators must allow direct access to all original records for each patient (eg, clinic charts).

- Ensure withdrawal of informed consent to the use of the patient's biological samples is reported and biological samples are identified and disposed/destructed accordingly, and the action is documented, and reported to the patient.

The PAREXEL representative will be available between visits if the investigator(s) or other staff at the centre needs information and advice about the study conduct.

10.3.1 Source data

Refer to the CSA for location of source data.

10.4 Study agreements

The principal investigator at each centre must comply with all the terms, conditions, and obligations of the CSA, or equivalent, for this study. In the event of any inconsistency between this Clinical Study Protocol and the CSA, the Clinical Study Protocol shall prevail with respect to the conduct of the study and the treatment of patients and in all other respects, not relating to study conduct or treatment of patients, the terms of the CSA shall prevail.

Agreements between AstraZeneca and the principal investigator must be in place before any study-related procedures can take place, or patients be enrolled.

10.4.1 Archiving of study documents.

The investigator follows the principles outlined in the CSA.

10.5 Study timetable and end of study

The end of the entire study is defined as "the last visit of the last patient undergoing the study".

The study may be terminated at individual centres if the study procedures are not being performed according to GCP, or if recruitment is slow. AstraZeneca may also terminate the entire study prematurely if concerns for safety arise within this study or in any other study with AZD9773. If AstraZeneca decides to prematurely terminate or suspend the study, PAREXEL, the investigators and regulatory authorities must receive written notification of the reasons for the premature termination or suspension. The investigators will immediately notify the decision to the patients, give appropriate medical treatment, take necessary measures, and record treatment or measures provided on the source documents.

11. DATA MANAGEMENT

A WBDC system will be used for data collection and query handling. The investigator will ensure that data are recorded on the eCRFs as specified in the study protocol and in

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accordance with the instructions provided. The investigator ensures the accuracy, completeness, and timeliness of the data recorded and of the provision of answers to data queries according to the CSA.

Clinical data will be sent in a secured validated format to PAREXEL Data Management on an ongoing basis. However, as the PK data would unblind the study, these data will not be transferred to PAREXEL Data Management until database lock has been declared. All processes will be documented in the PAREXEL Data Management study files.

Data will be entered in the WBDC system at the study site. Trained study personnel will be responsible for entering data on the observations, tests and assessments specified in the protocol into the WBDC system and according to the eCRF instructions. The eCRF instructions will also provide the study site with data entry instructions. A monitor from PAREXEL will visit the investigational site and review the eCRFs. Data entered in the WBDC system will be immediately saved to a central database and changes tracked to provide an audit trail. When data have been entered, reviewed, edited and Source Data Verification performed the investigator will be notified to sign the eCRF electronically as per the agreed project process and data will be locked to prevent further editing. A copy of the eCRF will be archived at the study site. eCRF records of SAEs will be reconciled against reports made to AstraZeneca Drug Safety.

Raw data collected by third party vendors (cytokines, procalcitonin, troponin I, protein C activity, ECGs, PK analyte concentration measurements, HASA Igs and total HASA bridging assay, NAB assays) will be electronically transferred to PAREXEL Data Management for inclusion in the PAREXEL Data Management study database.

Data verification and data validation checks will be performed by PAREXEL Data Management utilising electronic edit checks comprised of validated computer programs and manual data review. Any data discrepancies will be referred back to the investigator via the site monitor. A clean database will be declared by PAREXEL Data Management after consistency checks have been run, all SAE reconciliations have been resolved, all data in a clean data transfer have been received including third party vendor data, all the data in the database has been accounted for, all edit checks have been run and data discrepancies have been resolved or accepted and a Quality Check on a sample of the data has been performed. After the database has been declared clean it will be locked and editing in the database will only be allowed with the proper documentation. Further details of how the 2 database locks will be handled will be described in the SAP.

After database lock, data will be extracted to SAS® (SAS Institute, Inc., Cary, NC) for analysis as defined in the SAP. SAEs will be entered into the global AstraZeneca safety database.

AEs and prior and concomitant diseases will be coded according to the version of MedDRA agreed with AstraZeneca. Concomitant medications will be coded using the AstraZeneca drug dictionary.

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In the case of genetic and/or biomarker research, only the date the patient gave consent to participation in the genetic and/or biomarker research and the date the blood sample was taken from the patient will be recorded in the eCRF and database.

Data associated with biological samples will be transferred to laboratories internal or external to AstraZeneca.

The analysis of the multiplex assay for exploratory chemokines and the plasma renal panel for exploratory analysis are not planned to be included in the Clinical Study Report for this study.

Genotype data generated in this study will be stored in the AstraZeneca genotyping LIMS database, or other appropriate secure system, separate from the database used for the main study.

Some or all of the clinical datasets from the main study may be merged with the genetic data in a suitable secure environment separate from the clinical database. The results from this genetic research will be reported separately from the Clinical Study Report for the main study.

12. EVALUATION AND CALCULATION OF VARIABLES BY ASTRAZENECA

12.1 Calculation or derivation of safety variable(s)

12.1.1 Other significant adverse events

During the evaluation of the AE data, AstraZeneca medically qualified experts will review the list of AEs that were not reported as SAEs and AEs leading to withdrawal. Medically qualified experts on the study team will also review the safety data to select significant AEs of particular clinical importance/special interest, which will be considered OAEs/events of special interest and reported as such in the Clinical Study Report.

Examples of these are marked haematological and other laboratory abnormalities, and certain events that lead to intervention (other than those already classified as serious), dose reduction or significant additional treatment.

12.2 Calculation or derivation of demographic and efficacy variables

12.2.1 Calculation and derivation of Charlson Comorbidity Scale

The calculation of the Charlson Comorbidity Scale score will be done electronically; investigators will only need to confirm that the patient has any of the co-morbid conditions by term.

12.2.2 Calculation and derivation of PRO variables

The SF-36v2 Acute scoring will be used (SF-36 health survey manual and interpretation guide, Ware et al, 2000). Two overall summary scores, the physical component summary score and the mental health component summary score, will be derived as the principal

method of reporting SF-36v2 Acute results. Each domain score will also be derived individually.

The Day 29 value will be taken as the initial value, and the Day 90 value will be taken as the follow-up value.

12.2.3 Calculation and derivation of Acute Physiology and Chronic Health Evaluation (APACHE) II Score

The calculation of the APACHE II score will be done electronically; investigators will only need to enter the values of the parameters measured into the eCRF.

12.2.4 Calculation and derivation of Glasgow Coma Score

The calculation of the Glasgow Coma Score will be done electronically; investigators will only need to answer the individual questions in the eCRF.

For each of the categories of eye, verbal and motor response, a point score is assigned to the level of response. The Glasgow Coma Score is the sum of these three scores. For further details, see Appendix F.

12.2.5 Calculation and derivation of the modified Sequential Organ Failure Assessment (SOFA) Scores

A point score is given to each of the variables recorded for the 5 categories of respiration, coagulation, liver, cardiovascular, and renal. The total modified SOFA score is calculated from the sum of these individual scores. A modified SOFA score will be calculated (five categories: respiration, coagulation, liver, cardiovascular, and renal) for all timepoints in Table 1. The calculation of the modified SOFA score will be done electronically; investigators will only need to enter the values of the parameters measured into the eCRF.

The worst BP and saturation values of the day should be used, and if a drug holiday or no value is collected, the last assessment performed should be the value for that day.

For further details of the modified SOFA Score, see Appendix G.

12.2.6 Calculation and derivation of ventilator use and pulmonary assessment parameters

The predicted body weight will be calculated using the height at screening. The value for males is calculated by:

50 + 0.91 x (centimetres of height – 152.4).

The predicted body weight for females is calculated by:

45.5 + 0.91 x (centimetres of height – 152.4).

Ventilator-free days

VFD at Day 29 (over 28) days is defined as:

- The number of days after starting unassisted breathing up to and including Day 29, assuming a patient survives for at least 2 consecutive calendar days after starting unassisted breathing and remains free of assisted breathing
  - If a patient returns to assisted breathing and subsequently achieves unassisted breathing prior to Day 29, VFD will be counted from the end of the last period of assisted breathing up to and including Day 29 (unless the period of assisted breathing was less than 24 hours and the purpose of the assisted breathing was a surgical procedure).
  - If a patient was receiving assisted breathing at Day 29 or dies prior to Day 29, VFD will be zero.
  - If a patient never requires assisted breathing, the VFD will be 28 days.
- The 28-day study period is from Day 2 to the Day 29+2 telephone contact.

Unassisted breathing is defined as:

- Extubated with face mask, nasal prong oxygen or room air, OR
- T-tube breathing, OR
- Tracheostomy mask or collar, OR
- Continuous positive airway pressure less than or equal to 5 cm water without pressure support or intermittent mandatory ventilation assistance.

Investigators will not be required to calculate VFDs; VFDs will be derived. VFDs at Day 15 (over 14 days) will be derived in a similar manner to above.

12.2.7 Calculation and derivation of organ failure assessment

Failure of an organ system will be recorded the first time any of the criteria specified in the individual components of the modified SOFA score are >1 after the start of study drug up to Day 15 (over 14 days). Organ failure-free days will be designated for those days when the organ system modified SOFA score is ≤1. The worst BP and saturation values of the day should be used, and if a drug holiday or no value is collected, the last assessment performed should be the value for that day.

12.2.8 Calculation and derivation of ICU-free days

The number of days alive and ICU-free up to and including Day 15 (over 14 days) will be derived from the assessment detailed in Section 7.6.9.

12.2.9 Calculation and derivation of shock-free days

The number of shock-free days up to and including Day 15 (over 14 days) will be derived from the assessment detailed in Section 7.6.10.

12.3 Calculation or derivation of pharmacokinetic variables

The PK analyses will be performed at AstraZeneca Research & Development. The actual sampling times will be used in the PK calculations. Full details of the population PK and PK-PD analysis will be given in the Pharmacokinetic Analysis Plan approved before the start of analysis. Results will be reported in a separate report.

12.4 Calculation or derivation of pharmacodynamic variables

12.4.1 Population analysis of pharmacokinetic/pharmacodynamic variables

Full details of the population PK and PK-PD analysis will be given in the Pharmacokinetic Analysis Plan approved before the start of analysis. Results will be reported in a separate report.

12.4.2 Calculation or derivation of the relationship between pharmacokinetic and pharmacodynamic variables

The relationship between drug serum concentration and effect of PD variables will be presented graphically. If appropriate, concentration-effect relationships will be explored.

12.4.3 Calculation or derivation of the relationship between pharmacokinetic and efficacy variables

The relationship between drug serum concentration and efficacy variables will be presented graphically. If appropriate, concentration-effect relationships will be explored.

12.4.4 Calculation or derivation of the relationship between pharmacokinetic variables and adverse events

The relationship between drug serum concentration and AEs will be explored.

12.5 Calculation or derivation of pharmacogenetic variables

Not applicable.

12.6 Calculation or derivation of health economics variables

Not applicable.

[redacted]

13. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION BY ASTRAZENECA

13.1 General principles

A comprehensive SAP will be finalised before the last patient visit. All statistical analyses will be performed by PAREXEL. Any deviations from those analyses presented here and/or in the SAP will be detailed in the clinical study report. All outputs will be produced using SAS® version 9 or later in accordance with AstraZeneca standards.

All study data will be analysed after the 28-day follow up is complete for all patients. A further analysis will be performed using the Day 90 assessment to understand longer-term patient outcomes (survival and HRQoL).

The following efficacy endpoints will be subject to formal statistical analysis: VFDs, 7-day mortality, 28-day mortality, mortality at Day 90, organ failure-free days, shock-free days and ICU-free days. All other data will only be summarised.

All efficacy data will be summarised and analysed using the per protocol (PP) population. Additionally, an ITT analysis of the endpoints listed above for formal analysis will also be undertaken using the ITT population.

For each of the endpoints subject to statistical analysis the following statistical comparisons will be performed: AZD9773 dose 1 versus placebo, AZD9773 dose 2 versus placebo, and combined AZD9773 dose arms 1 and 2 versus placebo. Although there are three primary comparisons, this is an exploratory Phase IIb study and consequently no adjustment for multiple comparisons will be made.

Unless stated below, no imputation of missing data will be performed. All data recorded on the database will be included in data listings. Any spurious or erroneous data will be queried and followed up until satisfactorily resolved.

The nominal significance level used for this study will be 10% one-sided. However, it is important to note that the study has only been sized based on VFDs over 28 days; this study is not powered to detect a statistically significant difference in 7-day mortality, 28-day mortality or mortality at Day 90. In this case the confidence intervals (CIs) will provide a guide to the possible range of the true treatment effect. This may also be the case for the other secondary endpoints.

Demography data will be summarised using the PP and ITT populations and safety data will be summarised using the safety population. For all summaries of change from baseline, baseline is defined as the latest non-missing assessment prior to first study drug infusion.

The results of the genetic research will not form part of the Clinical Study Report for this study. The number of patients who will agree to participate in the genetic research is unknown. It is therefore not possible to establish whether sufficient data will be collected to

[redacted]

allow a formal statistical evaluation or whether only descriptive statistics will be generated. A separate SAP will be prepared where appropriate. This also applies to the blood samples obtained for use in future sepsis biomarker assays that may become available. In addition, the analysis of the multiplex assay for exploratory chemokines and the plasma renal panel for exploratory analysis are not planned to be included in the Clinical Study Report for this study.

The results from any exploratory biomarker analyses may be pooled with biomarker data from other studies on AZD9773 to generate or validate emerging hypotheses.

13.2 Description of analysis sets

The following three analysis sets will be defined for this study.

13.2.1 Safety population

All patients who start an infusion of study drug will be included in the safety population and data will be summarised according to the actual treatment first received.

13.2.2 Intention-to-treat population

All randomised patients will be included in the ITT population and data will be analysed and summarised according to the randomised treatment.

13.2.3 Per-Protocol population

This population will be a subset of the ITT population including only patients without important detected protocol deviations affecting the efficacy endpoints. Patients will be summarised according to the actual treatment first received.

The patients with important protocol deviations will include those failing the inclusion/exclusion criteria as well as any patients taking medications that are prohibited during the study treatment period (see Section 6.5.2). Prior to clean file and code break, the patients to be excluded from the PP population will be reviewed and agreed by the study team physician and statistician.

13.3 Methods of statistical analyses

13.3.1 Demographics, baseline characteristics, and concomitant medications

Demographic data, medical history, surgical history, Charlson Comorbidity Scale, physical examination (including dermal examination and lung auscultation), and key concomitant medications will be summarised. Concomitant medications will be coded using the AstraZeneca Drug Dictionary.

Patients who have to discontinue study treatment due to the administration of immunosuppressant medications, corticosteroids other than for adrenal replacement therapy, and anti-TNF antibodies during Days 1 to 6 will be summarised by treatment group.

Baseline disease characteristics including APACHE II Score, Glasgow Coma Score, TNFα, time of initial antibiotic dose relative to the qualifying organ failure and the number of patients with shock, on a ventilator, on vasopressors, with a positive culture or with renal impairment will also be summarised.

13.3.2 Protocol deviations

Important protocol deviations will be summarised by treatment group.

13.3.3 Pharmacokinetics

Serum concentrations for AZD9773 specific and total Fabs will be listed by treatment group.

13.3.4 Ventilator-free days

Summary statistics (mean, median, standard deviation [SD], minimum, and maximum) of VFDs over 28 days will be presented by treatment group. Missing data will be handled using a last observation carried forward (LOCF) approach when calculating VFDs for each patient. A histogram of VFD will also be produced for each treatment group.

For the formal statistical analysis, an analysis of covariance model will be fitted for VFDs allowing for treatment group and the following baseline covariates:

APACHE II score (four categories based on the quartiles of the baseline score), age (two categories: <60 and 60 or older), region (three categories: Australia, North America [Canada & USA] and All Other) and an indicator variable if the patient was on mechanical ventilation at baseline (two categories: yes or no).

The difference in VFDs for each of the comparisons: AZD9773 dose 1 versus placebo, AZD9773 dose 2 versus placebo, AZD9773 dose 1 and 2 versus placebo will be presented in terms of the difference in the Least Square Means (LSMeans) and the associated two-sided 80% CI and one-sided p-value. Additionally, a two-sided 95% CI and two-sided p-value will also be presented.

For the PP population, the effect of other baseline variables (examples include baseline TNF, Xigris use prior to study treatment and presence of shock at baseline) on the treatment comparisons will also be explored via a series of analyses including the covariates as specified above for each of the levels of these baseline variables separately. The difference in the treatment LSMeans and the associated two-sided 80% CI from these analyses (along with the results from the baseline covariates fitted in the statistical analysis above) will be presented graphically on the same plot. Additionally, an analysis of variance will also be performed for the PP and ITT populations (with no covariates and only treatment as a factor).

VFDs at Day 15 (over 14 days) will be analysed in a similar manner to above.

[redacted]

13.3.5 Modified Sequential Organ Failure Assessment (SOFA) Score

Summary statistics (mean, median, SD, minimum, and maximum) of the raw data and change from baseline to each scheduled study assessment for each component and the total modified SOFA Score will be presented by treatment group.

For missing coagulation, liver and renal of the total modified SOFA score, a LOCF approach will be used and the last assessment performed should be the value for that day. For cardiovascular and respiratory components, investigators will be encouraged to use other available data (on/off vasopressors, percentage oxygen saturation in order to complete the individual component score).

The worst BP and saturation values of the day should be used.

13.3.6 Organ failure-free days, shock-free days, and ICU-free days

Organ failure-free days, shock-free days, and ICU-free days will be summarised and analysed in the same way as for VFD (see Section 13.3.4).

13.3.7 7-day mortality, 28-day mortality and mortality at Day 90

Seven-day mortality and 28-day mortality will be summarised by treatment group. The formal analysis will be undertaken for each the comparisons: AZD9773 dose 1 versus placebo, AZD9773 dose 2 versus placebo, AZD9773 dose 1 and 2 versus placebo separately using a Cochran-Mantel-Haenszel test in which the test will be stratified using the same covariates as for VFD. The corresponding relative risk, two-sided 80% CI and one-sided p-value will be calculated using the procedure PROC FREQ in SAS. Additionally, a two-sided 95% CI and two-sided p-value will also be presented.

An unstratified analysis will also be performed for the PP and ITT populations. Additionally, for the PP population, the impact of other baseline variables (examples include baseline TNF, Xigris use prior to study treatment and presence of shock at baseline) on the treatment comparisons will be explored by undertaking a series of analyses for each of the levels of these baseline variables separately, and the relative risks along with the associated two-sided 80% CIs from these analyses will be presented graphically.

In the event that the 7-day mortality and 28-day mortality status is unknown for some patients, they will be excluded from the PP population. However, for the ITT population they will be included as though they had died. Further sensitivity analyses may be undertaken depending on the number of such patients.

A Kaplan-Meier curve of time to death will also be produced and both a stratified (using the same covariates as for the analysis of 7 and 28-day mortality) and unstratified log rank test will be undertaken. If the 7-day or 28-day mortality status is unknown for some patients, they will be censored at the last known date the patient was alive.

Mortality at Day 90 will be considered in the same way as 7-day and 28-day mortality.

13.3.8 PRO variables

The physical component summary score, mental health component summary score, Physical functioning and Bodily pain scales and individual question 2 of the raw data and change from baseline will be summarised (mean, median, SD, minimum, and maximum) by treatment group. Patients who complete an initial assessment at Day 29 and then subsequently die will be assigned a worst-case score for the Day 90 visit. Furthermore, as the initial value is collected at Day 29, there is the potential that the treatment groups may not be comparable in this summary. Consequently, a further summary will include ITT patients where any patients who die prior to the Day 29 assessment will be given a worst-case score at both assessments.

13.3.9 Safety

13.3.9.1 Extent of exposure

A summary of exposure to study drug, by treatment group, including the number of infusions, the total exposure (units/kg) and the duration of exposure (days), will be provided.

13.3.9.2 Adverse events

AEs will be coded according to MedDRA.

TEAEs (events which were not present at baseline or worsened in severity following the start of treatment) will be presented. AEs occurring prior to the start of treatment will be listed only.

The following summaries will be provided:

- A summary of the number and percentage of patients reporting any TEAE, death, at least one severe TEAE, at least one serious TEAE, at least one TEAE possibly related to study drug, at least one TEAE leading to withdrawal from study drug, at least one infusion reaction (as defined in Appendix C), at least one hypersensitivity reaction by treatment group
- A summary of the number and percentage of patients reporting a TEAE by treatment group, system organ class (SOC) and preferred term
- A summary of the number and percentage of patients reporting a TEAE by treatment group and preferred term
- A summary of the number and percentage of patients reporting a TEAE by treatment group, intensity, SOC and preferred term. For each patient and each TEAE, the maximum reported intensity recorded will be attributed and used in the by-intensity summaries
- A summary of the number and percentage of patients reporting a TEAE by treatment group, by relationship to study drug, SOC and preferred term. The worst

relationship to study drug (most related to treatment) will be attributed and used in the by-relationship summaries

- A summary of the number and percentage of patients reporting an infusion reaction by treatment group, SOC and preferred term
- A summary of the number and percentage of patients reporting hypersensitivity reactions by treatment group, SOC and preferred term.

The following by-patient listing will be provided:

- A listing of all AEs (including non-treatment-emergent events), by treatment group and including centre, patient identifier, AE (SOC, preferred term, reported term), date of onset, date of resolution, duration, severity, seriousness, action taken, outcome and relationship to study treatment.

13.3.9.3 Deaths, serious adverse events, adverse events leading to withdrawal, and other significant adverse events

The following summaries will be provided:

- A summary of the number and percentage of patients reporting a serious TEAE by treatment group, SOC and preferred term.
- A summary of the number and percentage of patients reporting a TEAE leading to withdrawal from study treatment by treatment group, SOC and preferred term.
- A summary of the number and percentage of patients with a SAE outcome of death by treatment group and preferred term.
- A summary of the number and percentage of patients reporting any treatment-emergent OAE by treatment group, SOC and preferred term.
- A summary of the number and percentage of patients reporting any infection by treatment group, SOC, preferred term and category (healthcare-associated, community-acquired).

The following by-patient listings will be presented, each of which will follow the format described for AEs in Section 13.3.9.2.

- A by-patient listing of all SAEs.
- A by-patient listing of all OAEs.
- A by-patient listing of all deaths that occurred during the study.
- A by-patient listing of all AEs leading to withdrawal from study treatment.

13.3.9.4 Laboratory evaluation

All laboratory data will be converted from the recorded units to the SI units for presentation. A project reference range will be used for the assessment of out of range parameters.

Summary statistics (mean, median, SD, minimum, and maximum) of the raw data and change from baseline to each scheduled study assessment will be presented for all continuous laboratory parameters. Graphical representations and shift tables of the laboratory data will also be produced.

For categorical urinalysis parameters, shift tables of the number and percentage of patients by classification at baseline and each post-baseline visit will be presented.

13.3.9.5 Vital signs evaluation

Summary statistics (mean, median, SD, minimum, and maximum) of the raw data and change from baseline to each scheduled study assessment for systolic BP, diastolic BP, mean arterial pressure, PR, RR, blood oxygen-haemoglobin saturation and body temperature will be presented by treatment group.

13.3.9.6 Electrocardiogram evaluation

Summary statistics (mean, median, SD, minimum, and maximum) of the raw data and change from baseline to each scheduled study assessment for all ECG parameters will be presented by treatment group.

A shift table from baseline to maximum post-baseline ECG result of the number and percentage of patients with normal/abnormal results as determined by eRT expert assessment will be presented.

The number and percentage of patients meeting threshold criteria for QTcF and QTcB will be presented by treatment group. The threshold criteria for QTcF and QTcB are as follows (ICH E14):

>450 msec, >480 msec, >500 msec, and increases from baseline of >30 msec and >60 msec.

Plots of corrected QT versus serum concentration of AZD9773 will be presented.

13.4 Determination of sample size

The sample size has been based on the primary outcome variable of VFDs over 28 days. The Phase IIb study in 81 patients with D-CytoFab has been used as an estimate of the between-patient SD (11.380). Assuming this SD holds for the current study, then 100 patients per group will provide 90% power to detect an underlying true difference in means between a dose of AZD9773 and placebo of 4.2 days using a 10% one-sided significance level.

Given this is an exploratory Phase II study, a 10% one-sided significance level is considered appropriate as this implies a 1 in 10 chance of a false positive finding which is consistent with the aim in Phase II of identifying a promising therapy.

13.5 Interim analyses

No formal interim analyses are planned.

13.6 Data monitoring committee

An IDMC will be established comprising three independent experts. The committee will meet at planned times (at a minimum once 100 patients have reached Day 29) to review the safety data from the study. Following their meeting, the IDMC will report to the sponsor and may recommend changes in the conduct of the study.

The IDMC will meet in open session with the study sponsor, followed by a closed meeting attended only by IDMC members. In the presence of any serious toxicity, the IDMC will consider recommending changes to the study or stopping the study. The final decision to modify or stop the study will sit with the sponsor.

The sponsor or IDMC may call additional meetings if at any time there is concern about the safety of the study.

Futility analysis will not be a responsibility of the IDMC.

Full details of the IDMC procedures and processes can be found in the IDMC Charter.

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AstraZeneca

Clinical Study Protocol Appendix B

Drug Substance	AZD9773
Study Code	D0620C00003
Appendix Edition Number	1
Appendix Date	[redacted]

Appendix B
Additional Safety Information

[redacted]

FURTHER GUIDANCE ON THE DEFINITION OF A SERIOUS ADVERSE EVENT (SAE)

Life threatening

'Life-threatening' means that the subject was at immediate risk of death from the adverse event (AE) as it occurred or it is suspected that use or continued use of the product would result in the subject's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

Hospitalisation

Out-patient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (eg, bronchospasm, laryngeal oedema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the subject was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important medical event or medical intervention

Medical and scientific judgement should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life-threatening or result in death, hospitalisation, disability or incapacity but may jeopardize the subject or may require medical intervention to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgement must be used.

Examples of such events are:

- Angioedema not severe enough to require intubation but requiring iv hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (eg, neutropenia or anaemia requiring blood transfusion, etc) or convulsions that do not result in hospitalisation
- Development of drug dependency or drug abuse

A GUIDE TO INTERPRETING THE CAUSALITY QUESTION

The following factors should be considered when deciding if there is a "reasonable possibility" that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the subject actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?

- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? OR could the AE be anticipated from its pharmacological properties?

- Dechallenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?

- No alternative cause. The AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, other host or environmental factors.

- Rechallenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a rechallenge.

- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship?

A "reasonable possibility" could be considered to exist for an AE where one or more of these factors exist.

In contrast, there would not be a "reasonable possibility" of causality if none of the above criteria apply or where there is evidence of exposure and a reasonable time course but any dechallenge (if performed) is negative or ambiguous or there is another more likely cause of the AE.

In difficult cases, other factors could be considered such as:

- Is this a recognised feature of overdose of the drug?

- Is there a known mechanism?

Ambiguous cases should be considered as being a "reasonable possibility" of a causal relationship unless further evidence becomes available to refute this. Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

Clinical Study Protocol Appendix C

Drug Substance	AZD9773
Study Code	D0620C00003
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Appendix C
IATA 6.2 Guidance Document

[redacted]

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

International Airline Transportation Association (IATA) classifies biohazardous agents into 3 categories **(http://www.iata.org/whatwedo/cargo/dangerous_goods/infectious_substances.htm).** For transport purposes the classification of infectious substances according to risk groups was removed from the Dangerous Goods Regulations (DGR) in the 46th edition (2005). Infectious substances are now classified either as Category A, Category B or Exempt. There is no direct relationship between Risk Groups and categories A and B.

Category A Infectious Substances are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals. Cat A pathogens are eg. Ebola, Lassa fever virus

- are to be packed and shipped in accordance with IATA Instruction 602

Category B Infectious Substances are infectious Substances that do not meet the criteria for inclusion in Category A. Cat B pathogens are eg. Hepatitis A, B, C, D, and E viruses, Human immunodeficiency virus (HIV) types 1 and 2. They are assigned the following UN number and proper shipping name:

- UN 3373 – Biological Substance, Category B
- are to be packed in accordance with UN3373 and IATA 650

Exempt - all other materials with minimal risk of containing pathogens

- Clinical trial samples will fall into Cat B or exempt under IATA regulations.
- Clinical trial samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging **(http://www.iata.org/whatwedo/cargo/dangerous_goods/infectious_substances.htm).**
- **Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content.**
- IATA compliant courier and packaging materials should be used for packing and transportation and packing should be done by an IATA certified person, as applicable.

[redacted]

- Samples routinely transported by road or rail are subject to local regulations which require that they are also packed and transported in a safe and appropriate way to contain any risk of infection or contamination by using approved couriers and packaging / containment materials at all times. The IATA 650 biological sample containment standards are encouraged wherever possible when road or rail transport is used.

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Clinical Study Protocol: Appendix D

Drug Substance	AZD9773
Study Code	D0620C00003
Edition Number	2
Date	[redacted]

Appendix D
Medical Management of Infusion/Hypersensitivity Reactions in Patients with Severe Sepsis

[redacted]

MEDICAL MANAGEMENT OF INFUSION/HYPERSENSITIVITY REACTIONS IN PATIENTS WITH SEVERE SEPSIS

This management protocol is not intended to be exhaustive and all actions deemed to be in the patient's best interest by the Investigator(s) should be carried out. The patient population will have complex medical needs based on the underlying disease and this Appendix is intended to supplement established medical treatments for infusion or hypersensitivity reactions in the setting of severe sepsis treatment.

I Prior to infusion

(a) Preparation

- Monitored setting (intensive care unit [ICU]) with cardiac rhythm, blood pressure (BP), and pulse oximetry.
  - Ability to closely monitor drug infusion rate and manage any reactions.
  - Airway management capabilities (intubation, mechanical ventilation, oxygen) at bedside.
  - Trained staff.
- Dual intravenous (iv) access established/single large bore iv access eg, central line.
- Crash cart nearby with following medications available at bedside (need nearby, but not at bedside, each hospital might have slight modifications on drugs available):
  - Epinephrine 1:1000 for subcutaneous/intramuscular injection.
  - Diphenhydramine, parenteral (25 to 50 mg) or similar parenteral antihistamine.
  - Corticosteroids, parenteral (eg, methylprednisolone).
  - Albuterol, inhalable or similar Beta agonist.
  - iv fluids (eg, normal saline).
  - Epinephrine 1:10000 for iv administration as needed.
  - Physicians and staff informed of, and vigilant for, potential reactions.

(b) Patient history

- If any history of hypersensitivity reaction to sheep products, latex, papain or papaya, then exclude from study.

[redacted]

- If have previously received antivenom manufactured using ovine serum, digoxin immune Fab (DigiFab™, DIGIBIND®), crotalidae polyvalent immune fab (ovine) (CroFab™), or other sheep-derived product, exclude from study.

- Check patient meets inclusion and exclusion criteria.

II During infusion

(a) Monitoring

- Physiological monitoring (vital signs and cardiac).

- Laboratory estimations as detailed in the study plan (Table 1 of protocol) and a serum tryptase level, total immunoglobulin (Ig) E and quantitative eosinophil count at 20 to 60 minutes post suspected infusion or hypersensitivity reaction and repeated on blood draw at Day 29.

(b) Recommended management in the event of a reaction to drug administration.

- Assess severity: mild, moderate, or severe (see Section IV for details).

- Stop infusion and consider treatment options (see Section V for details).

  – Include: observation, acetaminophen, diphenhydramine, steroids, epinephrine, fluids, albuterol, pressors, airway management and other measures in line with accepted medical practice as deemed necessary by the treating physician eg, iv histamine H2 receptor blockers.

- Monitoring (see Section VI).

- Consider restarting infusion after appropriate management and stabilisation or improvement in symptoms.

- Completion of infusion reaction adverse event (AE) form.

III Post infusion

(a) Monitoring

- A minimum of lung auscultation and dermal examination (eg, for oedema, urticaria, rash) should be done after the infusion is complete. In the event of an infusion of hypersensitivity reaction (as evidenced by a causal change in BP, skin or lung examination), an additional full physical examination should be performed and changes (skin, lung, physical examination and BP) should be recorded in the electronic Case Report Form.

- Laboratory parameter measurements
  - At timepoints according to the study plan (Table 1 of protocol).
  - Serum tryptase, IgE and quantitative eosinophil count, 20 to 60 minutes post suspected infusion or hypersensitivity reaction and repeated on blood draw at Day 29.

(b) Classifying any infusion reactions

- Timing
  - Early (onset during infusion or within 1 to 4 hours after infusion).
  - Intermediate (4 to 24 hours after end of infusion).
  - Delayed (onset from 24 hours to 4 weeks after end of infusion).
- Severity (see Section IV).
- Type
  - Timing: early, late or intermediate.
  - Hypersensitivity reaction versus infusion reaction.

(i) Any adverse reaction, which occurs within the dosing time, is potentially an infusion reaction.

(ii) A clinical picture of chills, rigors, fever, myaglia, wheeze, cough dyspnoea, altered vital signs or combination of signs and symptoms consistent with allergic phenomena/infusion reaction. Differentiation will be in immune system activation as evidenced by blood parameters eg, tryptase rise and response to slowing the rate of infusion: this will not affect a true hypersensitivity reaction.

- Investigate relationship of frequency, severity to:
  - History (eg, atopy, asthma, drug allergies).
  - Infusion rate.
  - Infusion concentration.
  - Infusion dose.
  - Infusion number.

- Laboratory parameters (eg, total or specific IgE, complement, immune complex, tryptase) to help determine aetiology.
- Response to treatment.

(c) Re-treatment (after the full 5-day course, patients should not be re-treated)

(d) Information to patients

- When the blind is broken, tell a patient whether they had active or placebo. For those who have had active treatment say, "In future if you require any treatment derived from sheep you should inform your physician that you have received sheep derived products as a treatment for sepsis."

IV Classifying infusion reactions

(a) Severe; new onset, temporally-related **(any one or more of the following)**:

- Hypo/hypertension (eg, systolic BP [SBP] change >40 mmHg; absolute SBP <80 or >180 mmHg).
- Tachy/bradycardia (eg, heart rate [HR] change >20 beats per minute [bpm] or absolute HR >120 bpm or <60 bpm).
- Tachy/bradypnoea (eg, respiratory rate [RR] change >10/min).
- Hyperthermia (eg, temperature >40°C).
- Evidence of significant angioedema (eg, requiring intubation or treatment) or bronchospasm (eg, associated hypoxia or necessitating change in vent settings or treatment).

(b) Moderate; new onset, temporally-related **(any one or more of the following)**:

- SBP change of 20 to 40 mmHg.
- HR change of 10 to 20 bpm.
- RR change of 4 to 10/min.
- Temperature increase, but <40°C.
- Evidence of non-clinically significant angioedema or bronchospasm.
- Rash/urticaria/peripheral oedema requiring treatment.
- Vomiting requiring treatment.

[redacted]

- Symptoms (eg, pruritis, chills, myalgias, arthralgias) or other effects requiring treatment.

(c) Mild includes any other new onset, temporally-related symptoms or signs consistent with hypersensitivity reactions such as rash, wheeze or urticaria

V Management of suspected infusion reactions

This section includes but should not be limited to the following measures:

Early and intermediate reactions

(a) Stop or decrease infusion

- Stop if severe (see Section IV), progressive (continuing to worsen), refractory (eg, moderate reaction which does not respond to treatment) or at discretion of investigator.
- For other events, infusion will be stopped or slowed
  - If the infusion is not tolerated and there is no previously tolerated rate the investigator may prolong the infusion time to twice the initially planned infusion time for that timepoint (if warranted the infusion time can be doubled again to increase tolerability).
- If the infusion is stopped or decreased, wait until signs/symptoms have been stable for 15 minutes prior to restarting or increasing rate.
- Wait 15 minutes and consider restarting infusion at half the initial rate (equivalent to doubling the time planned for the infusion).

(b) Treatment options

- Signs/symptoms including but not limited to:
  - Hypotension (fluids, pressors).
  - Bronchospasm (inhaled albuterol, antihistamines, epinephrine, steroids).
  - Angioedema (intubation/airway management, antihistamines, epinephrine, steroids).
  - Hyperthermia (cooling measures, acetaminophen, antihistamines, steroids, epinephrine).
  - Rash/urticaria (antihistamines, steroids, epinephrine).
  - Vomiting (antiemetics).

  - Symptoms such as pruritis, chills, myalgias, arthralgias (acetaminophen, antihistamines, steroids, epinephrine).

- Treatment/drug, suggested doses including, but not limited to:
  - Epinephrine (1:1000 0.1 to 0.5 mL subcutaneously; repeat as necessary).
  - Diphenhydramine (25 to 50 mg iv; repeat as necessary).
  - Albuterol/salbutamol (0.5 mL of 0.5% solution, nebulised; repeat as necessary).
  - Methylprednisolone (20 to 40 mg iv).
  - Acetaminophen (625 mg orally if oral route can be tolerated).
  - Pressors (eg, dopamine, epinephrine, norepinephrine to maintain organ perfusion, SBP >90 mmHg, mean arterial pressure >70 mmHg).
  - Oxygen to keep oxygen saturation >92%; airway and ventilation setting adjustment to maintain normal ventilation.
  - iv fluids (500 to 1000 mL/hour to help maintain adequate perfusion).

Delayed infusion reactions

- Investigator discretion with following suggested treatment options:
  - Acetaminophen.
  - Steroids (orally, or iv if severe).
  - Antihistamines (orally, or iv if severe).
  - Monitoring; human anti-sheep antibodies, auto-antibody screen, routine laboratory measurements and total IgE.

VI Monitoring of suspected infusion reactions

(a) Standard medical monitoring for an ICU setting to include at least the following:

- Vital signs every 2 minutes until stable.
- Clinical examination every 5 minutes until stable.
- Laboratory parameter measurements to consider:

[redacted]

- Serum tryptase, IgE and quantitative eosinophil count, 20 to 60 minutes post suspected infusion or hypersensitivity reaction and repeated on blood draw at Day 29.

[redacted]

Clinical Study Protocol Appendix E	
Drug Substance	AZD9773
Study Code	D0620C00003
Appendix Edition Number	1
Appendix Date	[redacted]

Appendix E
Acute Physiology and Chronic Health Evaluation (APACHE) II Score

1. APACHE II SCORE

All patients will be assessed using the APACHE II scoring system for demographic characterisation only. APACHE II score will be calculated using completed standard of care laboratory assessments from the 24 hours preceding randomisation.

2. APACHE II WORKSHEET - PHYSIOLOGICAL COMPONENTS

	HIGH ABNORMAL RANGE					LOW ABNORMAL RANGE			
PHYSIOLOGIC VARIABLE	+4	+3	+2	+1	0	+1	+2	+3	+4
TEMPERATURE (DEGREES C)	☐ ≥ 41 °	☐ 39 - 40.9		☐ 38.5 - 38.9	☐ 36 - 38.4	☐ 34 - 35.9	☐ 32 - 33.9	☐ 30 - 31.9	☐ ≤ 29.9
MEAN ARTERIAL PRESSURE (mmHg)	☐ ≥ 160	☐ 130 - 159	☐ 110 - 129		☐ 70 - 109		☐ 50 - 69	,	☐ ≤ 49
HEART RATE (Ventricular response)	☐ ≥ 180	☐ 140 - 179	☐ 110 - 139		☐ 70 - 109		☐ 55 - 69	☐ 40 - 54	☐ ≤ 39
RESP. RATE (Nonventilated/ventilated)	☐ ≥ 50	☐ 35 - 49		☐ 25 - 34	☐ 12 - 24	☐ 10 - 11	☐ 6 - 9		☐ ≤ 5
OXYGENATION: $AaDO_2$ or PaO_2 (mmHg)									
a. $FIO_2 \geq 0.5$, record $AaDO_2$	☐ ≥ 500	☐ 350 - 499	☐ 200 - 349		☐ < 200				
b. $FIO_2 < 0.5$, record only PaO_2					☐ $PO_{2\ >\ 70}$	☐ $PO_{2,\ 61\ -\ 70}$		☐ $PO_{2,\ 55\ -\ 60}$	☐ $PO_{2\ <\ 55}$
ARTERIAL pH	☐ ≥ 7.7	☐ 7.6 - 7.69		☐ 7.5 - 7.59	☐ 7.33 - 7.49		☐ 7.25 - 7.32	☐ 7.15 - 7.24	☐ < 7.15
SERUM SODIUM (mmol/L)	☐ ≥ 180	☐ 160 - 179	☐ 155 - 159	☐ 150 - 154	☐ 130 - 149		☐ 120 - 129	☐ 111 - 119	☐ ≤ 110
SERUM POTASSIUM (mmol/L)	☐ ≥ 7	☐ 6 - 6.9		☐ 5.5 - 5.9	☐ 3.5 - 5.4	☐ 3.0 - 3.4	☐ 2.5 - 2.9		☐ < 2.5
SERUM CREATININE (mg/100 ml) (Double point score for acute renal failure)	☐ ≥ 3.5	☐ 2 - 3.4	☐ 1.5 - 1.9		☐ 0.6 - 1.4		☐ < 0.6		
HEMATOCRIT (%)	☐ ≥ 60		☐ 50 - 59.9	☐ 46 - 49.9	☐ 30 - 45.9		☐ 20 - 29.9		☐ < 20
WHITE BLOOD COUNT ($X10^3/mm^3$)	☐ ≥ 40		☐ 20 - 39.9	☐ 15 - 19.9	☐ 3.0 - 14.9		☐ 1.0 - 2.9		☐ < 1
GLASGOW COMA SCORE (GCS) SCORE = 15 - ACTUAL GCS									
A TOTAL ACUTE PHYSIOLOGY SCORE (APS) SUM OF 12 INDIVIDUALIZED POINTS									
SERUM HCO_3 (Venous-mmol/L) (Use if no ABGs)	☐ ≥ 52	☐ 41 - 51.9		☐ 32 - 40.9	☐ 22 - 31.9		☐ 18 - 21.9	☐ 15 - 17.9	☐ < 15

$AaDO_2$: alveolar-arterial oxygen difference; FiO_2: fractional inspired oxygen; HCO_3: bicarbonate; PaO_2: partial pressure of arterial oxygen.

APACHE II total score = A + B + C

A = total acute physiology score (Section 2)
B = age points (Section 2.1)
C = chronic health points (Section 2.2)

Knaus et al 1985

Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. Crit Care Med 1985;13(10):818-29.

2.1 Age Points

Points will be assigned based on patient's age at the time of the assessment.

Age	Points
≤ 44	0
45 - 54	2
55 - 64	3
65 - 74	5
≥ 75	6

2.2 Chronic Health Points

Chronic Health Evaluation

If any answer to the Chronic Health Evaluation is *YES,* then the patient has a positive Chronic Disease History. Assign Chronic Health Points (+5 for non-op or emergency post-op; +2 for elective post-op).

Organ insufficiency or immuno-compromised state must have been evident prior to this hospital admission and conform to the following criteria.	
LIVER: Biopsy-proven cirrhosis and documented portal hypertension, or episodes of past upper GI bleeding attributed to portal hypertension, or prior episodes of hepatic failure/encephalopathy/coma.	Y N
CARDIOVASCULAR: New York Heart Association Class IV.	Y N
RESPIRATORY: Chronic restrictive, obstructive, or vascular disease resulting in severe exercise restriction, (ie, unable to climb stairs or perform household duties); or documented chronic hypoxia, hypercapnia, secondary polycythemia, severe pulmonary hypertension (>40 mm Hg), or respirator dependency.	Y N
RENAL: Receiving chronic haemo- or peritoneal dialysis.	Y N
IMMUNO-COMPROMISED:	
The patient has received therapy that suppresses resistance to infection, eg immuno-suppressive agents, chemotherapy, radiation, long term low dose steroids, 10 mg/day prednisone for >1 month prior to hospitalization) or recent high dose steroids (>15 mg/kg/day of hydrocortisone or >3 mg/kg/day of methylprednisolone for >5 days).	Y N
The patient has a disease that is sufficiently advanced to suppress resistance to infection, eg leukemia, lymphoma, AIDS, documented diffuse metastatic cancer.	Y N

AIDS: acquired human immuno-deficiency syndrome; GI: gastrointestinal

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Clinical Study Protocol Appendix F

Drug Substance	AZD9773
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Appendix F
Glasgow Coma Score

[redacted]

1. GLASGOW COMA SCORE

date: **time:** **subject ID:** **Enter one score for each response (Eyes, Motor and Verbal).**			
Eyes Open	Motor Responses	Verbal - Nonintubated	Verbal - Intubated
4 = spontaneously 3 = to verbal 2 = to painful stimuli 1 = no response	6 = to verbal command 5 = localized to pain 4 = withdraws to pain 3 = decorticate 2 = decerebrate 1 = no response	5 = oriented and converses 4 = disoriented and talks 3 = inappropriate words 2 = incomprehensible words 1 = no response	5 = seems able to talk 3 = questionable ability to talk 1 = generally unresponsive
Score =	Score =	Score =	
Total Glasgow Coma Score (Eyes + Motor + Verbal) =			

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Clinical Study Protocol: Appendix G	
Drug Substance	AZD9773
Study Code	D0620C00003
Appendix Edition Number	2
Appendix Date	[redacted]

Appendix G
Modified Sequential Organ Failure Assessment (SOFA) Score

[redacted]

1. MODIFIED SEQUENTIAL ORGAN FAILURE ASSESSMENT (SOFA) SCORE

	Modified SOFA Score				
	0	**1**	**2**	**3**	**4**
Respiration					
PaO_2/FiO_2 (torr)[a]	>400	≤400	≤300	≤200 With respiratory support	≤100 With respiratory support
SpO_2/FiO_2 (torr)[a, b]	≥512	<512	<357	<214 With respiratory support	<89 With respiratory support
Coagulation					
Platelets ($x10^3/mm^3$)	>150	≤150	≤100	≤50	≤20
Liver					
Bilirubin (mg/dL)	<1.2	1.2-1.9	2.0-5.9	6.0-11.9	>12.0
(µmol/L)	<20	20-32	33-101	102-204	>204
Cardiovascular					
Hypotension[a]	No hypotension	MAP <70 mm Hg	Dopamine ≤5 or dobutamine (any dose)[b]	Dopamine >5 or epi ≤0.1 or norepi ≤0.1 or phenylephrine ≤300[c] or vasopressin <0.04 units/min	Dopamine >15 or epi >0.1 or norepi >0.1 or phenylephrine >300[c] or vasopressin ≥0.04 units/min
Renal					
Creatinine (mg/dL)	<1.2	1.2-1.9	2.0-3.4	3.5-4.9	>5.0
(µmol/L)	<110	110-170	171-299	300-440	>440
or urine output				or <500 mL/day	or <200 mL/day

PaO_2: partial pressure of arterial oxygen; FiO_2: fraction of inspired oxygen; SpO_2: oxygen saturation by pulse oximetry; epi: epinephrine; norepi: norepinephrine; MAP: mean arterial pressure.

[a] The worst blood pressure and saturation values of the day should be used, and if no value is collected, the last assessment performed should be the value for that day or the last available (if within 48 hours). On days when laboratory results are unavailable, values will be extrapolated from the previous available values.

[b] Data on file.

c Adrenergic agents administered for at least 1 hour (doses given are in µg/kg/min).

To convert torr to kPa, multiply the value by 0.1333.

Vincent et al 1998

Vincent JL, de Mendonca A, Cantraine F, Moreno R, Takala J, Suter PM, et al. Use of the SOFA score to assess the incidence of organ dysfunction/failure in intensive care units: results of a multicenter, prospective study. Working group on "sepsis-related problems" of the European Society of Intensive Care Medicine. Crit Care Med 1998;26(11):1793-800.

[redacted]

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Clinical Study Protocol Appendix H

Drug Substance	AZD9773
Study Code	D0620C00003
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Appendix H
Ventilator Weaning and Management Protocol

[redacted]

1. VENTILATOR WEANING

1.1 Ventilator procedures

A modified, simplified version of the ARDS Network lung protective lower tidal volume strategy will be used in this trial. This strategy will ensure that the study subjects receive the beneficial effects of lung protection as part of their participation in this trial.

1. Any mode of ventilation capable of delivering the prescribed tidal volume (6mL/kg Predicted Body Weight (PBW) ± 2 mL/kg) may be used, provided the VT target is monitored and adjusted appropriately. During APRV, tidal volume is defined as the sum of the volume that results from the ventilator pressure-release and an estimation of the average spontaneous VT.

2. Tidal Volume (VT) goal = 6 mL/kg PBW.

3. Measure and record inspiratory plateau pressure (Pplat) according to ICU routine (at least every four hours and after changes in VT and PEEP recommended).

4. If Pplat greater than 30 cm H_2O, reduce VT to 5 mL/kg and then to 4 mL/kg PBW if necessary to decrease Pplat to less than or equal to 30.

5. If VT less than 6 mL/kg PBW and Pplat less than 25, raise VT by 1 mL/kg PBW to a maximum of 6 mL/kg.

6. If "severe dyspnoea" (more than 3 double breaths/minute or airway pressure remains at or below PEEP level during inspiration), then raise VT to 7 or 8 mL/kg PBW if Pplat remains below 30. If Pplat exceeds 30 on 7 or 8 mL/kg PBW, then revert to lower VT and consider more sedation.

7. If pH less than 7.15, VT may be raised and Pplat limit suspended (not required).

8. Oxygenation target: PaO_2 = 55-80 Hg or SpO_2 = 88-95%.

9. Minimum PEEP = 5 cm H_2O.

10. Adjust FiO_2 or PEEP upward within 5 minutes of consistent measurements that are below the oxygenation target range.

11. Adjust FiO_2 or PEEP downward within 30 minutes of consistent measurements above the oxygenation target range.

12. No specific rules for how to use PEEP and FiO_2 (except for minimum PEEP of 5). The lower PEEP/higher FiO_2 table represents a consensus approach developed by investigators in 1995. The higher PEEP/lower FiO_2 table yielded equivalent results in a randomised trial (Brower, 2003) and would be acceptable and perhaps

[redacted]

preferable in patients who appear to respond with substantial increase in arterial oxygenation in the transition from lower to higher PEEP.

Table 1 Lower ELV/Higher FiO_2 Treatment Group

FiO_2	.30	.40	.40	.50	.50	.60	.70	.70	.70	.80	.90	.90	.90	1.0
PEEP	5	5	8	8	10	10	10	12	14	14	14	16	18	18-24

Table 2 Higher ELV/Lower FiO_2 Treatment Group

FiO_2	.30	.30	.30	.30	.30	.40	.40	.50	.50	.50-.80	.80	.90	1.0	1.0
PEEP	5	8	10	12	14	14	16	16	18	20	22	22	22	24

- Levels of PEEP in these FiO_2/PEEP scales represent levels set on the ventilator, not levels of total-PEEP, auto-PEEP, or intrinsic-PEEP).
- No specific rules for respiratory rate. Recommend to raise respiratory rate in increments to 35/minute (maximum set rate) if pH less than 7.30.
- No specific rules about I:E. Recommend that duration of Inspiration be less than or equal to duration of Expiration.
- Bicarbonate is allowed (neither encouraged nor discouraged) if pH less than or equal to 7.30.

1.2 Weaning procedures

Patients will be assessed for readiness to perform a spontaneous breathing trial using the following weaning readiness criteria each day between 0600 and 1000. If a patient procedure, test, or other extenuating circumstance prevents assessment for these criteria between 0600 and 1000, then the assessment and initiation of subsequent weaning procedures may be delayed for up to six hours.

1. At least 12 hours since enrolment in the trial.
2. FiO_2 = 0.40 and PEEP = 8 cm H_2O or FiO_2 = 0.50 and PEEP = 5 cm H_2O).
3. Values of both PEEP and FiO_2 = values from previous day (comparing Reference Measurement values).
4. Not receiving neuromuscular blocking agents and without neuromuscular blockade.

5. Patient exhibiting inspiratory efforts. If no efforts are evident at baseline, ventilator set rate will be decreased to 50% of baseline level for up to 5 minutes to detect inspiratory efforts.

6. Systolic arterial pressure greater than or equal to 90 mmHg without vasopressor support.

If criteria 1 to 6 are met, then initiate a trial of up to 120 minutes of spontaneous breathing with $FiO_2 = 0.5$ using any of the following approaches:

1. Pressure support = 5 cm H_2O, PEEP = 5 cm H_2O

2. CPAP = 5 cm H_2O

3. T-piece

4. Tracheostomy mask

Monitor for tolerance using the following:

1. $SpO_2 = 90\%$ or $PaO_2 = 60$ mmHg.

2. Mean spontaneous tidal volute = 4 mL/kg PBW, if measured.

3. Respiratory rate = 35/min.

4. pH = 7.30, if measure.

5. No respiratory distress (**2 or more of the following**):

    (a) Heart rate greater than or equal to 120% of the 0600 rate (less than or equal to 5 min at greater than 120% may be tolerated).

    (b) Marked use of accessory muscles

    (c) Abdominal paradox.

    (d) Diaphoresis.

    (e) Marked subjective dyspnoea.

If any of goals 1 to 5 are not met, revert to previous ventilator settings or to Pressure Support (PS) greater than or equal to 10 cm H_2O with Positive End-expiratory Pressure and FiO_2 = previous settings and reassess for weaning the next morning. The clinical team may decide to change mode of support during spontaneous breathing (PS = 5, CPAP, tracheostomy mask, or T-piece) at any time.

[redacted]

Decision to remove ventilatory support

For intubated patients, if tolerance criteria for spontaneous breathing trial (1 to 5) above are met for at least 30 minutes, the clinical team may decide to extubate. However, the spontaneous breathing trial can continue for up to 120 minutes if tolerance remains in question. If any of criteria 1-5 are not met during unassisted breathing (or 120 minutes has passed without clear tolerance), then the ventilator settings that were in use before the attempt to wean will be restored and the patient will be reassessed for weaning the following day.

Completion of ventilator procedures

Patient will be considered to have completed the study ventilator procedures if any of the following conditions occur:

- Death
- Hospital discharge
- Alive 28 days after enrolment

If a patient requires positive pressure ventilation after a period of unassisted breathing, the study ventilator procedures will resume unless the patient was discharged from the hospital or greater than 28 days elapsed since enrolment.

AstraZeneca

Clinical Study Protocol Appendix I

Drug Substance	AZD9773
Study Code	D0620C00003
Edition Number	2
Date	[redacted]

Appendix I
Recommendations for Immunosuppressive Agents

[redacted]

1. RECOMMENDATIONS FOR IMMUNOSUPPRESSIVE AGENTS

Immunosuppressive Agent[a]	Upper limit dosage use	
1. Corticosteroid	• If for >7 days within 1 month prior to screening/informed consent, a subject has received a mean dose > 0.5 mg/kg/day of prednisone, or the equivalent dose of another agent (see below), the subject is excluded from the study. • If a subject has received a mean dose of prednisone (or the equivalent dose of another agent) <0.5 mg/kg/day, the subject will be excluded from the study if their daily dosage exceeds 40 mg/day. **Adrenal replacement therapy as discussed in the Surviving Sepsis Campaign, up to 300 mg/day of <u>hydrocortisone,</u> will be an allowed exception to this restriction. Steroids, other than hydrocortisone, with greater anti-inflammatory effects (such as prednisone or equivalent) are not the preferred steroid preparation for adrenal replacement therapy in this study.**	
Equivalent Dose (mg)		
a) Prednisone	0.5 mg/kg/day	40 mg
b) Hydrocortisone	2.0 mg/kg/day	160 mg
c) Methylprednisolone	0.4 mg/kg/day	32 mg
d) Dexamethasone	0.075 mg/kg/day	6 mg
e) Betamethasone	0.06 mg/kg/day	4.8 mg
2. Methotrexate (Rheumatrex, Trexall)	Excluded at any dose.	
3. Leflunomide (Arava)	Acceptable if being used as monotherapy.	
4. Cyclophosphamide (Cytoxan)	Excluded at any dose.	
5. Cyclosporine A	Excluded at any dose. Ophthalmic formulation (Restatis) is permitted	
6. FK506 (Tacrolimus)	Excluded at any dose. **Topical formulation (Protopic) is permitted.**	
7. Azathioprine	Excluded at any dose.	
8. Cancer Chemotherapy	Patients having received cancer chemotherapy in the previous 4 weeks are excluded.	

[redacted]

Immunosuppressive Agent[a]	Upper limit dosage use
9. Mycophenolate Mofetil (MMF) (CellCept)	Solid organ transplant and bone marrow tumour patients. **MMF is acceptable if on stable dose.**
10. Sirolimus (Rapamycin, rapamune)	Acceptable if on stable dose.
11. Everolimus (Certican)	Acceptable if on stable dose.
12. Thalidomide	Patients receiving this drug within the last 72 hours are excluded.
13. Efalizumab (Raptiva)	Patients receiving this drug within the last 8 weeks are excluded.
Biologics	
(a) Anti-tumour necrosis factor (TNF) agents	Patients receiving anti-TNF agents within the past 8 weeks are excluded.
– Entanercept (Enbrel)	
– Adalimumab (Humira)	
– Infliximab (Remicade)	
(b) Interleukin-1 Receptor Antagonist (IL-1 RA) (Kineret)	Patients receiving IL-1 RA within the last 8 weeks are excluded.
(c) Antilymphocyte antibodies	Patients receiving any of these drugs within the last 2 years are excluded.
– Muromonab-CD3 (Orthoclone OKT3)	
– Antithymocyte Globulin- ATG (Thymoblobulin)	
– Antilymphocyte Globulin- ALG (Euro variant on ATG)	

Immunosuppressive Agent[a]		Upper limit dosage use
(d)	**Anti-CD52**	
	– Alemtuzumab (Campath)	Patients receiving this drug within the last 2 years are excluded.
	– Alefacept (AMEVIVE)	Patients receiving this drug in the past 12 weeks and patients having received this drug >12 weeks ago but with a CD4 count of <250 mm^3 excluded.
(e)	**Anti-IL2**	Patients receiving any of these drugs within the last 2 years are excluded.
	– Daclizumab or Anti-Tac (Zenapax)	
	– Basiliximab (Simulect)	

[a] For agents not listed, patients should be off such therapies for a time sufficient to restore immune function.

Clinical Study Protocol Appendix J

Drug Substance	AZD9773
Study Code	D0620C00003
Edition Number	2
Date	[redacted]

Appendix J
Guidelines for Exclusion due to Comorbid Malignant Conditions

[redacted]

Bladder Cancer - Exclude Stages III and IV

Stage III (T3 or T4a, N0, M0):

The cancer has grown completely through the bladder into the layer of fatty tissue that surrounds the bladder (T3). It may have spread into the prostate, uterus or vagina (T4a). It is not growing into the pelvic or abdominal wall. The cancer has not spread to lymph nodes or to distant sites.

Stage IV (T4b, N0, M0) or (any T, N 1 to 3, M0) or (any T, any N M1):

The cancer has spread through the bladder wall to the pelvic or abdominal wall (T4b) and/or has spread to lymph nodes (N1-3) and/or to distant sites such as bones, liver or lungs (M1).

Colorectal Cancer - Exclude Stage III and IV, Duke's Stage C or MAC Stage C1, C2, C3, D

Stage IIIA: cancer has spread from the innermost tissue layer of the colon wall to the rectum and has spread to as many as 3 lymph nodes.

Stage IIIB: cancer has spread to as many as 3 nearby lymph nodes and has spread

- Beyond the middle tissue layers of the colon wall or
- To nearby tissues around the colon or rectum or
- Beyond the colon wall into nearby organs and/or through the peritoneum

Stage IIIC or Duke's C or MAC C1-C3: cancer has spread to 4 or more nearby lymph nodes and has spread

- To or beyond the middle tissue layers of the colon wall or
- To nearby tissues around the colon or rectum or
- To nearby organs and/or through the peritoneum

Stage IV: cancer may have spread to nearby lymph nodes and has spread to other parts such as the liver or lungs.

Lung –Non Small Cell - Exclude Stage III and IV
Stage I & II okay IF "curative resection" done

Stage IIIA (T1 to T3, N2 M0): the tumor can be any size or have any of the following features

- The tumor involves a main bronchus without growing into the carina

[redacted]

- The tumor has grown into the visceral pleura (membranes surrounding the lung)
- The cancer is partially clogging the airways
- It has grown into the airways enough to cause an entire lung to collapse or cause pneumonia in the entire lung
- It has grown into the chest wall, the diaphragm, the mediastinal pleura or the parietal pericardium
- Two or more separate tumor nodules are present in the same lobe of a lung

OR

- (T3, N1, M0) the tumor has 1 or more of the following features
- It is larger than 7 cm across
- It has grown into the chest wall, the diaphragm, the mediastinal pleura or the parietal pericardium
- It invades a main bronchus and is closer than 2 cm to the carina but does not involve the carina itself
- Two or more separate tumor nodules are present in the same lobe of a lung
- It has grown into the airways enough to cause an entire lung to collapse or cause pneumonia in the entire lung
- It has also spread to lymph nodes within the lung and/or around the area where the bronchus enters the lung (hilar lymph nodes). These lymph nodes are on the same side as the cancer. It has not spread to distant sites

OR

- (T4, N0 or N1, M0) The cancer has 1 or more of the following features
- A tumor of any size has grown into the mediastinum, the heart, the large blood vessels near the heart (aorta), the trachea, the esophagus, spine or carina
- Two or more separate tumor nodules are present in different lobes of the same lung

It may have also spread to lymph nodes within the lung and/or around the area where the bronchus enters the lung (hilar lymph nodes). Any affected lymph nodes are on the same side of the cancer. It has not spread to distant sites.

[redacted]

Stage IIIB (Any T, N3, M0): The cancer can be of any size. It may or may not have grown into nearby structures or caused pneumonia or lung collapse. It has spread to lymph nodes near the collarbone on either side, and/or has spread to hilar or mediastinal lymph nodes on the side opposite the primary tumor. The cancer has not spread to distant sites.

OR

(T4, N2, M0): The cancer has 1 or more of the following features:

- A tumor of any size has grown in to the mediastinum, the heart, the large blood vessels near the heart, the trachea, the esophagus, the spine or carina
- Two or more separate tumor nodules are present in different lobes of the same lung

The cancer has also spread to lymph nodes around the carina or the mediastinum. Affected lymph nodes are on the same side as the main lung tumor. It has not spread to distant sites.

Stage IV

(Any T, any N, M1a): The cancer can be any size and may or may not have grown into the nearby structures or reached nearby lymph nodes. In addition, any of the following is true:

- The cancer has spread to the other lung
- Cancer cells are found in the fluid around the lung (malignant pleural effusion)
- Cancer cells are found in the fluid around the heart (malignant pericardial effusion)

OR

(Any T, any N, M1b) the cancer can be any size and may or may not have grown into nearby structures or reached nearby lymph nodes. It has spread to distant sites (another organ)

Small Cell Lung Cancer - Exclude extensive stage – limited stage evaluated on a case by case basis

Extensive stage small cell lung cancer is defined as a small cell lung cancer that has spread (metastasized) to other regions of the body such as another lobe of the lung or the brain.

Prostate Cancer
Exclude the following, if the patient is not expected to live 90 days, or is on excluded chemotherapy agents, or if the patient is not committed to aggressive care of the sepsis:
AJCC (TNM) Stage 3 & 4 Jewett Staging System Stage C & D

Stage III (T3, N0, M0 and Gleason score, any PSA): The cancer has begun to spread outside the prostate and may have spread to the seminal vesicles [T3], but it has not spread to the lymph nodes [N0] or elsewhere in the body [M0]. The tumor can have any Gleason score or PSA of any value.

Stage IV One of the following applies:

(T4, N0 M0 any Gleason score, any PSA) the cancer has spread to the tissues next to the prostate [other than the seminal vesicles], such as the bladder's external sphincter, rectum and/or the wall of the pelvis [T4]. The cancer has not spread to nearby lymph nodes [N0} or elsewhere in the body [M0]. The tumor can have any Gleason score and the PSA can be any value.

OR

(Any T, N1, M0 any Gleason score, any PSA) the tumor may be growing into tissues near the prostate [any T]. The cancer has spread to the lymph nodes [N1] but has not spread elsewhere in the body [M0]. The tumor can have any Gleason score or any PSA value.

OR

(Any T, any N, M1, any Gleason score, any PSA) the cancer may be growing into tissues near the prostate [any T] and may have spread to nearby lymph nodes [any N]. It has spread to other, more distant sites in the body [M1]. The tumor can have any Gleason score and the PSA can be any value.

Jewett Stage C: the tumor is still only found in the area surrounding the prostate but has extended through the capsule that covers the prostate and could also have entered the seminal vesicles.

- The cancer has spread into through the capsule that contains the prostate
- The cancer has spread through the capsule that contains the prostate and has begun to block the flow of urine from the bladder outlet or the ureters

Jewett Stage D: the cancer has metastasized or spread distantly from the prostate

- The cancer is found only in the prostate by examination and with imaging tests but blood tests continue to show high levels of certain enzymes that mean the cancer has spread or
- The cancer has spread to the lymph nodes near the prostate or
- The cancer has spread to distant lymph nodes, to bones or other organ

[redacted]

Breast Cancer -Exclude Stage IIIB, IIIC and IV

Stage IIIB the tumor may be any size and the cancer:

- Has spread to the chest wall and/or the skin of the breast and
- May have spread to the axillary lymph nodes that may be attached to each other or to other structures or cancer may have spread to lymph nodes near the breast bone

Stage IIIC there may be no sign of cancer in the breast or the tumor may be any size and may have spread to the chest wall and/or the skin of the breast. Also

- Has spread to lymph nodes above or below the collarbone and
- May have spread to axillary lymph nodes or to lymph nodes near the breastbone

Stage IV: the cancer has spread to other organs of the body, most often the bones and lungs

Hepatic Cancer Exclude Entirely

Lymphoma
Non-Hodgkin's Indolent: Exclude non-contiguous Stage II, III and IV
Non-Hodgkin's Aggressive: Exclude Stages III and IV

Indolent lymphomas: tend to grow and spread slowly and have few symptoms.

Non-contiguous lymphomas: lymphomas in which the lymph nodes containing cancer are not next to each other, but are on the same side of the diaphragm.

Aggressive lymphomas: these grow and spread quickly and have severe symptoms. Lymphoblastic lymphoma, diffuse small non-cleaved cell lymphoma/Burkitt lymphoma and mantle cell lymphoma are 3 types of aggressive adult non-Hodgkin lymphoma. Aggressive lymphomas are seen more often in patients who are HIV + (AIDS-related lymphoma).

Stage II is divided into stage II and IIE

- Cancer is found in 2 or more lymph node groups above or below the diaphragm OR
- Cancer is found in 1 or more lymph node groups above or below the diaphragm and outside the lymph nodes in a nearby organ or area.

Stage III is divided into stage III, stage IIIE, stage IIIS and stage IIIS + E

[redacted]

- III: cancer is found in one or more lymph node groups above and below the diaphragm
- IIIE: cancer is found in lymph node groups above and below the diaphragm and outside the lymph nodes in a nearby organ or area
- IIIS: cancer is found in lymph node groups above and below the diaphragm and in the spleen
- IIIS + E: cancer is found in lymph node groups above and below the diaphragm, outside the lymph nodes in a nearby organ or area and in the spleen

Stage IV

- The cancer is found outside the lymph nodes throughout one or more organs and may be in lymph nodes near those organs
- The cancer is found outside the lymph nodes in one organ and has spread to lymph nodes far away from that organ
- OR the cancer is found in the lung, liver or bone marrow

Renal Cancer - Enroll only if cancer is confined to capsule

Cervical Cancer - Exclude Stage III and IV

Stage III: the cancer has spread to the lower part of the vagina or the walls of the pelvis. The cancer may be blocking the ureters. It has not spread to nearby lymph nodes [N0] or distant sites [M0].

Stage IV: this is the most advanced stage of cervical cancer; the cancer has spread to nearby organs or other parts of the body.

Leukemia

Acute Myelocytic Leukemia (AML) - Excluded unless in remission. Exclude if BMT is planned.

Acute Lymphocytic Leukemia (ALL) - Excluded unless in remission. Exclude if BMT is planned.

Chronic Myeloctyic Leukemia (CML) - Exclude Blast or Accelerated Phase*

[redacted]

Chronic Lymphocytic Leukemia (CLL) – Exclude accelerated disease such as hemoglobin < 12 g/dL and absolute lymphocyte count > 30,000/µL, patients on excluded chemotherapy, or with evidence of transformation to acute leukemia.

***Blast phase**: Refers to advanced CML. In this phase, the number of immature, abnormal white blood cells in the bone marrow and blood is extremely high. Also called blast crisis.

Accelerated phase of leukemia: Refers to CML that is progressing. The number of immature, abnormal white blood cells in the bone marrow and blood is higher than in the chronic phase but not as high as in the blast phase.

Multiple Myeloma - Exclude ISS Stage II and III

Stage II: β2M < 3.5 and albumin < 3.5; or β2M ≥ 3.5 and < 5.5

Stage III: β2M ≥ 5.5

Skin- Exclude melanoma if evidence of metastasis

CNS Cancer (Intracranial mass lesions or spinal cord)

Evaluated on a case by case basis

Pancreatic Cancer - Exclude entirely

Stomach Cancer - Exclude Stage III & IV
Stage I & II okay if "curative resection" done

Stage III (divided into Stage IIIA and IIIB depending on where the cancer has spread)

Stage IIIA:

- Cancer has spread to the muscularis (middle) layer of the stomach wall and is found in 7-15 lymph nodes near the tumor
- Cancer has spread to the serosal (outermost) layer of the stomach wall and is found in 1-6 lymph nodes near the tumor
- Cancer has spread to organs next to the stomach but not to the lymph nodes or other parts of the body

Stage IIIB:

- Cancer has spread to the serosal layer of the stomach wall and is found in 7-15 lymph nodes near the tumor

Stage IV

Cancer has spread to:

- Organs next to the stomach and to at least one lymph node or
- More than 15 lymph nodes
- Other parts of the body

[redacted]

Clinical Study Protocol Appendix K

Drug Substance	AZD9773
Study Code	D0620C00003
Edition Number	1
Date	[redacted]

Appendix K
Short Form 36 Health Survey, Version 2 Acute

[redacted]

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. ***Thank you for completing this survey!***

For each of the following questions, please mark an ☒ in the one box that best describes your answer.

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
▼	▼	▼	▼	▼
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. <u>Compared to one year ago</u>, how would you rate your health in general <u>now</u>?

Much better now than one week ago	Somewhat better now than one week ago	About the same as one week ago	Somewhat Worse now than one week ago	Much worse now than one week ago
▼	▼	▼	▼	▼
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

3. The following questions are about activities you might do during a typical day. Does <u>your health now limit you</u> in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a <u>Vigorous activities</u>, such as running, lifting heavy objects, participating in strenuous sports	☐ 1	☐ 2	☐ 3
b <u>Moderate activities</u>, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐ 1	☐ 2	☐ 3
c Lifting or carrying groceries	☐ 1	☐ 2	☐ 3
d Climbing <u>several</u> flights of stairs	☐ 1	☐ 2	☐ 3
e Climbing <u>one</u> flight of stairs	☐ 1	☐ 2	☐ 3
f Bending, kneeling, or stooping	☐ 1	☐ 2	☐ 3
g Walking <u>more than a mile</u>	☐ 1	☐ 2	☐ 3
h Walking <u>several hundred yards</u>	☐ 1	☐ 2	☐ 3
i Walking <u>one hundred yards</u>	☐ 1	☐ 2	☐ 3
j Bathing or dressing yourself	☐ 1	☐ 2	☐ 3

[redacted]

4. During the <u>past week</u>, how much of the time have you had any of the following problems with your work or other regular daily activities <u>as a result of your physical health</u>?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the <u>amount of time</u> you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b <u>Accomplished less</u> than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Were limited in the <u>kind</u> of work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d Had <u>difficulty</u> performing the work or other activities (for example, it took extra effort)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

5. During the <u>past week</u>, how much of the time have you had any of the following problems with your work or other regular daily activities <u>as a result of any emotional problems</u> (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the <u>amount of time</u> you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b <u>Accomplished less</u> than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Did work or other activities <u>less carefully than usual</u>	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

[redacted]

6. During the <u>past week</u>, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

Not at all	Slightly	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

7. How much <u>bodily</u> pain have you had during the <u>past week</u>?

None	Very mild	Mild	Moderate	Severe	Very severe
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

8. During the <u>past week</u>, how much did <u>pain</u> interfere with your normal work (including both work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

9. These questions are about how you feel and how things have been with you <u>during the past week</u>. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the <u>past week</u>…

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Did you feel full of life?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Have you been very nervous?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Have you felt so down in the dumps that nothing could cheer you up?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d Have you felt calm and peaceful?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
e Did you have a lot of energy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
f Have you felt downhearted and depressed?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
g Did you feel worn out?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
h Have you been happy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
i Did you feel tired?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

10. During the <u>past week</u>, how much of the time has your <u>physical health or emotional problems</u> interfered with your social activities (like visiting with friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

11. How TRUE or FALSE is <u>each</u> of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a	I seem to get sick a little easier than other people	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b	I am as healthy as anybody I know	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c	I expect my health to get worse	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d	My health is excellent	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Thank you for completing these questions!

[redacted]

Clinical Study Protocol Appendix L

Drug Substance	AZD9773
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Edition Number	1
Date	[redacted]

Appendix L
Charlson Comorbidity Scale

From the combined score an estimate of 10-year survival is given which can be used in longitudinal studies.

Weighted Index of Comorbidity

Condition	Assigned Weight
myocardial infarction	1
congestive heart failure	1
peripheral vascular disease	1
cerebrovascular disease	1
dementia	1
chronic pulmonary disease	1
connective tissue disease	1
ulcer disease	1
liver disease mild	1
diabetes	1
hemiplegia	2
renal disease moderate or severe	2
diabetes with end organ damage	2
any malignancy	2
leukemia	2
malignant lymphoma	2
liver disease. moderate or severe	3
metastatic solid malignancy	6
AIDS	6

The index of comorbidity is the sum of all conditions present in the patient.

The age-related risk is calculated as the integral value of ([age-40]/10), where rounding of the age is not performed (eg, 49 is scored 0, 50 as 1).

The combined score is (weighted index of comorbidity) + (age-related risk) and the estimated 10-year survival is given by:

$$0.983^{(\mathrm{EXP}[0.9 * \{\text{combined score}\}])}$$

where: 0.983 is the 10-year survival in a low risk population.

Charlson et al 1987
Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. J Chron Dis. 1987;40: 373-83.