THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

Revised Clinical Study Protocol

Drug Substance	AZD9773
Study Code	D0620C00005
Edition Number	1
Date	[redacted]

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

Sponsor

[redacted]

AstraZeneca Research and Development site representative

[redacted]

Date

This submission /document contains trade secrets and confidential commercial information, disclosure of which is prohibited without providing advance notice to AstraZeneca and opportunity to object.

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

[redacted]

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

AstraZeneca

PROTOCOL SYNOPSIS

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

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

Study monitor

[redacted]

Medical Monitor

[redacted]

External Medical Advisor

[redacted]

Study sites and number of patients planned

The sample size has been based on practical requirements rather than any formal sample size justification. The number of patients was chosen so as to obtain sufficient safety and

[redacted]

pharmacokinetic (PK) data to progress the compound whilst exposing as few patients as possible to AZD9773.

The study will consist of 2 successive cohorts, with a total of 20 patients planned (10 patients per cohort) from approximately 10 Japanese sites. For each cohort, initially 10 patients will be randomised (7 on active treatment and 3 on placebo). A completely recruited Cohort 1, a minimum number of 4:1 (AZD9773: placebo) cohort-completers, with all patients having completed or at least reached 7 days after his/her last dose are required for Safety Review Committee (SRC) and Independent Data Monitoring Committee (IDMC) recommendations to progress to the second cohort in this dose escalation study.

If this total is not achieved after 10 patients have been randomised to a cohort, additional patient(s) will be enrolled, and will be allocated to the treatment of the non-cohort completer(s), unless a safety concern precludes further enrolment. Enrolment of additional patients will continue until at least 4 patients in the AZD9773 group and at least 1 patient in the placebo have completed the cohort. For these patients, the treatment group allocation will be forced but the blind will be maintained. All patients who receive a dose of study drug will be evaluated for safety and tolerability.

Each site is expected to recruit approximately 1-3 patients into this study. The study will be conducted in Japan. The list of Principal Investigators is available in Supplement A.

[redacted]

[redacted]

Study period

[redacted]

Phase of development

Phase II

Objectives

The two co-primary objectives of this study are to assess in Japanese patients with severe sepsis and/or septic shock: 1) the safety and tolerability of two different doses of AZD9773 and 2) the PK of AZD9773.

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

The safety and tolerability will be assessed in terms of the incidence and nature of adverse events (AEs), serious adverse events (SAEs), AEs leading to discontinuation of study drug, and deaths, 12-lead electrocardiogram (ECG), vital signs (blood pressure, pulse, body temperature, respiratory rate), oximetry, laboratory variables (haematology, clinical chemistry, coagulation, urinalysis), physical examination, and other safety monitoring (troponin I, human anti-sheep antibody [HASA] immunoglobulin [IgG], HASA bridging assay, neutralising antibody assay [nAb]).

The PK of AZD9773 will be assessed in terms of area under the serum concentration-time curve (AUC) from time zero to time t (AUC_{0-t}), AUC within the dosing interval (AUC_{τ}), serum concentration at the end of infusion (C_{inf}), maximum concentration at steady state ($C_{ss\ max(inf)}$), $C_{ss\ min}$, accumulation ratio, renal clearance (CL_R) and % of drug recovered in urine.

The secondary objective is to make a preliminary assessment of the pharmacodynamics (PD) of two different doses of AZD9773 in Japanese patients with severe sepsis and/or septic shock, in terms of the effect on tumour necrosis factor α (TNFα), interleukin (IL)-6 and IL-8.

The exploratory objectives are to obtain preliminary information on clinical outcomes in Japanese patients with severe sepsis and/or septic shock, in terms of ventilator-free days (VFDs), Sequential Organ Failure Assessment (SOFA) score, 28-day mortality, organ failure assessment, and infection assessment.

Study design

This is a Phase II, multicentre, randomised, double-blind, placebo-controlled, dose escalation study to assess the safety, tolerability, PK and PD of multiple intravenous (IV) infusions of two different doses of AZD9773 in Japanese patients with severe sepsis and/or septic shock (as soon as feasible but in no case later than 36 hrs of qualifying organ failure).

Target patient population

The target population for the study comprises adult Japanese patients with objective clinical evidence of infection requiring administration of parenteral antibiotics and severe sepsis and/or septic shock. They must meet the criteria for systemic inflammatory response syndrome (SIRS), and have cardiovascular and/or respiratory failure (see Table 2). Patients (or their legally authorised representative) must have provided written informed consent for participation in the study.

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 concentration.

AZD9773 is a [redacted]

[redacted]

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

AZD9773 is standardised by measuring its ability to neutralise the lethal or lytic effects of TNFα on L929 murine fibroblasts *in vitro*, with one potency unit protecting cells from approximately 13,000 International Units (IU) of TNFα. Therefore, 5,000 units of AZD9773 are capable of neutralising 65,000,000 IU of TNFα.

AZD9773 is administered by IV infusion. The initial infusion and subsequent doses of study drug will be given to patients in a monitored setting (ie, intensive care unit [ICU] or emergency department, with cardiac monitoring). Another location in the hospital may be acceptable if it meets these criteria and is approved by the CCC and/or the Medical Monitor.

Study drugs, in masked administration bags to maintain the blind, will be as follows:

AZD9773 250 units/kg (1 infusion) + 50 units/kg (9 infusions) (Dose Cohort 1):

Single loading infusion of 250 units AZD9773 per kg body weight (maximum 25000 units) over 30 minutes followed by 50 units AZD9773 per kg body weight over 30 minutes once every 12±2 hrs for 9 maintenance doses (maximum 5000 units each).

AZD9773 500 units/kg (1 infusion) + 100 units/kg (9 infusions) (Dose Cohort 2):

Single loading infusion of 500 units AZD9773 per kg body weight (maximum 50000 units) over 30 minutes followed by 100 units AZD9773 per kg body weight over 30 minutes once every 12±2 hrs for 9 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 with the same regimen and at the same times as noted for Dose Cohorts 1 and 2.

Duration of treatment

A total of 10 doses (a loading dose followed by 9 maintenance doses) of AZD9773 will be administered, one dose every 12±2 hrs for 30 minutes.

Dosing should not continue past Day 6.

For details about dosing interval adjustments, and procedures in case of missed dose, see Section 5.5.2.

Safety Review Committee (SRC) and Independent Data Monitoring Committee (IDMC):

At the end of Cohort 1, a SRC consisting of the External Medical Advisor in Japan, a Statistician, the Global Project Physician, the Japan Project Physician, and the Global Drug Safety Physician or their delegates, will evaluate safety data. The SRC will also consult with a clinical pharmacologist and an external consultant with experience in other AZD9773 trials. The SRC may bring in additional expertise if needed.

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

The SRC members will be unblinded, but the rest of the study team will remain blinded. Based on the reviewed data, the SRC will provide a safety assessment and make recommendations to the IDMC to proceed to Cohort 2, modify or stop escalation based on safety findings.

An IDMC will be established comprising three independent experts. The committee will meet to review data from Cohort 1 and at the end of the study. The IDMC will meet in open session with the SRC, 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, SRC, or IDMC may call additional meetings if, at any time, there is concern about the safety of the study.

For details about criteria for dose escalation, definition of cohort-completers and the roles of the SRC and IDMC, see Section 12.5.

Primary outcome variables:

- Safety
  - Incidence and nature of AEs.
  - Incidence and nature of SAEs, AEs leading to discontinuation of study drug, and deaths.
  - 28-day mortality.
  - 12-lead ECG.
  - Vital signs (blood pressure, pulse, body temperature, respiratory rate).
  - Oximetry.
  - Laboratory variables (haematology, clinical chemistry, coagulation, urinalysis).
  - Physical examination.
  - Other safety monitoring (troponin I, HASA IgG, HASA bridging assay, and nAb assay).
- PK
  - $AUC_{0\text{-}t}$, AUC_{τ}, C_{inf}, $C_{ss\ max(inf)}$, $C_{ss\ min}$, accumulation ratio, CL_R and % of drug recovered in urine.

Secondary outcome variables:

- PD
  - TNFα, IL-6 and IL-8.

Exploratory outcome variables:

- General assessment of sepsis care and clinical outcomes
  - VFDs.
  - SOFA score.
  - Organ failure assessment.
  - Lactate.
  - Infection assessment. (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 in hand prior to randomisation.)

Statistical methods

Three analysis sets will be defined for this study. The enrolled patients analysis set will consist of all patients who received an 8-digit E-code and signed the informed consent, regardless of whether they were randomised or treated. The Safety analysis set will consist of all patients who started an infusion of study drug. The PK analysis set will be a subset of the Safety analysis set including only those patients without important deviations that affect the PK. A strategy for dealing with data affected by protocol deviations will be agreed by the Study Team Physician, Study Team Pharmacokineticist and Study Team Statistician prior to clean file and code break.

For analysis of patients who received placebo, data from all patients in both cohorts will be combined. Data for patients who received AZD9773 will be presented by cohort.

Outcome variables will be listed and summarised using descriptive statistics, as appropriate.

No interim analyses are planned for this study.

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

[redacted]

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

TABLE OF CONTENTS PAGE

TITLE PAGE 1
PROTOCOL SYNOPSIS 2
TABLE OF CONTENTS 8
LIST OF ABBREVIATIONS AND DEFINITION OF TERMS 14
1. INTRODUCTION 18
1.1 Background 18
1.1.1 Sepsis 18
1.1.2 AZD9773 (CytoFab™) 18
1.1.3 Nonclinical studies 19
1.1.4 Clinical studies 20
1.2 Research hypothesis 20
1.3 Rationale for conducting this study 20
1.4 Benefit/risk and ethical assessment 20
2. STUDY OBJECTIVES 21
2.1 Primary objectives 21
2.2 Secondary objective 22
2.3 Exploratory objectives 22
3. STUDY PLAN AND PROCEDURES 22
3.1 Overall study design and flow chart 22
3.2 Rationale for study design, doses and control groups 32
4. PATIENT SELECTION CRITERIA 33
4.1 Inclusion criteria 33
4.2 Exclusion criteria 36
5. STUDY CONDUCT 39
5.1 Restrictions during the study 39
5.2 Patient enrolment and randomisation 40
5.2.1 Procedures for randomisation 41
5.3 Procedures for handling patients incorrectly included 42
5.4 Blinding and procedures for unblinding the study 42
5.4.1 Methods for ensuring blinding 42

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

5.4.2 Methods for unblinding the study 43

5.5 Treatments 43
5.5.1 Identity of investigational product(s) 43
5.5.2 Doses and treatment regimens 44
5.5.3 Labelling 46
5.5.4 Storage 46

5.6 Pre-study, concomitant and post-study treatment(s) 46
5.6.1 Pre-study treatments 46
5.6.2 Concomitant medications 47
5.6.3 Post-study medications 48

5.7 Treatment compliance 48
5.7.1 Accountability 49

5.8 Discontinuation of investigational product 49
5.8.1 Criteria for discontinuation of a patient from investigational product 49
5.8.2 Procedures for discontinuation of a patient from investigational product 50

5.9 Withdrawal from study 51
5.9.1 Criteria for discontinuation from the study 51
5.9.2 Procedures for discontinuation of a patient from the study 51

6. COLLECTION OF STUDY VARIABLES 52

6.1 Recording of data 52

6.2 Screening and demography procedures 52
6.2.1 Follow-up procedures 54

6.3 Efficacy – not applicable 54

6.4 General assessment of sepsis care 54
6.4.1 Acute Physiology and Chronic Health Evaluation (APACHE) II Scores 54
6.4.2 Glasgow Coma Score 55
6.4.3 Sequential Organ Failure Assessment (SOFA) Scores 55
6.4.4 Ventilator use and pulmonary assessment 55
6.4.5 Organ failure assessment 56
6.4.6 Lactate 56
6.4.7 Septic shock 56
6.4.8 Infection assessment 56
6.4.9 Antibiotic use 57
6.4.10 Assessment of ICU-free days 57
6.4.11 Daily volume status 57

6.5 Safety 58
6.5.1 Definition of adverse events 58
6.5.2 Definitions of serious adverse event 59
6.5.3 Recording of adverse events 60
6.5.4 Reporting of serious adverse events 63
6.5.5 Laboratory safety assessment 64

[redacted]

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

6.5.6 Physical examination 67
6.5.7 Electrocardiogram 67
6.5.8 Vital signs and blood oxygen-haemoglobin saturation 68
6.5.9 28-day mortality 68
6.6 Pharmacokinetics 68
6.6.1 Collection of samples 69
6.6.2 Determination of drug concentration 70
6.7 Pharmacodynamics 70
6.7.1 Collection of pharmacodynamic markers 70
6.7.2 Cytokine serum concentrations 71
6.8 Pharmacogenetics – not applicable 71
6.9 Health economics – not applicable 71
7. BIOLOGICAL SAMPLING PROCEDURES 71
7.1 Volume of blood 71
7.1.1 Clinical samples 72
7.1.2 Pharmacokinetic samples 73
7.2 Handling, storage and destruction of biological samples 73
7.2.1 Pharmacokinetic and/or pharmacodynamic samples 73
7.2.2 Pharmacogenetic samples – not applicable 73
7.3 Labelling and shipment of biohazard samples 73
7.4 Chain of custody of biological samples 73
7.5 Withdrawal of informed consent for donated biological samples – not applicable 74
8. ETHICAL AND REGULATORY REQUIREMENTS 74
8.1 Ethical conduct of the study 74
8.2 Patient data protection 74
8.3 Ethics and regulatory review 74
8.4 Informed consent 75
8.5 Changes to the protocol and informed consent form 76
8.6 Audits and inspections 76
9. STUDY MANAGEMENT 76
9.1 Pre-study activities 77
9.2 Training of study site personnel 77
9.3 Monitoring of the study 77
9.3.1 Source data 78
9.3.2 Direct access to source data in Japan 78

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

9.4 Study agreements 79
9.4.1 Archiving of study documents 79
9.5 Study timetable and end of study 79
10. DATA MANAGEMENT 80
11. EVALUATION AND CALCULATION OF VARIABLES 81
11.1 Calculation or derivation of variables used in the general assessment of sepsis care 81
11.1.1 Calculation and derivation of Acute Physiology and Chronic Health Evaluation (APACHE) II Score 81
11.1.2 Calculation and derivation of Glasgow Coma Score 81
11.1.3 Calculation and derivation of Sequential Organ Failure Assessment (SOFA) Scores 81
11.1.4 Calculation and derivation of ventilator use and pulmonary assessment parameters 82
11.1.5 Calculation and derivation of organ failure assessment 83
11.1.6 Septic shock recording 83
11.1.7 Calculation and derivation of ICU-free days 83
11.1.8 Daily volume status 83
11.2 Calculation or derivation of safety variable(s) 83
11.2.1 Other significant adverse events (OAE) 83
11.2.2 Extent of exposure 84
11.2.3 Creatinine clearance 84
11.2.4 Blood pressure 84
11.3 Calculation or derivation of patient reported outcome variables – not applicable 84
11.4 Calculation or derivation of pharmacokinetic variables 84
11.5 Calculation or derivation of pharmacodynamic variable(s) 85
11.5.1 Calculation or derivation of pharmacodynamic variables 85
11.5.2 Calculation or derivation of the relationship between pharmacokinetic and pharmacodynamic variables 85
11.5.3 Calculation or derivation of the relationship between pharmacokinetic and efficacy variables – not applicable 85
11.5.4 Calculation or derivation of the relationship between pharmacokinetic variables and adverse events 85
11.5.5 Population analysis of pharmacokinetic/pharmacodynamic variables 85
11.6 Calculation or derivation of pharmacogenetic variables – not applicable 86
11.7 Calculation or derivation of health economic variables – not applicable 86
12. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION 86
12.1 General principles 86
12.2 Description of analysis sets 87

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

12.2.1 Enrolled population 87
12.2.2 Safety population 87
12.2.3 Pharmacokinetic population 87
12.3 Methods of statistical analyses 87
12.3.1 Disposition, demographics and baseline characteristics 87
12.3.2 Concomitant medication and past/current medical and surgical history 89
12.3.3 Protocol deviations 89
12.3.4 Pharmacokinetics 90
12.3.5 Pharmacodynamics analysis 91
12.3.6 SOFA Score 92
12.3.7 Volume status in the 24 hrs prior to randomisation 92
12.3.8 Pulmonary assessment and ventilator use 92
12.3.9 Septic shock 93
12.3.10 Organ failure assessment 93
12.3.11 Infection assessment 93
12.3.12 28-day mortality 93
12.3.13 ICU-free days 93
12.3.14 Safety 94
12.3.14.1 Extent of exposure 94
12.3.14.2 Adverse events 94
12.3.14.3 Deaths, serious adverse events, adverse events leading to withdrawal, and other significant adverse events 95
12.3.14.4 Laboratory evaluation 96
12.3.14.5 Vital signs and blood oxygen-haemoglobin saturation evaluation 97
12.3.14.6 Electrocardiogram evaluation 97
12.3.15 Interim analyses 98
12.4 Determination of sample size 98
12.5 Safety Review Committee and Independent Data Monitoring Committee 98
13. IMPORTANT MEDICAL PROCEDURES TO BE FOLLOWED BY THE INVESTIGATOR 100
13.1 Medical emergencies and AstraZeneca/PAREXEL contacts 100
13.2 Overdose 101
13.3 Pregnancy 102
13.3.1 Maternal exposure 102
13.3.2 Paternal exposure 103
14. LIST OF REFERENCES 103

LIST OF TABLES

Table 1 Study plan 28

[redacted]

Table 2 Organ dysfunction definitions 35
Table 3 Investigational product 44
Table 4 Laboratory safety parameters 65
Table 5 Pharmacokinetic sampling.....69
Table 6 Approximate volume of blood to be drawn from each patient.....72

LIST OF FIGURES

Figure 1 Study flow chart 27
Figure 2 Timing of severe sepsis inclusion criteria 36

LIST OF APPENDICES

Appendix A Signatures (not applicable)
Appendix B Additional Safety Information
Appendix C International Airline Transportation Association (IATA) 6.2 Guidance Document
Appendix D Medical Management of Patients with Severe Sepsis
Appendix E Acute Physiology and Chronic Health Evaluation (APACHE) II Score
Appendix F Glasgow Coma Score
Appendix G Sequential Organ Failure Assessment (SOFA) Score
Appendix H Ventilator Weaning Protocol
Appendix I Recommendations for Immunosuppressive Agents
Supplement A Investigators and Study Administrative Structure

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

[redacted]

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study Clinical Study Protocol.

Abbreviation or special term	Explanation
AA	Alveolar to arterial
ACP	Above cut-point
AE	Adverse event (see definition in Section 6.5.1)
ALT	Alanine aminotransferase
APACHE II	Acute Physiology and Chronic Health Evaluation score
AST	Aspartate aminotransferase
AUC	Area under the serum concentration-time curve
AUC_{0-t}	AUC from time zero to time t
AUC_{τ}	AUC within the dosing interval
AUC_{0-12}	AUC from time zero to 12 hrs post infusion
AZD9773	AZD9773 refers to the active constituent of CytoFab™ ie, rhTNFα immune Fab (ovine) produced [redacted] t does not refer to any rhTNFα immune Fab (ovine), but only that produced by the manufacturing process outlined above.
BCP	Below cut-point
BMI	Body mass index
BP	Blood pressure
CCC	Clinical Coordinating Centre: Keio University
CD	Cluster of differentiation
C_{inf}	Serum concentration at the end of infusion
CL_R	Renal clearance
CNS	Central nervous system
CPR	Cardiopulmonary resuscitation
CRCL	Creatinine clearance
CRF	Case Report Form (electronic/paper)
CRO	Contract research organisation
C_{ss}	Concentration at steady state
CTC	Common Terminology Criteria

[redacted]

Abbreviation or special term	Explanation
CV	Coefficient of variation
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.
DBP	Diastolic blood pressure
D-CytoFab	Development-CytoFab. Material used in previously conducted Phase I and II studies in sepsis ([redacted])
DIC	Disseminated intravascular coagulation
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
ECG	Electrocardiogram
eCRF	Electronic case report form
ELISA	Enzyme-linked immunosorbent assay
eRT	eResearch Technology, Inc
Fab	Fragment of immunoglobulin produced by papain treatment
FiO_2	Fraction of inspired oxygen
GCP	Good Clinical Practice
GF	Gender correction factor
GGT	Gamma glutamyl transferase
GMP	Good Manufacturing Practice
HASA	Human anti-sheep antibody
HCG	Human chorionic gonadotropin
hr	Hour
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ICU	Intensive care unit
IDMC	Independent Data Monitoring Committee
Ig	Immunoglobulin
IL-6, -8, -10	Interleukin-6, -8, -10
IND	Investigational New Drug
IP	Investigational product
ISTH	International Society on Thrombosis and Haemostasis

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

[redacted]

Abbreviation or special term	Explanation
IRB	Institutional Review Board
IU	International units
IV	Intravenous
IVRS	Interactive voice response system
L929 assay	Determination of the tolerability of L929 cells to TNFα in the presence of diluted human serum from patients previously dosed with AZD9773, by reference to a standard curve of AZD9773.
LDH	Lactate-dehydrogenase
LOQ	Limit of quantification
LOCF	Last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
MHLW	Ministry of Health, Labour and Welfare
nAb	Neutralising antibody
NC	Not calculable
NQ	Non-quantifiable
OAE	Other significant adverse event (see definition in Section 11.2.1)
$PaCO_2$	Partial pressure of arterial carbon dioxide
PAO_2	Partial pressure of alveolar oxygen
PaO_2	Partial pressure of arterial oxygen
PD	Pharmacodynamic
PK	Pharmacokinetic
Pr	Pulse rate
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 6.5.2).
SBP	Systolic blood pressure
Scr	Serum creatinine
SD	Standard deviation
SIRS	Systemic inflammatory response syndrome

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

Abbreviation or special term	Explanation
SOFA	Sequential Organ Failure Assessment
SOC	System organ class
SpO_2	Oxygen saturation by pulse oximetry
SRC	Safety Review Committee
TEAE	Treatment-emergent adverse event
TNFα	Tumour necrosis factor α
TPN	Total parenteral nutrition
USA	United States of America
VFD	Ventilator-free day
WBC	White blood cells
WBDC	Web-based data capture

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

1. INTRODUCTION

1.1 Background

1.1.1 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.

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.

1.1.2 AZD9773 (CytoFab™)

AZD9773 (CytoFab™) is a concentrate of polyclonal fragments of immunoglobulin (Ig) [redacted]

[redacted]

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

AZD9773 is standardised by measuring its ability to neutralise the lethal or lytic effects of TNFα on L929 murine fibroblasts *in vitro*, with one potency unit protecting cells from approximately 13,000 International Units (IU) of TNFα. Therefore, 5,000 units of AZD9773 are capable of neutralising 65,000,000 IU of TNFα.

Other anti-TNF approaches have been tried in sepsis. The potential advantages of this product 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, 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 hrs)
- Unlike TNF-soluble receptors, AZD9773 has a high affinity for TNFα.

Prior to the development of AZD9773, related forms 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 1.1.4). 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 [redacted] 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 1.1.3). Most importantly, the safety and tolerability of AZD9773 have 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's Brochure (IB).

1.1.3 Nonclinical studies

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

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

1.1.4 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 (LOQ) 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.

1.2 Research hypothesis

The research hypotheses to be tested in this study are that AZD9773 is well tolerated in multiple doses in patients with sepsis and/or septic shock, and to understand the pharmacokinetic (PK) profile of AZD9773 in Japanese patients.

1.3 Rationale for conducting this study

This study is being conducted to assess the safety, tolerability and PK of AZD9773 in a Japanese population of severe sepsis and/or septic shock patients. It is intended to further substantiate the safety and tolerability of AZD9773 across doses, and to assess whether the Japanese PK profiles support inclusion in the global development program.

1.4 Benefit/risk and ethical assessment

Clinical studies of anti-TNFα approaches in patients with sepsis have, in aggregate, shown a statistically significant 3.5% reduction in 28-day mortality (Marshall 2000). The MONARCS trial, evaluating afelimomab (SEGARD™; Abbott Laboratories), arguably did demonstrate a statistically significant reduction in 28-day mortality in patients with raised IL-6 (Panacek et al 2004). However, the other studies with other antibodies failed to show a reduction. This failure to demonstrate a significant reduction in 28-day mortality could have been related to

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

the monoclonal nature of the agents used, the size of the antibody fragment, or to other factors such as patient selection and other aspects of trial design. However, no study showed significant safety concerns for anti-TNFα drugs given for a short period of time (3-5 days) to patients with severe sepsis.

Data from a Phase II clinical study with D-CytoFab have demonstrated a potential therapeutic benefit of treating patients with severe sepsis with polyclonal ovine Fab fragments targeted against TNFα in terms of an increase in VFDs with a numerical reduction of 28-day mortality (see Sections 1.1.2 and 1.1.4). In parallel, the number of AEs and serious AEs (SAEs) was comparable between the placebo and D-CytoFab groups. Based on data available to date, the TNF neutralising capabilities and the tolerability profile of AZD9773 appear to be similar to D-CytoFab.

The doses of AZD9773 selected for this study were considered well tolerated in the Phase IIa study (D0620C00004) and produced detectable suppression of circulating TNFα for the duration of dosing.

Thus, AZD9773 has a potentially favourable risk/benefit profile.

Dosing will happen only in an intensive are unit (ICU) or equivalent ward in order to minimise any safety risk for the patients. 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 needed. Patients with sepsis who are not treated in an ICU or equivalent ward will be excluded from entry into this study. In the unanticipated occurrence of development of immune complex-related side effects, prompt plasma filtration plus renal function support could form part of clinical management.

For more information about the rationale for the design of this study, see Section 3.2.

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

2. STUDY OBJECTIVES

2.1 Primary objectives

The two co-primary objectives of this study are to assess in Japanese patients with severe sepsis and/or septic shock: 1) the safety and tolerability of two different doses of AZD9773 and 2) the PK of AZD9773.

The safety and tolerability will be assessed in terms of the incidence and nature of AEs, SAEs, AEs leading to discontinuation of study drug, and deaths, 12-lead electrocardiogram (ECG), vital signs (blood pressure, pulse, body temperature, respiratory rate), oximetry, laboratory variables (haematology, clinical chemistry, coagulation, urinalysis), physical examination, and other safety monitoring (troponin I, human anti-sheep antibody [HASA] IgG, HASA bridging assay, neutralising antibody assay [nAb]).

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

The PK of AZD9773 will be assessed in terms of area under the serum concentration-time curve (AUC) from time zero to time t (AUC_{0-t}), AUC within the dosing interval (AUC_{τ}), serum concentration at the end of infusion (C_{inf}), maximum concentration at steady state ($C_{ss\ max(inf)}$), $C_{ss\ min}$, accumulation ratio, renal clearance (CL_R) and % of drug recovered in urine.

2.2 Secondary objective

The secondary objective is to make a preliminary assessment of the pharmacodynamics (PD) of two different doses of AZD9773 in Japanese patients with severe sepsis and/or septic shock, in terms of the effect on TNFα, IL-6 and IL-8.

2.3 Exploratory objectives

The exploratory objectives are to obtain preliminary information on clinical outcomes in Japanese patients with severe sepsis and/or septic shock, in terms of VFDs, Sequential Organ Failure Assessment (SOFA) score, 28-day mortality, organ failure assessment, and infection assessment.

3. STUDY PLAN AND PROCEDURES

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

3.1 Overall study design and flow chart

This is a Phase II, multicentre, randomised, double-blind, placebo-controlled, dose escalation study to assess the safety, tolerability, PK and PD of multiple IV infusions of two different doses of AZD9773 in Japanese patients with severe sepsis and/or septic shock (as soon as feasible but in no case later than 36 hrs of qualifying organ failure).

The target population for the study comprises adult Japanese patients who have objective clinical evidence of infection requiring administration of parenteral antibiotics and with severe sepsis and/or septic shock. They must meet the criteria for systemic inflammatory response syndrome (SIRS), and have cardiovascular and/or respiratory failure (see Table 2). Patients (or their legally authorised representative) must have provided written informed consent before any study-specific procedures are conducted.

The study will consist of 2 successive cohorts, with a total of 20 patients planned (10 patients per cohort) from approximately 10 Japanese centres. For each cohort, initially 10 patients will be randomised (7 on active treatment and 3 on placebo). A completely recruited Cohort 1, a minimum number of 4:1 (AZD9773: placebo) cohort-completers, with all patients having completed or at least reached 7 days after his/her last dose are required for Safety Review Committee (SRC) and IDMC recommendations to progress to the second cohort in this dose escalation study.

[redacted]

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

If this total is not achieved after 10 patients have been randomised to a cohort, additional patient(s) will be enrolled, and will be allocated to the treatment of the non-cohort completer(s), unless a safety concern precludes further enrolment. Enrolment of the additional patients will continue until at least 4 patients in the AZD9773 group and at least 1 patient in the placebo have completed the cohort. For these patients, the treatment group allocation will be forced but the blind will be maintained. All patients who receive a dose of study drug will be evaluated for safety and tolerability.

Each site is expected to recruit approximately 1-3 patients into this study. The study will be conducted in the Japan. The list of investigators for this study is available in Supplement A.

The maximum duration that a patient is expected to remain in the study including screening and the follow-up phone contact is approximately 28 days (about 4 weeks). At the end of Cohort 1, the SRC and IDMC will evaluate safety data. Based on the reviewed data, the SRC and IMDC will provide a safety assessment and make recommendations to proceed to Cohort 2, modify or stop escalation based on safety findings.

The study design is presented in Figure 1 and the study plan is presented in Table 1. Day 1 is defined as time 0 hrs (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 (or their legally authorised representative) who agree to take part in the study will be asked to sign an informed consent form before any study-specific procedure is applied.

Patients will then undergo all the baseline assessments as detailed in Table 1 (check of inclusion/exclusion criteria, medical/surgical history, demographic data, medical scores, blood and urine sampling for laboratory safety assessments, and PD measurements, physical examination and vital signs, oximetry, 12-lead ECG, and disease evaluations), AEs, and concomitant medications.

Eligible patients (ie, those who have met the study inclusion and exclusion criteria) will be randomised.

Treatment period (Day 1 up to Day 5/6)

Patients will receive either:

- In Cohort 1:
  - Initial loading dose of AZD9773 250 units/kg followed by 50 units/kg every 12 hrs for 9 maintenance doses.

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

- or placebo (saline).

- In Cohort 2:
  - Initial loading dose of AZD9773 500 units/kg followed by 100 units/kg every 12 hrs for 9 maintenance doses.
  - or placebo (saline).

Dosing of AZD9773 will be determined by body weight up to 100 kg. Patients with a body weight >100 kg will receive doses corresponding to a body weight of 100 kg.

Day 1 starts at the start of the first initial dose and continues until the end of that calendar day.

AZD9773 250 units/kg (1 infusion) + 50 units/kg (9 infusions) (Dose Cohort 1):

Single loading infusion of 250 units AZD9773 per kg body weight (maximum 25000 units) over 30 minutes followed by 50 units AZD9773 per kg body weight over 30 minutes once every 12±2 hrs for 9 maintenance doses (maximum 5000 units each).

AZD9773 500 units/kg (1 infusion) + 100 units/kg (9 infusions) (Dose Cohort 2):

Single loading infusion of 500 units AZD9773 per kg body weight (maximum 50000 units) over 30 minutes followed by 100 units AZD9773 kg body weight over 30 minutes once every 12±2 hrs for 9 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 with the same regimen and at the same times as noted for Cohorts 1 and 2. The pharmacy at each study site will supply masked saline for the study.

Duration of treatment

A total of 10 doses (a loading dose followed by 9 maintenance doses) of AZD9773 or placebo will be administered, one dose every 12±2 hrs for 30 minutes. Maximum duration of study drug treatment will be up to approximately 5 days for all patients.

The initial infusion of study drug will be given to patients in a monitored setting (ie, ICU or emergency department, with cardiac monitoring). Another location in the hospital may be acceptable if it meets these criteria and is approved by the Clinical Coordinating Centre (CCC) and/or the Medical Monitor. Subsequent doses will be given to patients in a monitored setting as above.

If necessary, a one-time dosing interval adjustment can be made after the loading dose to create a suitable morning/evening schedule 12 hrs apart. The dosing interval adjustment must be such that the first maintenance dose is given a minimum of 6 hrs and a maximum of 15 hrs after the loading dose.

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

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 hrs 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, X-ray suite, etc. If a dose is late by 2 to 5 hrs, the Medical Monitor should be contacted and 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 hrs, 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 Medical Monitor 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.

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

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 29 to further understand patient outcomes. Follow-up assessments in surviving patients are scheduled for Days 7-10, Day 15 and Day 29 (see Table 1 for time windows for these assessments). At Day 15 (±1 day) and 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 must visit the study site to have assessments and samples described in Table 1 performed. If a patient is not coming to the site for the Follow-up visit, the investigator will call the patient for follow-up purposes. A medically qualified physician will conduct an examination of patients at Day 29 or at discharge from hospital, whichever occurs first. A telephone contact is

planned (if patient is discharged) at Day 29+2 for assessment of AEs, survival, ventilator use (for assessment of VFDs) and presence of secondary infections or other AEs. 28-day survival assessment must take place after a minimum 28 WHOLE days have elapsed since start of study drug administration.

Safety Review Committee (SRC) and Independent Data Monitoring Committee (IDMC):

At the end of Cohort 1, a SRC consisting of the External Medical Advisor in Japan, a Statistician, the Global Project Physician, the Japan Project physician, and the Global Drug Safety Physician or their delegates, will evaluate safety data. The SRC will also consult with a clinical pharmacologist and an external consultant with experience in other AZD9773 trials. The SRC may bring in additional expertise if needed. The SRC members will be unblinded, but the rest of the study team will remain blinded. Based on the reviewed data, the SRC will provide a safety assessment and make recommendations to the IDMC to proceed to Cohort 2, modify or stop escalation based on safety findings.

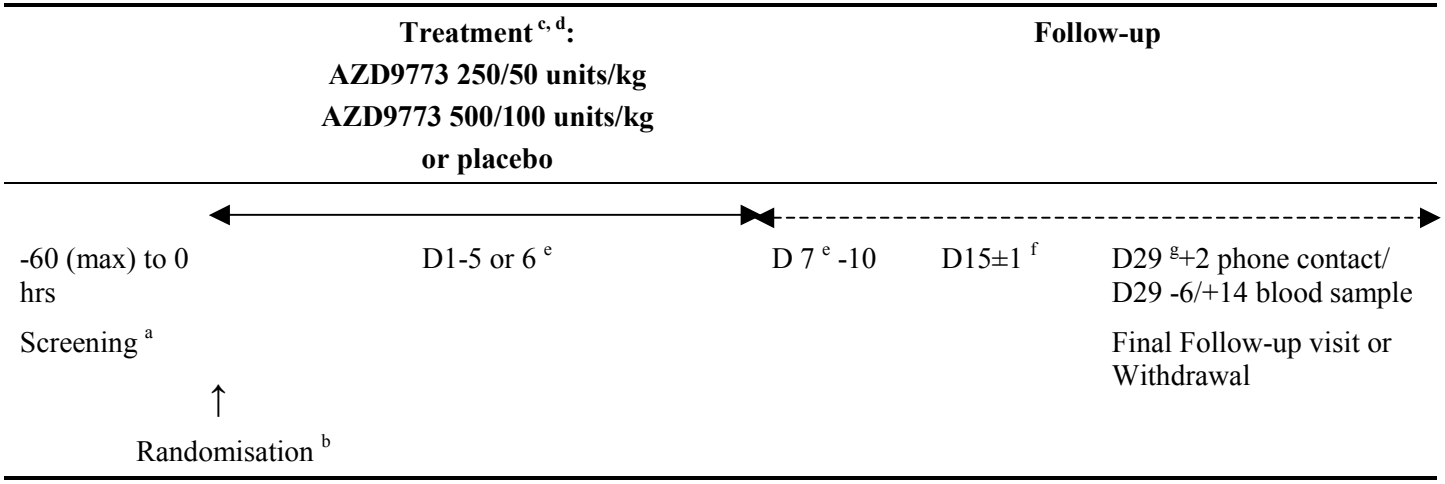
An IDMC will be established comprising three independent experts. The committee will meet to review data from Cohort 1 and at the end of the study. The IDMC will meet in open session with the SRC, followed by a closed meeting attended only by IDMC members. In the presence of any serious toxicity, the 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, SRC, or IDMC may call additional meetings if, at any time, there is concern about the safety of the study.

Details on the SRC and IDMC are provided in Section 12.5 and in the IDMC Charter.

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

Figure 1 Study flow chart



Abbreviations: AE = adverse event; CCC=Clinical Coordinating Centre; ICU=intensive care unit; VFD = ventilator-free day.

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

b Randomisation prior to dosing.

c Patients are to remain in the ICU or similarly monitored setting until 12 hrs after completion of last study treatment. Dosing must be performed in a monitored setting (ie, ICU or emergency department with cardiac monitoring). Another location in the hospital may be acceptable if it meets these criteria and is approved by the CCC and/or the Medical Monitor.

d Each maintenance dose will start at specified time ±2 hrs.
Doses are:
- Dose Cohort 1: AZD9773 250 units/kg (1 infusion) + 50 units/kg (9 infusions)
- Dose Cohort 2: AZD9773 500 units/kg (1 infusion) + 100 units/kg (9 infusions)

e If loading dose is in the afternoon of Day 1, then last maintenance dose will occur in the morning of Day 6.

f At Day 15 (±1 day), every effort will be made to obtain a blood sample for safety assessments. If no longer hospitalised, the patient must visit the study site to have assessments and samples described in Table 1 performed. If a patient is not coming to the site for the Follow-up visit, the investigator will call the patient for follow-up purposes.

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 must visit the study site to have assessments and samples described in Table 1 performed. If a patient is not coming to the site for the Follow-up visit, the investigator will call the patient for follow-up purposes. A medically qualified physician will conduct an examination of patients at Day 29 or at discharge from hospital, whichever occurs first. A telephone contact is planned (if patient is discharged) at Day 29+2 for assessment of AEs, survival, ventilator use (for assessment of VFDs) and presence of secondary infections or other AEs. 28-day survival assessment must take place after a minimum of 28 WHOLE days have elapsed since start of study.

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

Table 1 Study plan

Study period	**Screening and check eligibility**	**Treatment period**					**Follow-up period**						
Timepoint	**-60 (max) to 0 hr**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5/6[a] (last dose)**	**Day 7 [a]**	**Day 8**	**Day 9**	**Day 10**	**Day 15±1 [s]**	**Dis-charge [b]**	**Day 29[t] or Dis-continue**
Informed consent [c]	X												
Admission to ICU	X												
Medical/surgical history	X												
Inclusion/exclusion criteria	X												
Randomisation	X												
Drug administration [a]		X	X	X	X	X							
Demographics, APACHE II [g]	X												
Blood culture	X												
Pregnancy test (serum and urine)	X [d]												
Height	X												
Weight [q]	X												
AEs [o]	←	—	—	—	—	—	—	—	—	—	—	→	
Concomitant meds (from time of informed consent)	←	—	—	—	—	—	—	—	—	—	—	→	
Physical examination: Lung auscultation, dermal examination	-4 to 0 hr	X [e]	X [e]	X [e]	X [e]	X [e]						X	X
Vital signs, oximetry [f]	X [g]	X	X	X	X	X	X	X	X	X	X	X	
12-lead ECG	X [h]	X [h]		X [h]		At last dose [h]				X [h]			X [h]
Infection assessments	X [r]	X	X	X	X	X	X	X	X	X	X	X	X
Haematology	X [i]		X		X	X					X	X	X
Clinical chemistry	X [i]		X		X	X					X	X	X

[redacted]

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

Study period	**Screening and check eligibility**	**Treatment period**					**Follow-up period**						
Timepoint	**-60 (max) to 0 hr**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5/6[a] (last dose)**	**Day 7 [a]**	**Day 8**	**Day 9**	**Day 10**	**Day 15±1 [s]**	**Dis-charge [b]**	**Day 29[t] or Dis-continue**
Urinalysis	X [i]		X		X	X					X	X	X
Coagulation parameters	X [i]		X		X	X					X		
Troponin I	X [i]		X				X						
Lactate	X [i, u]	X [u]	X										
HASA IgG and total (HASA bridging assay) [i]	X [i]										X		X
Protein C activity	X [i]												
IgE	X [i]												
nAb assay	X [i]										X		X
Sample for blood PK [j]		X		X	X	X							
Sample for urine PK		X [k]				X [k]							
Cytokines [l]	X	X [m]	X		X	X	X [m]			X	X [m]		
Daily volume status	X [v]												
SOFA score	X	X	X			X							
Ventilator settings [n]		X	X	X	X	X	X						
Ventilator free days assessment		X	X	X	X	X	X	X	X	X	X		X
Mortality [p]													X [p]

Abbreviations: AE: adverse event, APACHE: Acute Physiology and Chronic Health Evaluation score, BP: blood pressure, ECG: electrocardiogram, eCRF: electronic case report form, ELISA: enzyme-linked immunosorbent assay, FiO_2: fraction of inspired oxygen, HASA: human anti-sheep antibody, ICU: intensive care unit and equivalent medical ward, Ig: immunoglobulin, IL: interleukin, nAb: neutralising antibody, $PaCO_2$: partial pressure of arterial carbon dioxide, PaO_2: partial pressure of arterial oxygen, PK: pharmacokinetics, RR: respiratory rate, SAE: serious adverse event, SOFA: Sequential Organ Failure Assessment, TNFα: tumour necrosis factor α, VFD: ventilator-free day.

a If loading dose is in the afternoon of Day 1, then last maintenance dose will occur in the morning of Day 6.
b If patient discharges on Day 7 or 15, then the assessments of the corresponding Day should be performed and no additional discharge visit is necessary.

[redacted]

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

c Written informed consent must be obtained from patient or his/her legally authorised representative prior to any study specific assessments. To reduce the burden of the patients, the assessment obtained before consent can be used if the examination took place within the specified time frames. This is applicable only when the patient agrees during the consenting procedure on the use of data measured before informed consent.

d 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.

e 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 change in BP, skin or lung examination), an additional full physical examination should be performed and changes (skin, lung, and general physical examination and BP) should be recorded on the eCRF. Any new physical examination findings, or deteriorations from baseline should be reported as AEs.

f Collect only those values closest to 8 am. Oximetry is meant to record blood oxygen-haemoglobin saturation.

g At screening, PaO_2, alveolar-arterial oxygen tension difference, pH and mean arterial pressure will be monitored for APACHE II score regardless of ventilator settings. APACHE II scoring requires either an arterial pH or a serum bicarbonate.

h 12-lead ECG should be recorded before infusion and at the end of infusion (at the same time post dosing as the PK blood draw for the loading dose). ECGs should be obtained pre-dose and end of infusion for the first dose on Days 3 and 5. ECGs should be obtained pre-dose and end of infusion for the last maintenance dose. Please ensure that these times coincide with PK blood draws. ECGs should also be recorded on Days 10 and 29. All ECGs will be obtained in triplicate within approximately 1 to 2 minutes.

i One sample will be collected within 12 hrs before the loading-dose administration (6 hrs for lactate).

j On Day 1, PK samples will be taken at pre-infusion, end infusion, and then 0.5, 1, 2, 8 & 12 hr after infusion completion but before the next infusion starts. On Days 3 and 4, samples will be taken before maintenance dose 5 and 7. On Day 5 (or 6), samples will be taken at pre-infusion, and end infusion, and 0.5, 1, 2, 8 & 12 hr after the last maintenance dose infusion. Samples taken during and up to 30 minutes after an infusion must be peripheral venous samples. All other samples may be taken either 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. At each point, window is –30 to 0 min (pre dose), ±5 min (≤2 hr after infusion) or ±1hr (≥4 hr after infusion). If study drug is withdrawn prematurely, the site should make every effort to obtain the intensive PK sampling with the last infusion following premature discontinuation (ie, as it would have been scheduled following the last maintenance infusion on Day 5/6).

k Total voided urine volume will be collected during the following time interval: start of first infusion to 12 hr after end of infusion and start of last infusion to 12 hr after end of infusion.

l Blood samples should be taken as follows: screening, pre-first infusion, Day 1 at 1-2 hrs after the end of infusion, before the morning dose on Days 2, 4, 6 and in the morning of Day 10. A screening sample for TNFα, IL-6, IL-8 and IL-10 will be analysed by flow cytometry. TNFα, IL-6 and IL-8 samples at pre-dose Day 1 and Days 1, 2, 4, 6 and 10 will be analysed by ELISA only. IL-10 sample will be taken only at screening. There will be no IL-6 or 8 assessment at Day 10. At each point, window is –30 to 0 min (pre-dose) or ±1 hr (after infusion).

m TNFα sample also 1-2 hrs after dose 2, and the morning on Days 7 and 15 (to be analysed by ELISA).

n For patients on mechanical ventilation the following ventilator settings at or closest to 08:00 will be recorded: Tidal volume, peak airway pressure over the last 24 hrs, positive end expiratory pressure, plateau pressure, RR, and arterial blood gas (pH, PaO_2, $PaCO_2$ and FiO_2 at the time the sample was obtained).

o Non-serious AEs are collected from time 0 (start of first dose of study drug) and SAEs from the provision of written informed consent. Both AEs and SAEs are collected throughout the study until Day 29. From Day 30 onwards, any new onset AEs/SAEs 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.

[redacted]

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

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

q Screening weight should be measured within 12 hrs prior to the first dose.

r The site of infection at screening should be noted. This should include primary bacteraemia if blood culture is positive but no local infection identified. All patients must have a blood culture prior to randomisation. The blood culture result does NOT have to be in hand prior to randomisation.

s At Day 15 (±1 day), every effort will be made to obtain a blood sample for safety assessments. If no longer hospitalised, the patient must visit the study site to have assessments and samples described above. If a patient is not coming to the site for the Follow-up visit, the investigator will call the patient for follow-up purposes.

t 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 must visit the study site to have assessments and samples described above. If a patient is not coming to the site for the Follow-up visit, the investigator will call the patient for follow-up purposes. A medically qualified physician will conduct an examination of patients at Day 29 or at discharge from hospital, whichever occurs first. A telephone contact is planned (if patient is discharged) at Day 29+2 for assessment of AEs, survival, ventilator use (for assessment of ventilator-free days [VFDs]) and presence of secondary infections or other AEs. 28-day survival assessment must take place after a minimum 28 WHOLE days have elapsed since start of study.

u There must be an interval of at least 6 hrs between the screening samples and the samples at Day 1.

v Total volume of fluid given to a patient and the total volume of fluid excreted from the patient will be recorded in accordance with standard procedures (eg, IV in for the 24 hrs prior to randomisation, or fluid in the abdomen in case of peritoneal dialysis, etc). Total parenteral nutrition (TPN), lipids, and blood product volumes will be collected as part of these data. Fluids administered for abdominal irrigation should not be counted.

GE [redacted]

3.2 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 hrs, 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. This dosing regimen was found to significantly improve clinical outcomes for the D-CytoFab-treated group with no adverse safety findings. The choice of an initial loading dose of 250 units/kg followed by 9 maintenance doses of 50 units/kg for the AZD9773 dose for Cohort 1 was based on these results and the data from study D0620C00004 which showed that the TNF suppression levels and PK were comparable for AZD9773 and D-CytoFab.

In a Phase IIa study with AZD9773 that has just been completed (D0620C00004), a higher dose range was also evaluated in order to provide adequate safety coverage over a wide dose range beyond the anticipated therapeutic dose. The dose level of 500 units/kg followed by 100 units/kg once every 12 hrs for 9 doses, and the dose level of 750 units/kg followed by 250 units/kg once every 12 hrs for 9 doses that were administered in this Phase IIa study. Both doses were well tolerated and with an acceptable safety profile. Assessments of the safety, PK and PD of AZD9773 dosed every 12 hrs in this Phase IIa study support continued study in severe sepsis patients of the dose regimens assessed in this trial.

For Cohort 2 of the present study, the initial loading dose of 500 units/kg followed by 9 maintenance doses of 100 units/kg was chosen in view of D0620C00004 results and to investigate the safety and tolerability of an increased AZD9773 dose in Japanese patients.

The inclusion of a placebo control arm in this study will help to put into context, within the sepsis setting, the AEs reported in the AZD9773 treatment arm. The placebo will consist of a masked saline solution, as saline and AZD9773 may not be visually similar. The study will be double-blinded to provide an unbiased comparison of the two treatment groups.

All patients will receive current standard of care for severe sepsis and/or septic shock in addition to AZD9773 or placebo. As medical management of patients with severe sepsis and septic shock is highly variable between units, regions and countries, this study will not attempt to mandate a single procedure for possible presentation of intercurrent diseases or medical conditions. However, the Surviving Sepsis Campaign Guidelines are the suggested reference for description of recommended care.

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. IgE is a class of immunoglobulin that plays an important role in allergy and especially associated with Type I hypersensitivity. Tryptase and IgE assessments may be helpful in the assessment of hypersensitivity or infusion reactions, should they occur.

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

This study intends to assess the PK of AZD9773 in Japanese patients with severe sepsis and/or septic shock to understand the AZD9773 PK profile in Japanese patients.

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 with AZD9773. Hence, most organ failure occur during the first 4 to 5 days after onset of sepsis. 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, nearly all patients receiving D-CytoFab had undetectable TNFα during dosing, but within 48 hrs 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 (20-22 hrs in Phase IIa study).

AZD9773 neutralises released TNFα and through this effect can decrease the production of other cytokines. This effect of AZD9773 will be assessed in this study by measuring serum levels of TNFα, IL-6 and IL-8.

4. PATIENT SELECTION CRITERIA

Investigators must keep a record of patients who entered pre-study screening by meeting inclusion/exclusion criteria but were never enrolled, ie, 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 hospital ICUs or equivalent wards in Japan.

4.1 Inclusion criteria

For inclusion in the study treatment period, patients must fulfil all of the following criteria (inclusion criterion 6 describes the time limits placed on these criteria).

1. Provision of signed informed consent (by the patient or his/her legally authorised representative).

2. Male or female Japanese aged ≥20 years.

3. Clinical evidence of infection requiring treatment with parenteral antibiotics as evidenced by **1** of the following (see also inclusion criterion 6):

   – Perforated viscus,

   – White blood cells (WBC) and/or pathogens in a normally sterile body fluid,

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

[redacted]

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

- Radiographic evidence of pneumonia in association with the production of purulent sputum, or a constellation of findings that suggest pneumonia over other causes of X-ray abnormalities if the patient is not producing sputum.
- 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.

4. Patients must meet at least **2** of the following 4 SIRS criteria, at least **1** of which must be the core temperature criterion or the WBC criterion (see also inclusion criterion 6); these criteria do not have to be met simultaneously; the actual values and the date and time criteria were met will be collected:

   - Core temperature of ≥38°C or ≤36°C measured via tympanic, oral, rectal (preferred), or thermistor method,
   - Heart rate of >90 beats per minute,
   - Respiratory rate (RR) of >20 breaths/minute related to septic event or partial pressure of arterial carbon dioxide ($PaCO_2$) <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, **2** other vital sign criteria must be met, one of which must be the core temperature criterion.

5. Patients must meet criteria for cardiovascular and/or respiratory dysfunction (see also inclusion criterion 6). Newly developed organ dysfunctions must be in the context of the acute septic process not explained by a chronic condition or by effects of concomitant therapy. Time of first organ failure will be recorded (see in Figure 2 for timing of severe sepsis inclusion criteria). Organ dysfunction definitions are provided in Table 2.

Table 2 Organ dysfunction definitions

System / organ	Definition
Cardiovascular System	Hypotension, as defined by a systolic blood pressure <90 mmHg, or a mean arterial blood pressure ≤65 mmHg, for at least 1 hr in the face of adequate filling pressures when measured or unresponsive to saline infusion (20 mL/kg), or requiring pressor support to maintain a blood pressure greater than above limits. If less than 20 mL/kg of fluid has been given before initiating pressors, documentation of filling pressures is required.
Pulmonary Dysfunction	Pulmonary dysfunction is defined as the patient requiring mechanical ventilation related to the septic process and having a PaO_2/FiO_2 ≤300. However, if lung is the primary site of infection then PaO_2/FiO_2 must be <200. Acute Respiratory Distress Syndrome will be noted on the electronic case report form (eCRF) if the patient's condition fulfils the following criteria: PaO_2/FiO_2 ≤200 with acute bilateral diffuse infiltrates on chest X-ray compatible with pulmonary oedema (infiltrates may be patchy, diffuse, homogenous or asymmetric, but must not be explained by lung masses, segmental or lobar atelectasis or pleural effusion) and pulmonary artery wedge pressure ≤18 mmHg (if measured).

Abbreviations: FiO_2: fraction of inspired oxygen; PaO_2: partial pressure of arterial oxygen; eCRF: electronic case report form.

6. Sepsis (infection + SIRS criteria) must be present prior to cardiovascular and/or respiratory dysfunction. SIRS criteria and cardiovascular and/or respiratory dysfunction do not need to be present simultaneously but SIRS criteria must have been demonstrated at some time within the 24 hrs preceding the initial cardiovascular and/or respiratory dysfunction, even if SIRS criteria have been present for more than 24 hrs. 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.

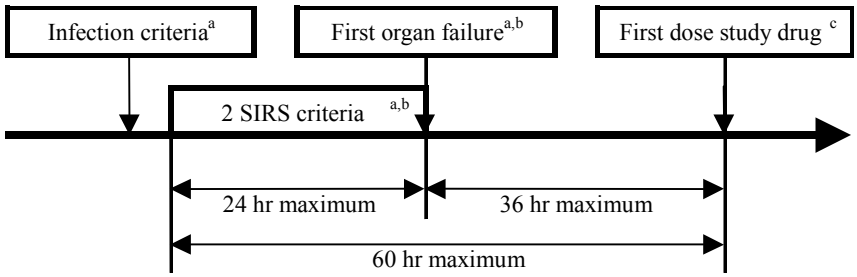
   Study drug administration must occur as soon as feasible but in no case later than 36 hrs after the cardiovascular and/or respiratory dysfunction resulting in severe sepsis. The timing of development of severe sepsis inclusion criteria is presented in Figure 2.

7. Before receiving the first dose of study drug, the patient must have received at least one dose of parenteral antibiotics.

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

[redacted]

Figure 2 Timing of severe sepsis inclusion criteria



a Sepsis (infection + systemic inflammatory response syndrome [SIRS] criteria) must be present prior to first qualifying organ failure.
b SIRS criteria do not have to be met simultaneously but at least 2 SIRS criteria must have been met within the 24 hrs preceding the initial organ failure.
c Study drug administration must occur as soon as feasible but in no case later than 36 hrs after organ failure resulting in severe sepsis.

4.2 Exclusion criteria

Any of the following is regarded as a criterion for exclusion from the study:

1. Clinical judgment by the investigator that the patient should not participate in the study.

2. Human immunodeficiency virus infection in association with a last known cluster of differentiation (CD) 4 count of $\leq 50/mm^3$, or opportunistic infection.

3. Moribund, and death is considered imminent (within 24 hrs of recognition of sepsis).

4. Patient not expected to survive 90 days because of underlying medical condition such as poorly controlled neoplasm.

5. Patient cannot attain a mean arterial pressure >60 mmHg when measured via an arterial line and/or a systolic blood pressure (BP) >80 mmHg in the presence of vasopressors and IV fluids within a period ≥2 hrs.

6. Classified as "Do Not Resuscitate", or "Do Not Treat", or the patient's family is not committed to aggressive management of the patient's condition. A "no cardiopulmonary resuscitation (CPR)" order is acceptable if the patient and/or the family are still committed to aggressive care short of CPR.

7. Any organ or bone marrow transplant within the 24 weeks prior to provision of written informed consent for the study.

8. Receiving immunosuppressants (for example, methotrexate, cyclosporine, tacrolimus), high dose steroids (eg, >40 mg or 0.5 mg/kg prednisone or a steroid with equivalent activity, daily for >7 days) within 8 weeks before study

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

[redacted]

participation (see Appendix I, contact CCC for advice, if necessary). Administration that intends topical action is acceptable.

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 (including non-cytotoxic) treatment for any type of malignancy (hormonal manipulation therapies for breast and prostate malignancies are permitted). Patients who received radiation or chemotherapy within 3 weeks before study treatment should be excluded.

11. Severe chronic liver disease associated with portal hypertension, cirrhosis, chronic ascites or Child-Pugh class C.

12. Second or 3rd degree burns involving more than 30% of body surface within 5 days before provision of written informed consent for the study.

13. Proven myocardial infarction within the last 6 weeks before provision of written informed consent for the study.

14. Documented history of moderate to severe chronic heart failure as defined by New York Heart Association (III and IV) or an ejection fraction <30%.

15. 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 must be withdrawn from study.

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

17. Previously administered antivenom manufactured using ovine serum, digoxin immune fab (DigiFab™, DIGIBIND®) crotalidae polyvalent immune fab (ovine) (CroFab™) (not registered in Japan), or other sheep-derived product.

18. Treatment with anti-TNF antibodies (eg, infliximab [REMICADE®], adalimumab [Humira®], etanercept [Enbrel®]) within 8 weeks before provision of written informed consent for the study.

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

19. Enrolment in another experimental protocol involving study drug administration or involving a medical device within 60 days before provision of written informed consent for the study. Involvement in a non-interventional protocol will not be an exclusion criterion for entering this protocol.

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

21. Active tuberculosis (documented, or strong clinical suspicion) or history of diagnosis thereof.

22. Severe chronic respiratory disease (ie, present before the onset of the current episode of severe sepsis and/or septic shock). Severe disease as defined by any one or more of the following:

    – 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 <88% on FiO_2 =0.21) within 6 months before provision of written informed consent for the study, OR

    – Chronic restrictive, obstructive, neuromuscular, chest wall or pulmonary vascular disease resulting in severe exercise restriction, eg, unable to climb stairs or perform household duties, secondary polycythemia, severe pulmonary hypertension (mean pulmonary artery pressure >40 mmHg), OR

    – Use of home oxygen prior to hospital admission. Sleep apnoea treated with continuous positive airway pressure or bilevel positive airway pressure during sleep is acceptable. Ambulatory oxygen is not allowed.

23. Neuromuscular disease that impairs the patient's ability to ventilate spontaneously (eg, C5 or higher spinal cord injury), cerebral vascular event (stroke), amyotrophic lateral sclerosis, Guillian-Barré syndrome and myasthenia gravis.

24. Granulocytopenia as evidenced by absolute neutrophil count <500/µL.

25. Patients with complete quadriplegia (traumatic or otherwise). All other patients not ambulatory prior to onset of sepsis will need to be reviewed and approved by the CCC prior to enrolment.

26. Patient required CPR prior to study drug administration within the past 30 days.

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

28. Previous enrolment or randomisation to treatment in the present study.

Procedures for withdrawal of incorrectly enrolled patients see Section 5.3.

5. STUDY CONDUCT

5.1 Restrictions during the study

The following are prohibited during the study treatment period:

- Immunosuppressant drugs (eg, methotrexate, cyclosporine, tacrolimus) (see Appendix I),
- High dose steroids (eg, >40 mg or 0.5 mg/kg prednisone or a steroid with equivalent activity for ≥2 days). Adrenal replacement therapy as discussed in the Surviving Sepsis Campaign International Guideline 2008 will be an allowed exception to this restriction. Steroids given for another therapeutic purpose in doses >40 mg prednisone or equivalent will not be permitted (also refer to Section 5.6),
- Polymixin B haemoperfusion (Toraymyxin™),
- Plasma exchange,
- Anti-TNF antibodies (eg, infliximab, adalimumab, etanercept) other than study drug,
- Administration of study drug outside of ICU or an adequately monitored setting during the study treatment period.

If any of the above criteria are fulfilled, the patient must be withdrawn from study treatment in accordance with Section 5.8.

If the median QT with Fridericia correction (QTcF) ≥530 msec (and unrelated to the presence of a pacemaker) on the initial pre-dose ECG, the investigator will need to call the CCC and/or AstraZeneca Study Team Physician before the patient is dosed with study drug to determine whether the patient is suitable for inclusion in the study, and whether any other medications or factors are contributing to the QTcF prolongation that can be discontinued or reversed, if warranted. If the median QTcF drops below 530 msec, and the patient meets other enrolment requirements (including timelines), the patient may be dosed with study drug. If the median QTcF is ≥530 msec, the investigator has the option of obtaining a cardiology consult in order to confirm the ECG machine generated QTcF value (eg, to assure that a QU interval is not being reported).

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

If, after the first dose or a subsequent dose of study drug, the median QTcF is ≥575 msec, dosing of study drug will be suspended. A cardiology consult at the site will be obtained with attention directed to contributing factors for the QT prolongation. If after such consultation, the cardiologist, investigator and the CCC and/or AstraZeneca Global Project Physician feel that the QT prolongation is likely due to factors other than study drug, the patient can resume dosing if the following QT duration condition is met. In order to resume study drug dosing after observing a median QTcF interval ≥575 msec, the median QTcF interval must have decreased to <550 msec (within 24 hrs of the last dose of study drug). If the median QTcF remains ≥550 msec for >24 hrs, the patient will permanently discontinue study drug administration but the patient will undergo study assessments and follow-up, as outlined in Table 1.

Study treatment and sampling do not need to be changed for patients undergoing dialysis and continuous haemodiafiltration.

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. 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. 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.

5.2 Patient enrolment and randomisation

Patient eligibility will be confirmed by the CCC following a telephone interview with the study site. If the patient meets the criteria for participation in the study, the CCC will provide the study site with an enrolment authorisation code. The study site pharmacist will call the Interactive Voice Response System (IVRS) and enter the enrolment authorisation code into the IVRS that will, in turn, issue a randomisation number and allocated treatment for that patient based upon a predetermined randomisation schedule.

The study 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 4.1 and 4.2).

4. Assign the CCC-approved patient a unique enrolment number, beginning with “E#” (E-code, see Section 5.2.1).

5. Be provided with an 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 site pharmacists will be provided with patient demographic data (including E-code, date of birth, weight, height, enrolment authorisation code) by the investigator and enter the IVRS to receive the randomisation number and allocated treatment for each patient.

Randomisation codes will be assigned strictly sequentially as patients become eligible for randomisation.

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

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

5.2.1 Procedures for randomisation

Patients will be assigned a unique identifying number (E-code). The patient E-code will be assigned on enrolment (ie, provision of written informed consent) in chronological order of screening 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 site identifier and yyy is a 3-digit patient identifier.

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 within each cohort (AZD9773: 7 patients, placebo: 3 patients) and avoid selection bias. To allow the evaluation of data by the SRC and IDMC, a minimum of 4:1 AZD9773: placebo cohort-completers receiving at least 6 doses and alive for at least 7 days after his/her last dose, for each cohort, will be required. If the number of cohort-completers does not reach the above criteria after the originally planned 10 patients have been enrolled in a cohort, additional patients will be enrolled until at least 4 patients in the AZD9773 group and at least 1 patient in the placebo have completed the cohort. These additional replacement patients will be assigned a forced randomisation number by the IVRS system which corresponds to the same treatment as the patient they are replacing. Double-blind procedures will be maintained.

Prior to enrolment, all pre-qualified patients will be evaluated by the CCC to assure study entrance criteria are met. Following notification that informed consent has been obtained for CCC-approved qualified patients, the CCC will provide an authorisation number to the site. Pharmacists will use this authorisation number when calling into the IVRS to receive the randomisation number and associated study treatment for each patient.

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

[redacted]

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 sites. Randomisation will not be stratified. The randomisation scheme will randomly assign the study drug to the randomisation numbers.

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.

If a patient discontinues from the study, the patient number will not be reused, and the patient will not be allowed to re-enter the study.

Sections 5.4.1 and 5.4.2 describes procedures for blinding and breaking the blind.

5.3 Procedures for handling patients incorrectly included

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 the patient must discontinue study treatment. However, any such patient must be followed up according to the study plan. Decisions must be appropriately documented by the Medical Monitor.

5.4 Blinding and procedures for unblinding the study

5.4.1 Methods for ensuring blinding

The study will be performed in a double-blind manner. The patient, the investigator and study site staff will be blinded to study drug allocation. The study site pharmacist or delegate 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 drugs 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. Batch numbers of AZD9773 dispensed will be recorded by the pharmacist and monitored by an unblinded monitor. The unblinded monitor will be a specific PAREXEL clinical research associate only doing this type of monitoring and not involved in any other aspect of the study. Other study site 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 5.4.2.

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

[redacted]

5.4.2 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, and the personnel who are independent to the study evaluation at the Patient Safety Department, AstraZeneca from the IVRS. The process for unblinding will be described in the IVRS user manual that will be provided to each site.

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. If the treatment code is broken then the investigator(s) must document and report to AstraZeneca, without revealing the treatment given to the patient to the AstraZeneca and PAREXEL staff.

AstraZeneca retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to an investigational product (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, the time and reason must be recorded via 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 5.8.1.

Since this study is not hypothesis-testing, the blind may be broken for business and project decision-making prior to clean database. However, treatment codes will not be broken for a cohort until all decisions on the evaluability of the data from each patient in that cohort have been made and documented.

5.5 Treatments

5.5.1 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. 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.

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

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)	Manufactured by Baxter BioPharma Solutions (Indiana US) and supplied to AstraZeneca KK via AstraZeneca Newark US.	F13605
Active Component	AZD9773 (rh TNFα immune Fab [ovine][redacted]		
Excipients	Di-sodium hydrogen phosphate, USP, Ph Eur Sodium chloride, USP, Ph Eur		
Placebo	Units 0.9% sodium chloride		Not applicable

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

Prior to use, AZD9773 must be reconstituted with saline. For IV infusion, the reconstituted solution will be diluted in 100 mL of saline solution for all doses less than 500 units/kg. For doses of 500 units/kg, the reconstituted solution will be diluted in 250 mL of saline solution. The administration bags of AZD9773 will be masked to maintain the blind.

Placebo

Placebo will be saline solution (0.9% sodium chloride) administered as an IV infusion in an equivalent volume to the active treatment. The administration bags of placebo will be masked to maintain the blind. The pharmacy at each study site will supply saline for the study.

The placebo will consist of a masked saline solution, as saline and AZD9773 are not visually similar.

5.5.2 Doses and treatment regimens

During the treatment period, patients in Cohort 1 will receive an initial loading dose of AZD9773 250 units/kg followed by 9 maintenance doses of 50 units/kg or placebo, and in Cohort 2 will receive an initial loading dose of AZD9773 500 units/kg followed by 9 maintenance doses of 100 units/kg or placebo. The first dose of study drug should be administered as soon as feasible but in no case later than 36 hrs after confirmation of the onset of qualifying organ failure resulting in severe sepsis and/or septic shock (see Section 4.1 for

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

[redacted]

further details on inclusion criteria). Study drug will be administered by IV infusion over 30 minutes.

Each infusion in all treatment arms will be administered over a 30-minute period. 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 electronic case report from (eCRF) together with the date and time of administration (using 24:00-hr clock).

Vasopressor use will be collected during the study.

Additionally, if during the loading dose vasopressors are required, the following should be recorded from 2 hrs 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.

The body weight measured at screening, within 12 hrs prior to 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 hrs apart. The dosing interval adjustment must be such that the first maintenance dose is given a minimum of 6 hrs and a maximum of 15 hrs after the loading dose.

Time windows for dosing of ±2 hrs 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, X-ray suite, etc. If a dose is late by 2 to 5 hrs, the Medical Monitor should be contacted and 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 hrs, 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.

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

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 Medical Monitor 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.

5.5.3 Labelling

Regulatory information as applicable to Japan will be displayed on the label according to local requirements.

Drug vial packaging will be labelled in accordance with Good Manufacturing Practice (GMP) and Good Clinical Practice (GCP). Labels will contain at least the following as applicable according to local regulations: protocol number, storage conditions, batch identification number, instructions for dosing and "for clinical use only"; 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.

5.5.4 Storage

All study drugs must be kept in a secure place under appropriate storage conditions. The IP label on the vial and the IB specifies the appropriate storage and shipment. A description of the appropriate storage conditions is specified in the document 'Procedure of storage conditions for investigational product'.

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

5.6.1 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

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

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 8 weeks before study participation (see Appendix I, contact CCC for advice).

- High dose steroids (eg, >40 mg or 0.5 mg/kg prednisone or a steroid with equivalent activity, daily for >7 days) within 8 weeks before provision of written informed consent for the study (see Appendix I, contact CCC for advice). Administration that intends topical action is acceptable.

- 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 (DigiFab™, DIGIBIND®) crotalidae polyvalent immune fab (ovine) (CroFab™)(not registered in Japan), or other sheep-derived product at any time.

- Anti-TNF antibodies (eg, infliximab [REMICADE®], adalimumab [Humira®], etanercept [Enbrel®]) within 8 weeks before provision of written informed consent for the study.

5.6.2 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).

- High dose corticosteroids given as anti inflammatory or immunosuppressive therapy (eg, >40 mg or 0.5 mg/kg prednisone or a steroid with equivalent activity for ≥2 days). Adrenal replacement therapy as discussed in the Surviving Sepsis Campaign will be an allowed exception to this restriction.

NOTE: Adrenal replacement therapy (corticosteroids) is permitted in patients with septic shock at the discretion of the investigator balancing the potential benefits and risks in this situation. The optimal treatment regimen in this setting is not resolved. Investigators are referred to current Surviving Sepsis Campaign guidelines (www.survivingsepsis.com) as a reasonable source of guidance for steroid replacement therapy in septic shock patients.

- Polymixin B haemoperfusion (Toraymyxin™),

- Plasma exchange,

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

[redacted]

- Anti-TNF antibodies (eg, infliximab [REMICADE®], adalimumab [Humira®], etanercept [Enbrel®]) other than study drug.

Patients requiring immunosuppressant drugs, high-dose steroids and/or anti-TNF antibodies during the treatment period (Days 1 to 6) will be discontinued from study treatment (see Section 5.8.1). 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 2 weeks prior to the loading dose until Day 29.

For antibiotics the following will be recorded: name of drug, start date and time, dose, route of administration, stop date and time, from 2 weeks prior to the loading dose until Day 29.

Vasopressor use will be collected during the study.

Additionally, if during the loading dose vasopressors are required, the following should be recorded from 2 hrs 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.

For all other concomitant medications, the following will be recorded: name of drug, start date, route of administration, and stop date from 2 weeks 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 hrs prior to the ECG will be recorded in the electronic case report form (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.

Medical management of infusion reactions is detailed in Appendix D.

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

5.6.3 Post-study medications

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

5.7 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.

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

5.7.1 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, destroyed and returned.

It is the study site'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,
- Reconstituted study drug and empty containers are destroyed at the site or through a destruction vendor after appropriate monitoring,
- Unused study drug that has never been reconstituted will be returned to AstraZeneca KK at the end of the study,
- 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 not be distributed to the study site until the contract is concluded between the study site, PAREXEL and AstraZeneca. The IP Storage Manager is responsible for managing the study drug from receipt by the institution until the return of all unused and non-reconstituted study drug to AstraZeneca. PAREXEL will deliver the study documents 'Procedures for drug accountability' and 'Procedures for drug storage' which describes the specific requirements. The investigator(s) is (are) responsible for ensuring that all of a patient's unused study drug is returned, as appropriate (see above).

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.

5.8 Discontinuation of investigational product

5.8.1 Criteria for discontinuation of a patient from investigational product

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

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

- Positive pregnancy test (except 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 (see Appendix D),
- Study drug is not tolerated,
- AE (eg, risk to patients as judged by the investigator and/or SRC, IDMC, CCC, PAREXEL or AstraZeneca),
- Voluntary discontinuation by the patient who is at any time free to discontinue receiving study treatment, without prejudice to further treatment (incapacitated patients may be withdrawn from study treatment by their legally authorised representative),
- Severe non-compliance to protocol as judged by the investigator and/or CCC, PAREXEL or AstraZeneca,
- Withdrawal from the ICU or an adequately monitored setting during the study treatment period,
- Treatment is unblinded by the site investigator or designee,
- Need for immunosuppressant drugs, high dose steroids 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 5.6.2 on concomitant medications),
- See Section 5.1 for QTcF restrictions,
- Incorrect inclusion in the study, ie, the patient does not meet the required inclusion/exclusion criteria for the study; if a patient is already in the study, study treatment must be discontinued and patient should be followed-up (see Section 5.3 for the procedures for handling incorrectly enrolled patients),

Patients who die should not be considered as discontinuing. See Section 6.5.2 and 6.5.3 for more details about the procedures to follow in case of death of patients.

5.8.2 Procedures for discontinuation of a patient from investigational product

Patients who discontinue study drug should remain in the study and continue to have all scheduled assessments as shown in Table 1 (eg, an assessment of all-cause mortality is required at Day 29, and a blood sample is required at Day 29 [-6/+14]) unless consent is withdrawn for participation in the study. See also Section 5.9.2.

If a patient is withdrawn from the study, see Section 5.9 for the procedures to be followed.

Patients who discontinue from the study drug will be given appropriate treatment in accordance with institutional protocol and best practice. Every effort will be made to collect safety data and PK samples (see section 6.6.1) from patients who discontinue study drug. If a patient is randomised but not treated, at least the screening visit page and termination page of the eCRF should be completed (with reason for which study drug was never started).

Discontinuation of patients from study drug will be recorded in the IVRS.

5.9 Withdrawal from study

5.9.1 Criteria for discontinuation from the study

Patients may be discontinued from the study at any time. See Section 5.9.2 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.

Patients who die before Day 29 will be classified as completing the study.

5.9.2 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. The Principal Investigator/sub-investigator will perform the best possible observation(s), test(s) and evaluation(s) as well as give appropriate medication and all possible measures for the safety of the patient. They will also immediately inform PAREXEL and/or AstraZeneca of the withdrawal. AEs will be followed up (See Sections 6.5.3 and 6.5.4). The reason for discontinuation from study drug or from the study must be recorded in the eCRF.

Patients who discontinue study treatment and from the study will be given appropriate treatment in accordance with institutional protocol and best practice. Every effort will be made to collect safety data (such as AE follow-up), and PK samples if discontinuation occurs

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

during the treatment period (see Section 6.6.1), from patients who discontinue the study (see Table 1).

Discontinuation of patients will be recorded in the IVRS.

6. COLLECTION OF STUDY VARIABLES

6.1 Recording of data

The investigator will ensure that all data collected in the study are provided to PAREXEL. 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.

The Principal Investigator/sub-investigator will record data on the observations, tests and assessments specified in the protocol on the eCRFs provided by PAREXEL. The eCRF will be accompanied with 'Instructions for the Investigator', which should be followed. These instructions provide guidance for the recording of study data in the CRF including how to change data incorrectly recorded. He/she ensures the accuracy, completeness, legibility, and timeliness of the data reported to PAREXEL 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 PAREXEL representative, the data will be frozen to prevent further editing. The Principal 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.

6.2 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-hr clock.

- Provision of written informed consent by the patient or his/her legally authorised representative. This must be obtained at screening for all patients.
- 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 5.6.1) and concomitant medications.

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

- Physical examination, plus measurement of height and weight (within 12 hrs prior to the first dose), lung auscultation and a dermal examination (the baseline physical examination at screening must be done within 4 hrs before study drug administration) (see Section 6.5.6).
- 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 hrs prior to start of first infusion (within 6 hrs for lactate) (see Section 6.5.5),
  - Cytokines,
  - Immunoglobulin E (IgE)
  - Blood culture.
- Urine sample (see Section 6.5.5):
  - Urinalysis.
- Daily volume status (see Section 6.4.10)
- Vital signs (see Section 6.5.8),
- Oximetry (see Section 6.5.8),
- 12-lead ECG (see Section 6.5.7),
- APACHE II score and SOFA score (see Sections 6.4.1 and 6.4.3)
- AEs from time 0 (start of first dose of study drug), and SAEs from signature of informed consent.
- Assessment of organ failure (see Section 6.4.5)
- Infection assessment (see Section 6.4.8). 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 in hand prior to randomisation.

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

6.2.1 Follow-up procedures

The follow-up data will be collected for all assessments as shown in Table 1 (eg, an assessment of all-cause mortality is required at Day 29, and a blood sample is required at Day 29 [-6/+14]) and recorded in the appropriate sections of the eCRF. Whether a patient is alive or not at Day 29 should be recorded in the eCRF (see Table 1). Additionally, the question will be asked "Was aggressive medical care withdrawn?"

If no longer hospitalised, the patient must visit the study site to have assessments and samples described in Table 1 performed. If a patient is not coming to the site for the Follow-up visit, the investigator will call the patient for follow-up purposes.

6.3 Efficacy – not applicable

6.4 General assessment of sepsis care

Objective	Variables
Exploratory: To obtain a preliminary information on clinical outcomes in Japanese patients with severe sepsis and/or septic shock	- VFDs - SOFA score - Organ failure assessment· - Lactate - Infection assessment

6.4.1 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 hrs 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.

6.4.2 Glasgow Coma Score

The assessments needed to calculate the Glasgow Coma Score will be performed as part of the APACHE II and SOFA score assessments 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 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. For Glasgow Coma Score, the best value will be recorded in the eCRF.

6.4.3 Sequential Organ Failure Assessment (SOFA) Scores

SOFA Scores 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 SpO_2/FiO_2 (mmHg), platelet count (x $10^3/mm^3$), bilirubin (mg/dL), vasopressor use (µg/kg/min, mmHg), and creatinine (mg/dL [or urine output]). For laboratory values, use last available (if within 48 hrs). On days when laboratory results are unavailable, values will be extrapolated from the previous available values. Glasgow Coma Score will be performed as described in Section 6.4.2 and recorded in the eCRF.

SOFA scores will be assessed as described in Appendix G.

6.4.4 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).

For patients on mechanical ventilation, the following ventilator settings will be recorded daily at the timepoints specified in Table 1: tidal volume, peak airway pressure over the last 24 hrs, plateau pressure, positive end expiratory pressure, RR and any ventilator weaning which has been attempted.

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.

If no arterial blood gas values are available, oxygen saturation by pulse oximetry (SpO_2) will be recorded.

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

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

Ventilator-free days

The number of VFDs will be calculated using the ventilator assistance VFD page of the eCRF. This is a composite endpoint including days free of mechanical ventilation and mortality.

6.4.5 Organ failure assessment

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

6.4.6 Lactate

Blood samples for analysis of serum lactate will be collected according to local standard procedures at the timepoints scheduled in Table 1 by the investigator or medically qualified personnel. However, there must be an interval of at least 6 hrs between the screening samples and the samples at Day 1. Stasis of blood must be avoided.

Blood samples for lactate assessments will be analysed locally. Each laboratory will be required to provide up-to-date reference ranges. See Table 6 for the total estimated volume of blood samples to be collected.

6.4.7 Septic shock

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

6.4.8 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. This should include primary bacteraemia if blood culture is positive but no local infection identified. All patients must have a blood culture prior to randomisation. The blood culture result does NOT have to be in hand 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.

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

5. Home wound care.

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

6.4.9 Antibiotic use

The use of antibiotics will be recorded as part of concomitant medication monitoring as described in Section 5.6.2.

The time to first administration of antibiotics for a sepsis infection is defined as the time from the 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.

6.4.10 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.

6.4.11 Daily volume status

Daily volume status will be recorded at screening using standard procedure (see Section 11.1.7 for more details).

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

6.5 Safety

It is of the utmost importance that all staff involved in the study are familiar with the content of this section. The Principal Investigator is responsible for ensuring this.

Objective	Variables
Primary: To assess the safety and tolerability of AZD9773 in Japanese patients with severe sepsis and/or septic shock.	- Incidence and nature of AEs - Incidence and nature of SAEs, AEs leading to discontinuation of study drug, and deaths - 12-lead ECG - Vital signs (blood pressure, pulse, body temperature, respiratory rate) - Oximetry - Laboratory variables (haematology, clinical chemistry, coagulation, urinalysis) - Physical examination - Other safety monitoring (troponin I, HASA IgG, HASA bridging assay, and nAb)

See Sections 6.5.1 to 6.5.8.

Objective	Variables
Exploratory: To obtain preliminary information on clinical outcomes in Japanese patients with severe sepsis and/or septic shock	- 28-day mortality

See Section 6.5.9.

6.5.1 Definition of adverse events

An AE 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.

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

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

For cases where it could be suspected that a tissue-derived medicine has been contaminated by a pathogen, information about any of the above conditions (including infection) should be collected.

6.5.2 Definitions of serious adverse event

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

- Results in death. All deaths from provision of informed consent to Day 29 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 (although a death narrative will be required).
  - Deaths between provision of informed consent and Day 29, if NOT considered unequivocally due to sepsis by the investigator, **must** be reported as a SAE on the relevant SAE forms in addition to reporting the death on the statement of death page.
- 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 a SAE and is reported in an expedited manner as any other SAEs. 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”.

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

6.5.3 Recording of adverse events

Time period for collection of adverse events

Non-serious AEs are collected from time 0 (start of first dose of study drug), and SAEs from the provision of written informed consent. Both AEs and SAEs are collected throughout the study until Day 29 (see Section 6.5.4). From Day 30 onwards, any new onset AEs/SAEs 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 caregiver.

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 himself or herself, his/her caregiver 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?"

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 the PAREXEL clinical research associate and/or AstraZeneca 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 29 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.

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. Additional variables will be collected for SAEs (see Section 6.5.4).

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

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

Severity of adverse events

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

- mild (awareness of sign or symptom, but easily tolerated; as judged by the investigator),
- moderate (discomfort sufficient to cause interference with normal activities; as judged by the investigator),
- severe (incapacitating, with inability to perform normal activities; as judged by the investigator).

Further details on classifying the severity of infusion 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 6.5.2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hrs may be considered severe nausea, but not a SAE. On the other hand, a stroke 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 each AE, 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

[redacted]

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 laboratory/vital signs/ECG parameters not listed in Sections 6.5.5, 6.5.7 and 6.5.8 should be reported as AEs. Clinically relevant deterioration in unscheduled assessments of laboratory/vital signs/ECG parameters listed in the sections above should be reported on additional eCRF pages. Any new physical examination findings, or deteriorations from baseline should be reported as AEs.

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

Overdose

Please refer to Section 13.2.

Pregnancy

Please refer to Section 13.3.

Deaths

All deaths occurring from provision of informed consent until Day 29 must be reported on the statement of death page. All deaths that occur during the study and that qualify for a reporting as an SAE owing to Section 6.5.2 must be reported as described in Section 6.5.4.

Other significant adverse events

Other significant AEs (OAEs) of particular clinical importance, other than SAEs and those AEs leading to discontinuation of the patient from study treatment, are AEs of special interest. OAEs will be identified by the Sponsor's Study Physician in consultation with the appropriate Global Patient Safety Physician during the evaluation of safety data for the Clinical Study Report. For each OAE, a narrative may be written and included in the Clinical Study Report.

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

[redacted]

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

Hypersensitivity and infusion reactions

Full details on classifying hypersensitivity and infusion reactions are provided in Appendix D. In the event a patient experiences such a 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.

6.5.4 Reporting of serious adverse events

All SAEs have to be reported, whether or not considered causally related to the IP, or to the study procedure(s). All SAEs will be recorded in the eCRF.

Investigators and other site personnel should inform (emergency report) appropriate AstraZeneca representatives of any SAE that occurs at his or her site in the course of the study within 1 day (in this section, within 1 day is defined as 'immediately but no later than the end of the next business day') of when he or she becomes aware of it (initial SAE report). This should apply whether or not the SAE is considered causally related to the study treatment or to the study procedure(s). The Principal Investigator should provide detailed information to AstraZeneca in writing within 4 calendar days of the initial report. The Principal Investigator should notify the SAEs in writing to the head of the study site immediately.

Follow-up information on SAEs should also be reported to AstraZeneca by the investigator(s) within the same timeframes. If a non-serious AE becomes serious, this and other relevant follow-up information should also be provided to AstraZeneca within 1 day as described above.

The following information is required in the initial SAE report to AstraZeneca from the investigator(s): study code, site number, E-code, AE, seriousness, start date.

The following detailed information should be sent to AstraZeneca as soon as it becomes available: severity, outcome (including stop date, if available), causality (IP and if applicable any other concomitant drug), date when a non-serious AE became serious, withdrawal of study treatment, treatment of AE, concurrent therapy (except for treatment of AE), concurrent medication (including pre-study drug if the causality of the AE cannot be assessed), date of birth, sex, other current illnesses, relevant medical history and if applicable, date and course of death.

In addition, AstraZeneca will provide details of any serious adverse drug reactions reported with regard to the test product and the control drug if not unblinded in this study, to the Head of the study site, Principal Investigator and the regulatory agency. The Head of the study site should submit a written report to the Institutional Review Board (IRB) providing the details of all AE case(s) reported by AstraZeneca.

Reporting Procedure of Serious Adverse Events will be using a WBDC system.

The investigator(s) and other site personnel will access the WBDC system and report SAE information by entering it into the relevant eCRF module. Upon entry of the SAE information, an automated email alert will be sent to the designated AstraZeneca representative. If the system is unavailable, the investigator(s) should take other appropriate measures to provide a SAE report to the AstraZeneca representative immediately, recognising that the same reporting time frames still apply. The investigator(s) is responsible for completing the eCRF as soon as the system becomes available again.

If initial or the subsequent reports are made by means other than WBDC, necessary information on any SAEs should finally be entered into the eCRF via WBDC system by the investigator(s).

If the WBDC system is down the investigator can submit a paper SAE report to PAREXEL clinical research associate or AstraZeneca representative.

6.5.5 Laboratory safety 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 7.1.

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

Table 4 Laboratory safety parameters

Haematology[a]	Clinical chemistry[a]	Coagulation[a]	Safety monitoring	Urinalysis[a]
Haemoglobin	ALT	PT	Troponin I	Protein
Haematocrit	AST	Activated partial thromboplastin time	HASA IgG	Blood
WBC with differential	GGT	D-dimer	HASA bridging assay	Ketones
Platelets	Alkaline phosphatase	Fibrinogen	nAb	Microscopic analysis
	Serum albumin	INR	Protein C activity	pH
	Creatinine		IgE	Clarity
	Blood urea nitrogen			Colour
	Total protein			Specific gravity
	Total bilirubin			Glucose
	Creatine kinase			
	LDH			
	Lactate			
	Calcium[b]			
	Sodium			
	Potassium			
	Chloride			
	Glucose			

[a] To be performed at local laboratory.
[b] Calcium (total).
Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; GGT = gamma glutamyl transferase; HASA = human anti-sheep antibody; Ig = immunoglobulin; INR = international normalised ratio; LDH = lactate-dehydrogenase; nAb= neutralising antibody; 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.

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

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 protein 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 the following parameters will be done [redacted] troponin I, IgE and protein C activity.

Tryptase samples (if obtained for infusion or hypersensitivity reactions) will be analysed by [redacted] Blood samples will be sent to [redacted]

Collection of human anti-sheep antibody (HASA) IgG and 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. 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.

Bioanalytical evaluation of the analyte concentrations will be done by [redacted] Blood samples will be sent to [redacted] Samples will be labelled, stored and shipped according to AstraZeneca Standard Operating Procedures.

Collection of nAb

Blood samples for analysis using the 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 [redacted] In addition, samples may be used for the improvement or development of further analytical assay. Details on

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

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 [redacted]. Samples will be labelled, stored and shipped according to AstraZeneca Standard Operating Procedures.

6.5.6 Physical examination

Physical examinations will be performed at screening and Days 1, 2, 3, 4, 5/6, 29 (or the discharge visit) (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 and weight will be recorded at screening. Screening weight should be measured within 12 hrs prior to the first dose.

Any new findings or deteriorations from baseline should be reported as AEs.

6.5.7 Electrocardiogram

A digital 12-lead ECG will be recorded at the timepoints specified in Table 1 using equipment provided by the central ECG laboratory eResearch Technology, Inc (eRT). All ECGs will be obtained in triplicate within 1 to 2 minutes. 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.

ECG should be recorded before infusion and at the end of infusion (at the same time post dosing as the PK blood draw for the loading dose). ECGs should be obtained pre-dose and end of infusion for the first dose on Days 3 and 5. ECGs should be obtained pre-dose and end of infusion for the last maintenance dose. Please ensure that these times coincide with PK blood draws. ECGs should be obtained on Days 10 and 29.

Each ECG will define heart rate, 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 site if alert criteria are found on any ECG.

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

[redacted]

Specific procedures for use of the ECG recorder and transfer process, as well as detailed alert criteria, will be provided in separate study documentation.

See Section 5.1 for further guidance on ECG procedures.

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.

6.5.8 Vital signs and blood oxygen-haemoglobin saturation

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.

6.5.9 28-day mortality

28-day mortality will be assessed at the timepoints specified in Table 1.

6.6 Pharmacokinetics

Objective	Variables
Primary: To assess the PK of AZD9773 in Japanese patients with severe sepsis and/or septic shock.	- AUC_{0-t} - AUC_{τ} - C_{inf} - $C_{ss\ max(inf)}$ - $C_{ss\ min}$ - Accumulation ratio - CL_R - % of drug recovered in urine

The methods for collection of biological samples and derivation of PK variables are presented below in Sections 6.6.1 and 6.6.2.

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

6.6.1 Collection of samples

Blood samples for measurement of AZD9773 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 must be peripheral venous 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. If it is not possible to obtain a good peripheral venous or arterial sample at the timepoints up to 30 minutes post-dose, then the site should record the sample as unobtainable. At each point, window is -30 to 0 min (pre-dose), ±5 min (≤2 hr after infusion) or ±1 hr (≥4 hr after infusion).

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 dose that has been missed, the PK sample should be taken at the next dose and the dose and sample time and date should be recorded.

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-infusion, end infusion, and then 0.5, 1, 2, 8 & 12 hr after infusion completion but before the next infusion starts. Days 3 and 4: before maintenance dose 5 and 7. Day 5 (or 6): pre-infusion, and end infusion, and 0.5, 1, 2, 8 & 12 hr after the last maintenance dose infusion [b]. **Actual times of sampling must be recorded [c].**

[a] Blood samples taken during and up to 30 minutes after an infusion must be peripheral venous 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. 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.

[b] If study drug is withdrawn prematurely, the site should make every effort to obtain the intensive PK sampling with the last infusion following premature discontinuation (ie, as it would have been scheduled following the last maintenance infusion on Day 5/6).

[c] If a PK sample was scheduled for the missed dose, the PK sample should be taken at the next dose and the dose and 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 [redacted] For

[redacted]

[redacted] transfer to [redacted] samples will be labelled, stored and shipped according to AstraZeneca or [redacted] Standard Operating Procedures.

For estimated blood volume, see Section 7.1.

Urine samples will also be collected for PK purposes.

Total voided urine volume will be collected during the following time interval: first infusion start to 12 hr after infusion and last infusion start to 12 hr after infusion.

Details on sampling and handling procedures will be specified in the study laboratory manual. Urine samples will also be analysed by [redacted]

6.6.2 Determination of drug concentration

Bioanalytical evaluation of the analyte concentrations will be done by [redacted] will perform derivation of PK data.

PK parameters that best describe the PK of AZD9773 are, as a minimum: area under the serum concentration-time curve (AUC) from time zero to time t (AUC_{0-t}), AUC within the dosing interval (AUC_{τ}), serum concentration at the end of infusion (C_{inf}), $C_{ss\ max(inf)}$, $C_{ss\ min}$, and accumulation ratio. Renal clearance (CL_R), will also be calculated.

For urine samples, CL_R and % of drug recovered in urine will be derived.

Incurred sample reproducibility and stability analysis, if any, will be performed alongside the bioanalysis of the test samples and reported in a separate bioanalytical report or as an appendix to the bioanalytical report.

6.7 Pharmacodynamics

Objective	Variables
Secondary: To make a preliminary assessment of the PD of two different doses of AZD9773 in Japanese patients with severe sepsis and/or septic shock.	- TNFα - IL-6 - IL-8

6.7.1 Collection of pharmacodynamic markers

Samples will be collected, labelled, stored and shipped as detailed in the laboratory manual.

For blood volume, see Section 7.1.

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

[redacted]

6.7.2 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 blood samples will be taken as follows:

- At screening, pre-first infusion, Day 1 at 1-2 hrs after the end of infusion, before the morning dose on Days 2, 4, 6 and in the morning on Day 10.
- A screening sample for TNFα, IL-6, IL-8 and IL-10 will be analysed by flow cytometry.
- TNFα, IL-6 and IL-8 samples at pre-dose Day 1 and Days 1, 2, 4, 6 and 10 will be analysed by enzyme-linked immunosorbent assay (ELISA) only. There will be no IL-6 or 8 assessment at Day 10.
- At each point, window is –30 to 0 min (pre-dose) or ±1 hr (after infusion).
- TNFα sample also 1-2 hrs after dose 2, and the morning on Days 7 and 15 (to be analysed by ELISA).

6.8 Pharmacogenetics – not applicable

6.9 Health economics – not applicable

7. BIOLOGICAL SAMPLING PROCEDURES

7.1 Volume of blood

The total volume of blood that will be drawn from each patient in the study will be approximately 243 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.

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

[redacted]

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

Assessment	Sample volume (mL)	Number of samples	Total volume (mL)
Pharmacodynamics:			
IL-6, IL-8 [a]	2 x 3	6	36
IL-10 [a]	3	1	3
TNFα [b]	4	10	40
Lactate	3	3	9
Pharmacokinetics	3	16	48
Clinical chemistry [c, d]	5	6	30
Haematology [d]	3	6	18
Coagulation	3	5	15
Safety monitoring			
nAb	3.5	3	10.5
Troponin I	2.5	3	7.5
Protein C activity	2.5	1	2.5
HASA IgG and HASA bridging assay	7	3	21
IgE	2.5	1	2.5
Total			**243**

a IL-6 and IL-8 samples will be taken at screening, pre-infusion; Day 1 at 1-2 hrs after the end of infusion, and before the morning dose on Days 2, 4 and 6. IL-10 sample will be taken only at screening.
b TNFα samples will be taken at screening, pre-infusion; Day 1 at 1-2 hrs after the end of infusion, and before the morning dose on Days 2, 4, 6 and the morning on Day 10, but also 1-2 hrs after dose 2, and the morning on Days 7 and 15.
c Including pregnancy test for the sample at screening.
d If discharge does not occur on Day 7 or Day 15, an additional sample will be needed for clinical chemistry and for haematology (adding 8 mL to the total volume above).

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

7.1.1 Clinical samples

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. The central and local laboratories will inform AstraZeneca and/or PAREXEL of the stability limits relevant to this study before the first patient gives informed consent to take part in the study.

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

[redacted]

7.1.2 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. Documentation of the time period for which stability has been demonstrated should be available at AstraZeneca before the first patient gives informed consent to take part in the study.

7.2 Handling, storage and destruction of biological samples

The samples will be used up or disposed of after use.

7.2.1 Pharmacokinetic and/or pharmacodynamic samples

Samples will be disposed of after the clinical study report has been finalised.

7.2.2 Pharmacogenetic samples – not applicable

7.3 Labelling and shipment of biohazard samples

The Principal 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.

7.4 Chain of custody of biological samples

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

The Principal Investigator at each site keeps full tractability of collected biological samples from the patients while in storage at the site 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.

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

HASA IgG and HASA bridging assay as well nAb assay samples may be used for the improvement or development of further analytical assays.

7.5 Withdrawal of informed consent for donated biological samples – not applicable

8. ETHICAL AND REGULATORY REQUIREMENTS

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

8.1 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 International Conference on Harmonisation (ICH)/GCP, applicable regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples. The applicable regulatory requirements in Japan are 'Good Clinical Practice for Trials on Drugs (Ministry of Health, Labour and Welfare [MHLW] Ordinance No. 28, 27 March 1997, partially revised by MHLW Ordinance and their related notifications).

8.2 Patient data protection

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. Patient data will be maintaining confidentiality in accordance with national data legislation. For data verification purposes, authorised representatives of AstraZeneca, a regulatory authority, 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 computer processed by PAREXEL and/or AstraZeneca will be identified by study code and enrolment code (E-code).

8.3 Ethics and regulatory review

An IRB 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 Head of the study site will ensure the distribution of these documents to the applicable IRB, and to the study site staff.

The Head of the study site should submit a notification of direction/determination as well as a copy of the IRB written approval to PAREXEL / AstraZeneca before enrolment of any patient should 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 IRB must approve all advertising used to recruit patients for the study.

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

[redacted]

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

The protocol should be re-approved by the IRB annually. The Principal Investigator should submit progress reports to the IRB via the head of the study site at the time of the protocol re-approval.

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.

PAREXEL and/or AstraZeneca will provide IRBs and Principal Investigators with safety updates/reports according to local requirements.

The Principal Investigator is also responsible for providing the IRB 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 IRB according to local regulations and guidelines.

8.4 Informed consent

The Principal Investigator(s) at each site 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.

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

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

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

[redacted]

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.

If any new information on the study drug becomes available which may influence the decision of the patient to continue the study, the investigator(s) should inform the patient of such information immediately, record this in a written form, and confirm with the patient if he or she wishes to continue the participation in the study. In addition, if the investigator(s) deem it necessary to revise the Informed Consent Form, they should revise it immediately (Refer to Section 9.5). The investigator(s) should re-explain the patients using updated Informed Consent Form even if although the patients have already been informed of the new information verbally. Written informed consent to continue participation in the study should be provided separately.

8.5 Changes to the protocol and informed consent form

Study procedures will not be changed without the mutual agreement of the Principal Investigator, PAREXEL and AstraZeneca. If it is necessary for the study protocol to be amended, the amendment should be submitted to the Head of the Study Site and be approved by its IRB. For distribution to IRBs see Section 8.3. If applicable, AstraZeneca should submit a notification to the regulatory authority before it is implemented. If a protocol amendment requires a change to a particular site's Informed Consent Form, then AstraZeneca and the site's IRB should be notified. Approval of the revised Informed Consent Form by AstraZeneca and by the IRB is required before the revised form is used. If an administrative change is required, such a change should be notified to or approved by each IRB according to local requirements.

8.6 Audits and inspections

Authorised representatives of AstraZeneca, a regulatory authority, or an EC may perform audits or inspections at the site, 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 AstraZeneca immediately if contacted by a regulatory agency about an inspection at the site. All study data may undergo a reliability review and onsite-GCP inspection by the regulatory authorities.

The list of AstraZeneca KK auditors for this study is available in Supplement A.

9. STUDY MANAGEMENT

PAREXEL is responsible for all aspects of study management, monitoring, medical monitoring, data management, statistical analysis and report writing as documented in the relevant agreements between PAREXEL and AstraZeneca. Patient eligibility will be handled by Keio University CCC.

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

9.1 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.
- Determine availability of appropriate patients for the study.
- Discuss with the investigator(s) (and other personnel involved with the study) their responsibilities with regard to protocol adherence, and the responsibilities of AstraZeneca or its representatives. This will be documented in a Clinical Study Agreement between PAREXEL, AstraZeneca and the investigator.

9.2 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 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).

9.3 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, that biological samples are handled in accordance with the laboratory manual and that study drug 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. This will require 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 of/destroyed 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 site needs information and advice about the study conduct.

The list of monitors for this study is available in Supplement A.

9.3.1 Source data

Refer to the Clinical Study Agreement for location of source data.

Source data are any data generated as a result of the patient's inclusion in the study (including run-in and/or follow up related to the study) and includes all related medical examinations and other records.

9.3.2 Direct access to source data in Japan

The Head of the institution and the Principal Investigator/sub-investigator will cooperate for monitoring and audit by AstraZeneca or delegates (see also Section 8.6), and accept inspection by the IRB or regulatory authorities. All study documents such as raw data will be open for direct access to source data at the request of the monitor and the auditor of AstraZeneca, the IRB, or regulatory authorities.

Data from the study will be collected via electronic data capture. 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 will be electronically transferred to PAREXEL Data Management for inclusion in the PAREXEL Data Management study database.

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

[redacted]

[redacted]

9.4 Study agreements

The Principal Investigator at each/the site should comply with all the terms, conditions, and obligations of the Clinical Study Agreement, or equivalent, for this study. In the event of any inconsistency between this Clinical Study Protocol and the Clinical Study Agreement, the terms of 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 Clinical Study Agreement shall prevail.

Agreements between AstraZeneca, PAREXEL and the Principal Investigator should be in place before any study-related procedures can take place, or patients are enrolled.

9.4.1 Archiving of study documents

(i) **Study files.** PAREXEL will provide the Principal Investigator with a file in which to organise and retain all study-related documents. All study documents (including letters from AstraZeneca and/or PAREXEL) should be retained in this file by the Principal Investigator. The monitor will regularly check the file to ensure that all relevant documents are retained. The contents of the file may be audited/inspected by AstraZeneca's auditor, regulatory authorities, or IRB.

(ii) **Period of record retention**. The study site (and the Principal Investigator) will retain the essential documents specified in the ICH GCP (eg, source document such as medical records, contract, signed consent form). Essential documents should be retained at the study site for at least 15 years following completion of the study, or per regulatory obligations if longer, and thereafter destroyed only after agreement with AstraZeneca. However this is not always applied to those that are not preservable such as blood samples. In the event of any inconsistency between the above-mentioned contents and the contract with the study site, the contract shall prevail. These documents should be retained for a longer period however if needed by AstraZeneca, and the specific period and method of retention will be separately discussed between the study site and AstraZeneca. AstraZeneca should notify the head of the study site in writing when the study related records are no longer needed. The records should be managed by a responsible person appointed by the head of the study site.

9.5 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".

[redacted]

Discontinuation or suspension of the whole study programme

If AstraZeneca decides to prematurely terminate or suspend the study, the Principal Investigator, sub-investigator, the head of the institution, and regulatory authorities should receive written notification of the reasons for the premature termination or suspension.

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

[redacted]

The Principal Investigator/sub-investigator 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.

Completion of the study

Upon terminating the study, the Principal Investigator/sub-investigator will report in writing the completion of the study as well as the summary of the results to the head of the study site in accordance with the institution's rules. The Head of the study site, who is informed of the termination by the investigator, will provide a written notification of the results to the IRB and AstraZeneca or delegate.

10. DATA MANAGEMENT

Data entered in the WBDC system will be immediately saved to a central database and changes tracked to provide an audit trail. When the Principal Investigator has signed the eCRF electronically as per eCRF instructions, then the patient's data will be locked.

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

AEs and medical/surgical history will be classified according to the terminology of the latest version the MedDRA. Medications will be classified according to the AstraZeneca Drug Dictionary. All coding will be performed by PAREXEL.

Data queries will be raised for inconsistent, impossible or missing data. All entries to the study database will be available in an audit trail.

The data will be validated as defined in the Data Management Plan. Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

There will be a blinded data review meeting prior to database lock where the review of analysis populations and protocol deviations will be performed. The meeting minutes from this meeting will have an "acceptance form". Database lock and unblinding will happen only when this form will be signed.

When all data have been coded, validated and locked, clean file will be declared. Any treatment revealing data may thereafter be added and the final database that will be locked.

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

[redacted]

11. EVALUATION AND CALCULATION OF VARIABLES

11.1 Calculation or derivation of variables used in the general assessment of sepsis care

11.1.1 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.

11.1.2 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.

11.1.3 Calculation and derivation of Sequential Organ Failure Assessment (SOFA) Scores

A point score is given to each of the variables recorded for the six categories of Glasgow Coma Score, respiration, coagulation, liver, cardiovascular, and renal. The total SOFA score is calculated from the sum of these individual scores. The calculation of the SOFA score will be done electronically; investigators will only need to enter the values of the parameters measured into the eCRF.

Baseline will be defined as the screening visit which was taken in the 24 hrs prior to the start of study drug.

For missing coagulation, liver, renal and central nervous system (CNS) components of the total SOFA score, a last observation carried forward (LOCF) approach will be used (from last protocol-related measurement). For cardiovascular and respiratory components, investigators will be encouraged to use other available data (on/off vasopressors and oxygen saturation percentage) in order to complete the individual component score. The worst BP and saturation values of the day should be used.

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

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

11.1.4 Calculation and derivation of ventilator use and pulmonary assessment parameters

Assuming that PAO_2 (the partial pressure of alveolar oxygen) is obtained from the alveolar gas equation:

$$PAO_2 = (FiO_2 \times (760\text{-}47)) - (PaCO_2/0.8)$$

then alveolar to arterial (AA) gradient will be calculated as:

$$\text{AA gradient} = PAO_2 - PaO_2.$$

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

VFDs 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 hrs and the purpose of the assisted breathing was a surgical procedure).
  - If a patient was receiving assisted breathing at Day 28 or dies prior to Day 29, VFDs will be zero.
  - If a patient never requires assisted breathing, the VFDs will be 29 days.
- The 28-day study period is from the start of the first infusion 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.

11.1.5 Calculation and derivation of organ failure assessment

Organ failure developing after study entry, regardless of cause, will be assessed using SOFA scores and therefore only assessed on the days on which the SOFA score is collected (see Table 1). Failure of an organ at study entry is defined as a SOFA score for an individual component >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.

11.1.6 Septic shock recording

Septic shock will be defined as a score >2 taken from the cardiovascular component of the SOFA score.

11.1.7 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 6.4.10.

11.1.8 Daily volume status

At screening, the total volume of fluid given to a patient and the total volume of fluid excreted from the patient will be recorded in accordance with standard procedures (eg, intravenous volume in for the 24 hrs prior to randomisation, or fluid in the abdomen in case of peritoneal dialysis, etc). Total parenteral nutrition (TPN), lipids, and blood product volumes will be collected as part of these data. Fluids administered for abdominal irrigation should not be counted. The total daily fluid status will be calculated as follows:

daily volume status, in the 24 hrs prior to randomisation	=	total daily volume in, in the 24 hrs prior to randomisation	-	total daily volume out, in the 24 hrs prior to randomisation

11.2 Calculation or derivation of safety variable(s)

11.2.1 Other significant adverse events (OAE)

During the evaluation of the AE data, an AstraZeneca medically qualified expert will 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.

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

11.2.2 Extent of exposure

The total exposure (units/kg) will be calculated as:

Sum for each dose [(planned dose (units/kg) / planned duration (30 mins)) * actual duration (mins)].

Where planned dose corresponds to 250 units/kg for the loading dose of Cohort 1, 50 units/kg for the maintenance doses of Cohort 1, 500 units/kg for the loading dose of Cohort 2 and 100 units/kg for the maintenance doses for Cohort 2. The duration of exposure is calculated as the sum of the actual durations of each dose. Compliance with the study regimen will be calculated as total exposure divided by planned total exposure.

11.2.3 Creatinine clearance

In addition to those parameters recorded on the database, creatinine clearance (CRCL) (mL/min) will be estimated. The Cochroft-Gault formula, given below, will be used to estimate CRCL from serum creatinine (Scr) (mg/dL), age at the date of consent (years), actual body weight at the date of consent (kg) and gender correction factor (GF: 0.85 in women, 1.00 in men).

$$CRCL = \frac{(140 - age) \times weight}{72 \times Scr} \times GF$$

11.2.4 Blood pressure

Mean arterial pressure will be calculated as: [(2 x DBP) + SBP] / 3

Where DBP stands for diastolic BP and SBP for systolic BP.

11.3 Calculation or derivation of patient reported outcome variables – not applicable

11.4 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. PK parameters will be determined using standard non-compartmental methods. Full details of the population PK and PK-PD analysis will be given in the Pharmacokinetic Analysis Plan approved before the start of analysis.

All PK parameters will be derived using non-compartmental methods using WinNonLin Version 5.2.1, by AstraZeneca.

Methods for the calculation of PK parameters

C_{inf} and $C_{ss\ max(inf)}$ will be determined by visual inspection of the plasma concentration-time profile. Where more than one maxima occurs, the reported value will be assigned to the first occurrence.

AUC_{0-t} and AUC_{τ} will be calculated by the linear trapezoidal rule.

Accumulation ratio will be calculated as the ratio of AUC_{τ} on Day 5 (or 6) / AUC_{0-t} on Day 1. This calculation will be done outside WinNonlin, using the appropriate software (SAS or other software including MS-Excel)

The excreted amount of the compounds in urine collected over 0-12 hr periods on Day 1 and Day 5 (or 6) will be calculated by urine concentration and urine volume for each period. The total amount of the compound excreted in urine will be calculated by multiplying the urine concentration by the urine volume.

% of drug recovered in urine will be calculated by dividing the total amount of the compound excreted in urine within 0-12 hr periods by dose.

CL_R will be calculated by dividing total amount of the compound excreted into urine within 0-12 hr periods by AUC_{0-12} on Day 1 and Day 5 (or 6).

These calculations will be also done outside WinNonLin, using the appropriate software (SAS or other software including MS-Excel).

See Section 6.6.2 for details on derived PK parameters planned.

11.5 Calculation or derivation of pharmacodynamic variable(s)

11.5.1 Calculation or derivation of pharmacodynamic variables

See Section 12.3.5 for more details about analyses performed on PD variables.

11.5.2 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 the data are appropriate, concentration-effect relationships may be explored.

11.5.3 Calculation or derivation of the relationship between pharmacokinetic and efficacy variables – not applicable

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

The relationship between drug serum concentration and AEs may be explored, if data are appropriate.

11.5.5 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.

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

[redacted]

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

11.6 Calculation or derivation of pharmacogenetic variables – not applicable

11.7 Calculation or derivation of health economic variables – not applicable

12. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

12.1 General principles

Apart from calculation of the total SOFA score (see Section 11.1.3), 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 prior to database lock.

Apart from the SOFA score (see Section 11.1.3), baseline is defined as the latest non-missing assessment prior to the time of first study drug infusion. For all change from baseline assessments, patients will only be included if they have both baseline and relevant post-baseline data.

Continuous data, which are assumed to be normally distributed, will be summarised in terms of the mean, standard deviation (SD), median, minimum, maximum and number of observations. The minimum and maximum will be reported to the same number of decimal places as the raw data recorded in the database. The mean, SD and median will be reported to one more decimal place than the raw data recorded in the database. In general, the maximum number of decimal places reported shall be four for any summary statistic. For the PK summaries, the reported results will be summarised using appropriate significant figures rather than decimal places.

Categorical data will be summarised in terms of frequency counts and percentages. Percentages will be presented to one decimal place.

Following review of the data, figures of the key findings will be produced. These figures may comprise box-plots, summaries of the mean ±SD, or patient profile plots as applicable, but the exact nature of the plots and the parameters that they will be produced for will be determined after database lock.

Due to the small number of patients recruited in each site, all sites will be combined for the summaries.

All tables will be presented by AZD9773 Cohort 1 (250/50 units/kg), AZD9773 Cohort 2 (500/100 units/kg), AZD9773 Total and Placebo. Placebo will consist of data for all patients receiving placebo, pooled across the two cohorts.

[redacted]

Demography, safety and PD data will be summarised using the safety population. PK data will be summarised using the PK population.

12.2 Description of analysis sets

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

12.2.1 Enrolled population

The enrolled patients analysis set will consist of all patients who received an 8-digit E-code and signed the informed consent, regardless of whether they were randomised or treated.

12.2.2 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.

12.2.3 Pharmacokinetic population

This population will be a subset of the safety population including only patients without important detected deviations affecting the PK. Patients will be summarised according to the treatment they actually received.

A strategy for dealing with PK data affected by deviations will be agreed by the Study Team Physician, Pharmacokineticist and Statistician, prior to clean file and code break.

The number of patients in each analysis set will be summarised. By-patients listings of eligibility criteria and inclusion/exclusion from the safety and PK analysis sets will be provided.

12.3 Methods of statistical analyses

12.3.1 Disposition, demographics and baseline characteristics

A summary of the number of patients who were enrolled, randomised, received treatment and completed the study will be presented. Reasons for patients not being randomised, and not receiving treatment will be presented along with summaries of the reasons for discontinuation from the study post-randomisation and discontinuation of the study drug.

By-patient listings of randomisation details, discontinuation of study drug, withdrawal/study completion and ICU admission, readmission, transfer and discharge details will be provided.

Demographic data and selected co-morbidities will be summarised. Age will be calculated as the number of complete years between a patient's birth date and the date of their consent. Age will be summarised using descriptive statistics and grouped into the following categories: 18-<65 years, 65-<75 years and ≥75 years.

Body mass index (BMI) will be calculated as:

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

[redacted]

$$BMI = \frac{\text{Weight (kg)}}{(\text{Height [m]})^2}$$

Baseline Glasgow Coma Scores and baseline APACHE II scores will be summarised. The derivation of these scores can be found in Appendix F and Appendix E, respectively. For the serum creatinine APACHE score, each patient's score will be doubled if the patient has acute renal failure.

By-patient listings of demographic data, patient narrative details, baseline Glasgow Coma Scores and baseline APACHE II scores will be provided.

Pregnancy test results and pregnancy reports will be listed.

Summary statistics (n, mean, median, SD, minimum and maximum) of time to first administration of antibiotics for a sepsis infection will be presented. Two definitions will be used. Time to first antibiotic use from time initial health care sought (the time of first administration of antibiotics - time of initial health care sought for infection leading to sepsis in hrs) and time to first antibiotic use from qualifying organ failure (the time of first administration of antibiotics for sepsis case - time of qualifying organ failure in hrs).

By-patient listings of antibiotic use will be presented.

A summary of baseline disease characteristics will be presented. Baseline disease characteristics will include time from qualifying organ failure, number of patients with shock, on a ventilator, on pressors, with a positive culture or with renal impairment and whether a patient has overt disseminated intravascular coagulation (DIC). Time from qualifying organ failure to start of treatment will be calculated as date and time of treatment start – date and time of qualifying organ failure and will be presented in hrs. A medical review of concomitant medications will identify those patients on pressors. Overt DIC will be diagnosed using a scoring algorithm developed by the International Society on Thrombosis and Haemostasis (ISTH). Details of the algorithm, which uses platelet count, prothrombin time (PT), fibrinogen and D-dimer to diagnose overt DIC, are given in the table below. A score of ≥5 indicates overt DIC.

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

	Overt DIC by ISTH
Platelet Count	50,000 - 100,000/μL: 1 point <50,000/ μL: 2 points
PT	Prolongation of PT 3-6 sec: 1 point >6 sec: 2 points
Fibrinogen	<100 mg/dL: 1 point
D-dimer	0.5 - <1: 1 point 1 - <2: 2 points ≥2 (μg/mL): 3 points

Physical examination at entry will be summarised along with by-patient listings.

12.3.2 Concomitant medication and past/current medical and surgical history

Concomitant medications will be coded using the AstraZeneca drug dictionary and listed by drug class and generic name. In addition, all patients with an ECG median QTcF value greater than or equal to 500 msec will have all of their concomitant medications taken within the 8 hrs prior to the ECG listed, to identify whether any elevated QTcFs may be related to the concomitant medications the patient was taking.

Summaries of relevant medical history and surgical history will be presented.

A summary of all concomitant medications and all disallowed concomitant medications taken post-randomisation will be presented.

By-patient listings of concomitant medication, nutritional supplements, past and current medical history and relevant surgical history will be presented.

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.

12.3.3 Protocol deviations

The following will be considered important protocol deviations:

1. Patient received no study drug.

2. Patient received incorrect study drug.

3. Patient violated eligibility criteria at entry and was enrolled incorrectly.

4. Patient took disallowed concomitant medication during the study treatment period:

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

[redacted]

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

(a) Patient took immunosuppressant drugs (eg, methotrexate, cyclosporine, tacrolimus).

(b) Patient took high dose corticosteroids as anti inflammatory or immunosuppressive therapy (eg, >40 mg or 0.5 mg/kg prednisone or a steroid with equivalent activity for ≥2 days).

(c) Patient took anti-TNF antibodies (eg, infliximab [REMICADE®], adalimumab [Humira®], etanercept [Enbrel®]) other than study drug.

(d) Plasma exchange.

(e) Polymixin B haemoperfusion (Toraymyxin™).

Patient developed discontinuation criteria but was not withdrawn

Identification of important deviations affecting the PK (and therefore leading to exclusion from the PK population) will also be undertaken. PAREXEL will produce blinded listings as appropriate, for review by blinded team members at the clean file stage (see Section 10), to enable the protocol deviation and analysis population classification process to be completed. These listings will be separate and should be produced only when the patients' data are complete for a cohort.

A summary of important protocol deviations will be presented. A listing of important protocol deviations will also be presented.

12.3.4 Pharmacokinetics

All PK parameters will be derived using non-compartmental methods using WinNonLin Version 5.2.1, by AstraZeneca. Actual sampling times will be used for the computation of PK parameters. Serum concentration data and all PK parameters will be summarised using descriptive statistics for each analyte.

PK parameters will be derived using data from both the first (loading) dose and after the final maintenance dose.

Summary statistics (geometric mean, coefficient of variation (CV [calculated as:

$$100 \times \sqrt{(\exp(s^2)-1)}$$

where s is the SD on a logarithmic scale]), n, mean, median, SD, minimum, and maximum) for $AUC_{0\text{-}t}$, AUC_{τ}, C_{inf}, $C_{ss\ max(inf)}$, $C_{ss\ min}$, accumulation ratio, CL_R, and % of drug recovered in urine for each analyte will be presented by cohort for the PK analysis set. In order to determine the accumulation ratio, the loading dose will need to be normalised to the maintenance dose.

Summary statistics (geometric mean, CV, geometric mean ±SD, n, mean, SD, minimum, and maximum) for serum concentration of AZD9773 specific Fabs and AZD9773 total Fabs, at each nominal time point, will also be presented by cohort.

Non-quantifiable (NQ) values of serum concentrations will be handled as follows:

- If, at a given time point, 50% or less of the serum concentrations are NQ, the geometric mean, CV, geometric mean ±SD, mean and SD will be calculated by substituting the LOQ for values which are NQ.
- If more than 50%, but not all, of the concentrations are NQ, the geometric mean, CV, geometric mean ±SD, mean and SD will be reported as not calculable (NC).
- If all the concentrations are NQ, the geometric mean and mean will be reported as NQ and the CV, geometric mean ±SD and SD as NC.

If the calculation of the geometric mean - SD results in a value less than the LOQ, NQ will be displayed.

The following figures will be presented:

- Semi-log plots of serum concentration against time (one plot per dose level, all patients on plot) for AZD9773 specific Fabs and AZD9773 total Fabs separately.
- Semi-log plot of the geometric mean concentration (±SD) against time (symbols indicating dose levels) for AZD9773 specific Fabs and AZD9773 total Fabs separately.
- Linear plot of the geometric mean concentration (±SD) (on a log scale) against time for each dose separately with AZD9773 specific Fabs and AZD9773 total Fabs on the same plot.
- Scatter plots of AUC_τ against dose and dose normalised AUC_τ against dose.
- A figure showing linear geometric mean C_{min} concentrations, ie, all 12 hrs post and pre-dose concentrations, versus time.

By-patient listings of all serum and urine concentrations for both analytes and ratios of AZD9773 specific Fabs to AZD9773 total Fabs, and derived PK parameters will be presented. By-patient listings of dialysate, urine and blood sample collections for PK will also be provided.

12.3.5 Pharmacodynamics analysis

Summary statistics (n, mean, median, SD, minimum and maximum) of the raw data and change from baseline to each scheduled study assessment for TNFα ELISA, IL-6 ELISA and IL-8 ELISA will be presented by cohort and treatment. The number of TNFα ELISA results

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

below the LOQ will also be presented at each visit by cohort and treatment. Baseline is defined as the latest non-missing assessment prior to the first study drug infusion. Baseline cytokine panel data (TNFα, IL-6, IL-8, IL-10) for flow cytometry analysis will be listed.

By-patient listings of all PD parameters will be presented.

By-patient listings of blood cytokine collection will also be provided.

Plots for PD variables will be presented as required.

12.3.6 SOFA Score

Summary statistics (n, mean, median, SD, minimum, and maximum) of the individual components of the SOFA score and the total score at each timepoint will be presented by cohort and treatment. Summary statistics of the change from baseline will also be presented for each component and for the total score.

A by-patient listing of the individual components of the SOFA score will be presented along with the total of the six scores at each timepoint.

See Section 11.1.3 for more details on recorded data and missing data imputation.

12.3.7 Volume status in the 24 hrs prior to randomisation

Summary statistics (n, mean, median, SD, minimum, and maximum) of the total volume of blood products (mL), the total fluid volume in in the 24 hrs prior to randomisation (mL), the total fluid volume out in the 24 hrs prior to randomisation (mL) and the fluid volume status (in-out) in the 24 hrs prior to randomisation will be presented by cohort and treatment.

A by-patient listing of the total volume of blood products (mL), the total fluid volume in in the 24 hrs prior to randomisation (mL), the total fluid volume out in the 24 hrs prior to randomisation (mL) and the fluid volume status in the 24 hrs prior to randomisation will be presented.

See Section 11.1.7 for more details on the volume status in the 24 hrs prior to randomisation recording and calculation.

12.3.8 Pulmonary assessment and ventilator use

Summary statistics (mean, median, SD, minimum, and maximum) of pulmonary assessment (tidal volume, tidal volume/predicted body weight, peak airway pressure, plateau pressure, positive end expiratory pressure, respiratory rate and arterial blood gas use to include: pH, PaO_2, $PaCO_2$, FiO_2 and AA gradient) will be presented at each timepoint by cohort and treatment. Summary statistics of the change from baseline will also be presented.

A by-patient listing of the pulmonary assessment data will be presented.

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

[redacted]

Summary statistics (n, mean, median, SD, minimum and maximum) of VFDs over the study duration will be presented. In addition, the number of patients with a VFD of 0 will be summarised along with the summary statistics for the remaining patients with a VFD greater than 0.

By-patient listings of all ventilator use information and VFD assessments will be presented.

12.3.9 Septic shock

The number and percentage of patients with any septic shock and septic shock by visit will be presented.

By-patient listings of septic shock details will be presented.

12.3.10 Organ failure assessment

The number and percentage of patients with any organ failures by visit (assessed as any SOFA scores component >1) will be presented. In addition, the number and percentage of patients with 0, 1, 2, 3, 4, 5 or 6 types of organ failure will be summarised by visit and overall. Overall is defined as the number of different SOFA score components > 1 at any time.

The number and percentage of patients with organ failures, which were present at study entry and resolved prior to Day 29 will be summarised. This summary will be broken down by resolution of all organ failures at entry and resolution of the qualifying organ failure.

By-patient listings of organ failure data will be presented to include type of organ failure, organ failure start date and time, if the organ failure resolved before Day 29 and the date and time of resolution.

A by-patient listing of renal replacement therapy will be provided.

12.3.11 Infection assessment

The number and percentage of patients with infections (identified by a compatible clinical syndrome or documented culture or non-culture rapid test) occurring prior or infections occurring after first dose will be presented by cohort and treatment.

By-patient listings of infection data including type and site of infection, associated pathogen(s) and antimicrobial susceptibility results will be presented.

12.3.12 28-day mortality

28-day mortality will be summarised by the proportion of patients who are alive or dead at Day 29 (phone contact). A by-patient listing of all deaths that occurred during the study will be presented along with a listing of 28-day mortality.

12.3.13 ICU-free days

ICU-free days will be summarised in the same way as for VFDs (see Section 12.3.8).

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

[redacted]

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

12.3.14 Safety

12.3.14.1 Extent of exposure

Summary statistics (mean, median, SD, minimum, and maximum) of the number of infusions, the total exposure (units/kg), the duration of exposure (mins) and compliance, will be provided.

By-patient listings of treatment exposure will also be provided.

12.3.14.2 Adverse events

AEs will be coded according to the version of the MedDRA agreed with AstraZeneca. Only treatment-emergent adverse events (TEAEs) (events which were not present at baseline or worsened in severity after the start of treatment) will be presented in the summaries.

The onset date and time of an AE will be compared to the date and time of first infusion of study drug to determine if the AE is treatment-emergent or not. AEs with an onset date and time on or after the date and time of first infusion of study drug will be classified as treatment-emergent.

If the AE onset date or time is missing or partial, the date and time will be compared as far as possible with the date and time of first dose of study drug. AEs will be assumed to be treatment-emergent, unless there is clear evidence (through comparison of partial dates and times) to suggest that the AE started prior to the first dose of study drug.

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, and at least one hypersensitivity reaction.
- A summary of the number of TEAEs, deaths, severe TEAEs, serious TEAEs, TEAEs possibly related to study drug, TEAEs leading to withdrawal from study drug, the number of infusion reactions, and the number of hypersensitivity reactions (Episode level).
- A summary of the number and percentage of patients reporting a TEAE by system organ class (SOC) and preferred term.
- A summary of the number and percentage of patients reporting a TEAE by preferred term.
- A summary of the number of TEAEs by preferred term (Episode level).
- A summary of the number and percentage of patients reporting a TEAE by intensity, SOC and preferred term. For each patient and each TEAE, the maximum

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

reported intensity will be attributed and used in the by-intensity summaries. The order from most severe to least severe will be severe, missing, moderate and then mild.

- A summary of the number and percentage of patients reporting a TEAE 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 SOC and preferred term (including the number of infusion reactions at the episode level).

- A summary of the number and percentage of patients reporting hypersensitivity reactions by SOC and preferred term.

- A summary of the number of hypersensitivity reactions by preferred term (Episode level).

The following by-patient listing will be provided:

- A listing of all AEs (including non-treatment-emergent events), by cohort and treatment, and including E-code, AE (SOC, preferred term, reported term), date of onset, date of resolution, duration, severity, seriousness, action taken, outcome, relationship to study treatment and time from last dose to start of AE.

12.3.14.3 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 with an TEAE outcome of death by preferred term.

- A summary of the primary cause of death by preferred term.

- A summary of the number and percentage of patients reporting a serious TEAE by SOC and preferred term.

- A summary of the number of serious TEAEs by SOC and preferred term (Episode level).

- A summary of the number and percentage of patients reporting a TEAE leading to withdrawal from study treatment by SOC and preferred term.

- A summary of treatment-emergent OAEs. A physician review of the TEAEs will identify the treatment-emergent OAEs if they exist.

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

The following by-patient listings will be presented:

- A by-patient listing of deaths, including the date of death, the primary and secondary cause of death and whether an autopsy was performed.
- A by-patient listing of key information for TEAEs with an outcome of death.
- A by-patient listing of key information for SAEs.
- A by-patient listing of key information for TEAEs leading to discontinuation of study treatment.
- A by-patient listing of key information for treatment-emergent OAEs.
- A by-patient listing of infusion reactions.
- A by-patient listing of hypersensitivity reactions.

The following by-patient listings will be presented in the same format as the AE listings in the AEs section:

- A by-patient listing of all SAEs.
- A by-patient listing of all AEs leading to withdrawal from study treatment.

The following patient narratives will be provided:

- Narratives of deaths.
- Narratives of SAEs other than death.
- Narratives of discontinuation of study drug due to AEs.
- Narratives of OAEs.

12.3.14.4 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.

In addition to those parameters recorded on the database, CRCL (mL/min) will be calculated.

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. In addition, laboratory parameters will be reviewed via graphical presentations to explore the safety profile of AZD9773.

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

For continuous laboratory parameters, shift tables of the number and percentage of patients with normal, low or high results, as defined by the project standard ranges, will be presented from baseline to the most extreme post-baseline value by treatment group. In addition, laboratory parameters will be classified using the National Cancer Institute Common Toxicity Criteria (CTC) version 3 into CTC grades. These grades will be summarised by shift tables from baseline to most extreme post-baseline grade similar to the normal ranges.

For categorical urinalysis parameters, shift tables of the number and percentage of patients by classification, will be presented from baseline to the most extreme post baseline value.

By-patient listings of all laboratory data (including reported and converted results) will be provided, with abnormal values and CTC grades highlighted, and including site, patient identifier, age, sex, race, weight and visit. Laboratory reference ranges will also be listed.

HASA IgG, HASA bridging assay and measurement of biological activity of AZD9773 by nAb assay will be presented separately to the laboratory data summaries/listings described above. Where the data allow, it will be presented as individual patient listings per time-point, as binary data, above cut-point (ACP) or below cut-point (BCP). For those data-points, which give a positive response (ie, ACP), a semi-quantitative value for end-point titre and a confirmatory individual analysis result will be presented.

Measurement of AZD9773 activity will be presented as individual patient listings, as semi-quantitative values of AZD9773 (ng/mL), as determined by activity within a nAb assay, per time point.

12.3.14.5 Vital signs and blood oxygen-haemoglobin saturation 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.

By-patient listings of all vital signs data will be presented.

12.3.14.6 Electrocardiogram evaluation

Summary statistics (mean, median, SD, minimum, and maximum) of the average of the triplicate raw data and change from baseline to each scheduled study assessment for all ECG parameters (heart rate, PR interval, RR interval, QRS duration, QT interval, QTcB and QTcF) will be presented by treatment group. Baseline is defined, after taking the average of the triplicates, as the latest non-missing averaged triplicate prior to the first study drug infusion.

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.

By-patient listings of ECG parameters will be presented along with the overall interpretation and expert evaluation of ECGs at all visits.

12.3.15 Interim analyses

No interim analysis is planned for this study.

12.4 Determination of sample size

The sample size for this study was selected to be consistent with the research hypothesis as described in Section 1.2.

The sample size has been based on practical requirements rather than any formal sample size justification. The number of patients was chosen so as to obtain sufficient safety and PK data to progress the compound whilst exposing as few patients as possible to AZD9773.

The study will consist of 2 successive cohorts, with a total of 20 patients planned (10 patients per cohort) from approximately 10 Japanese sites. For each cohort, initially 10 patients will be randomised (7 on active treatment and 3 on placebo). A completely recruited Cohort 1, a minimum number of 4:1 (AZD9773: placebo) cohort-completers (ie, at least 4 patients in the AZD9773 group and at least 1 patient in the placebo have completed the cohort), with all patients having completed or at least reached 7 days after his/her last dose are required for SRC/IDMC recommendations to progress to the second cohort in this dose escalation study.

If this total is not achieved after 10 patients have been randomised to a cohort, additional patient(s) will be enrolled, and will be allocated to the treatment of those patients who were not cohort completer(s), unless a safety concern precludes further enrolment. Enrolment of the additional patients will continue until at least 4 patients in the AZD9773 group and at least 1 patient in the placebo have completed the cohort. For these patients, the treatment group allocation will be forced but the blind will be maintained. All patients who receive a dose of study drug will be evaluated for safety and tolerability.

12.5 Safety Review Committee and Independent Data Monitoring Committee

At the end of Cohort 1, a SRC consisting of the External Medical Advisor in Japan, a Statistician, the Global Project Physician, the Japan Project Physician and the Global Drug Safety Physician or their delegates, will evaluate safety data. The SRC will also consult with a clinical pharmacologist and an external consultant with experience in other AZD9773 trials. The SRC may bring in additional expertise if needed. At minimum, the attendance of three physicians will be required. The SRC members will be unblinded, but the rest of the study team will remain blinded. Based on the reviewed data, the SRC will provide a safety

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

assessment and make recommendations to the IDMC to proceed to Cohort 2, modify or stop escalation based on safety findings.

The IDMC will be comprised of three independent experts. The committee will meet to review data from Cohort 1 and at the end of the study. The IDMC will meet in open session with the SRC, followed by a closed meeting attended only by IDMC members. Based on the reviewed data, the IDMC will provide an independent safety assessment and make recommendations to proceed to Cohort 2, modify or stop escalation based on safety findings.

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

SRC members are listed in Supplement A.

Criteria for Dose Escalation:

The SRC and IDMC will review safety data during the study and assess the planned dose escalation schedule. A data review is planned after the three following criteria are achieved:

- Cohort 1 has been completely recruited (at least 10 patients),
- When at least 4 AZD9773 and 1 placebo patients are cohort-completers 7 days after last dose,
- When all patients have completed or at least reached 7 days after the last dose.

All patients who receive a dose of study drug will be evaluated for safety and tolerability. Prior to dosing in Cohort 2, a satisfactory IDMC report must be generated after the review.

If one of the following occurs at a dose level for patient(s) on AZD9773, the SRC/IDMC will discuss the necessity of modifying or stopping dose escalation. All these should be considered by the SRC/IDMC relative to their occurrence in the placebo group and following review of the relevant data:

- Serious and/or clinically concerning unexplained AEs that occur(s) and appear(s) to be drug associated as judged by the SRC/IDMC.
- The discontinuation of 2 or more patients on AZD9773 in a cohort by an investigator for safety concerns believed to be drug-related.
- Death within 48 hrs after administration of AZD9773 that is suspected as being study drug-related by the SRC/IDMC or the investigator.

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

- Intolerance. If more than 3 patients on AZD9773 in a cohort develop (a) a moderate or severe reaction believed to be related to study drug in the opinion of the investigator and/or SRC/IDMC that does not respond to treatment, or (b) recurrent moderate and/or severe reactions, then decreasing the rate of dose escalation or altering doses in a subsequent cohort will be considered. In the event that the investigator believes an infusion reaction has occurred in a temporally associated manner to study drug in a patient receiving AZD9773, the SRC/IDMC will review objective markers of immune system activation to help determine potential hypersensitivity type reactions prior to making a recommendation on dose escalation for the next cohort.

- If 2 or more patients on AZD9773 in a cohort experience AEs of special significance as attributed by the investigator and/or AstraZeneca then an interim SRC/IDMC meeting will be convened to examine the data.

Cohort-completers:

A minimum of 4:1 AZD9773: placebo cohort-completers for each cohort will be required for the SRC/IDMC evaluation (ie, at least 4 patients in the AZD9773 group and at least 1 patient in the placebo have completed the cohort).

The patients who are given a minimum of 6 doses of study drug and survive at least 7 days after the last dose will be considered cohort-completers.

If the number of cohort-completers does not reach the above criteria after the originally planned 10 patients have been enrolled in a cohort, additional patients will be enrolled until the 4 AZD9773 and 1 placebo total is attained and have completed.

Details on the documents provided to the SRC and IDMC are provided in the IDMC Charter.

13. IMPORTANT MEDICAL PROCEDURES TO BE FOLLOWED BY THE INVESTIGATOR

13.1 Medical emergencies and AstraZeneca/PAREXEL contacts

The Principal Investigator is responsible for ensuring that procedures and expertise are available to handle medical emergencies during the study. **A medical emergency usually constitutes an SAE and is to be reported as such (see Section 6.5.4).**

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, the investigator should contact the Project Physician of AstraZeneca Global.

[redacted]

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

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

13.2 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 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 AstraZeneca and/or PAREXEL as appropriate.

Reporting requirements:

- An overdose with associated SAEs should be recorded as the SAE diagnosis/symptoms on the relevant AE forms in the 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 is only reported on the Overdose eCRF module.

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

If an overdose on an AstraZeneca study drug occurs in the course of the study, then investigators or other site personnel inform appropriate AstraZeneca and/or PAREXEL representatives **within one day**, ie, immediately but no later than **the end of the next business day** of when he or she becomes aware of it.

The designated AstraZeneca and/or PAREXEL representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site.

For overdoses associated with a SAE, standard reporting timelines apply (see Section 6.5.4). For other overdoses, reporting should be done within 30 days.

A patient experiencing an overdose should continue the study unless there is an intolerability that precludes continuing participation.

13.3 Pregnancy

The outcomes of any conception occurring from the date of the first dose until 90 days after the last dose and as indicated by previous studies (pre-clinical and clinical) should, if possible, be followed-up and documented.

All outcomes of pregnancy must be reported to AstraZeneca.

13.3.1 Maternal exposure

Pregnancy itself is not regarded as an AE unless there is a suspicion that the 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, elective termination, ectopic pregnancy, 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 (see Section 5.1).

If any pregnancy occurs in the course of the study, then investigators or other site personnel inform appropriate AstraZeneca and/or PAREXEL representatives **within one day** ie, immediately but no later than the **end of the next business day** of when he or she becomes aware of it.

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 or 5 days for SAEs (see Section 6.5.4) and within 30 days for all other pregnancies.

The PREGREP module in the eCRF is used to report the pregnancy and the PREGOUT is used to report the outcome of the pregnancy. The pregnancy outcomes report form may be completed and faxed to PAREXEL.

13.3.2 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, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should, if possible, be followed-up and documented.

14. LIST OF REFERENCES

Balk and Bone 1989
Balk RA, Bone RC. The septic syndrome: definition and clinical implications. Crit Care Clin 1989;5:1-8.

Bone et al 1989
Bone RC, Fisher CJ, Clemmer TP, Slotman GJ, Metx CA, Balk RA. Sepsis syndrome: A valid clinical entity. Crit Care Med 1989;17:389-93.

Covell et al 1986
Covell DG, Barbet J, Holton OD, Black CD, Parker RJ, Weinstein JN. Pharmacokinetics of monoclonal immunoglobulin G1, F(ab')2, and Fab' in mice. Cancer Res 1986;46:3969-78.

ICH E14
ICH Harmonised Tripartite Guideline E14. The clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs. International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use. Step 4, 12 May 2005.

Marshall 2000
Marshall JC. Clinical trials of mediator-directed therapy in sepsis: what have we learned? Intensive Care Med. 2000;26 Suppl 1:S75-83.

Marshall 2003
Marshall JC. Such stuff as dreams are made of: mediator-directed therapy in sepsis. Nature Rev Drug Discov 2003;2(5):391-405.

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

Nelson et al 2000
Nelson PN, Reynolds GM, Waldron EE, Ward E, Giannopoulos K, Murray PG. Monoclonal antibodies. Mol Pathol 2000;53:111-7.

Niederman et al 2005
Niederman MS, Craven DE, Bonten MJ, Chastre J, Craig WA, Fagon J-Y et al. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. Am J Respir Crit Care Med 2005;171:388-416.

Panacek et al 2004
Panacek EA, Marshall JC, Albertson TE, Johnson DH, Johnson S, MacArther RD, et al. Efficacy and safety of the monoclonal antitumor necrosis factor antibody F(ab')2 fragment afelimomab in patients with severe sepsis and elevated interleukin-6 levels. Crit Care Med 2004;32:2173-82.

Rice et al 2006
Rice TW, Wheeler AP, Morris PE, Paz HL, Russell JA, Edens TR, Bernard GR. Safety and efficacy of affinity-purified, anti-tumor necrosis factor-α, ovine fab for injection (CytoFab) in severe sepsis. Crit Care Med 2006;34(9):2271-81.

Schaumann et al 1986
Schaumann W, Kaufmann B, Neubert P, Smolarz A. Kinetics of the Fab fragments of digoxin antibodies and of bound digoxin in patients with severe digoxin intoxication. Eur J Clin Pharmacol 1986;30:527-33.

Thijs and Hack 1995
Thijs LG, Hack CE. Time course of cytokine levels in sepsis. Intensive Care Med 1995;21(Suppl. 2):S258.

van der Poll and van Deventer 1999
van der Poll, van Deventer SJH. Cytokines and anticytokines in the pathogenesis of sepsis. Infect Dis Clin North Am 1999;13:413-26.

[redacted]

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

Clinical Study Protocol: Appendix B

Drug Substance	AZD9773
Study Code	D0620C00005
Appendix Edition Number	2
Appendix Date	[redacted]

Appendix B
Additional Safety Information

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

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

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

[redacted]

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.

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

[redacted]

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

Clinical Study Protocol: Appendix C

Drug Substance	AZD9773
Study Code	D0620C00005
Appendix Edition Number	2
Appendix Date	[redacted]

Appendix C
International Airline Transportation Association (IATA) 6.2 Guidance Document

[redacted]

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

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 UN 3373 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.

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

AstraZeneca

Revised Clinical Study Protocol: Appendix D

Drug Substance	AZD9773
Study Code	D0620C00005
Appendix Edition Number	1
Appendix Date	[redacted]

Appendix D
Medical Management of Patients with Severe Sepsis

[redacted]

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

MEDICAL MANAGEMENT OF 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 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.

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

- If have previously received antivenom manufactured using ovine serum, digoxin immune Fab (DigiFab™, DIGIBIND®), crotalidae polyvalent immune fab (ovine) (CroFab™, not registered in Japan), 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, in case of suspected infusion or hypersensitivity reaction, a serum tryptase level and 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.

[redacted]

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

- Laboratory parameter measurements
  - At timepoints according to the study plan (Table 1 of protocol).
  - And in case of suspected infusion or hypersensitivity reaction, serum tryptase level, 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.

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

– Laboratory parameters (eg, 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).

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

[redacted]

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

  - 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.

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.

[redacted]

- Laboratory parameter measurements to consider:
  - Serum tryptase level, IgE, and quantitative eosinophil count 20 to 60 minutes post suspected infusion reaction and repeated on blood draw at Day 29.

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

Clinical Study Protocol: Appendix E	
Drug Substance	AZD9773
Study Code	D0620C00005
Appendix Edition Number	2
Appendix Date	[redacted]

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

[redacted]

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

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.

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

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 hospitalisation) 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

[redacted]

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

Clinical Study Protocol: Appendix F

Drug Substance	AZD9773
Study Code	D0620C00005
Appendix Edition Number	2
Appendix Date	[redacted]

Appendix F
Glasgow Coma Score

[redacted]

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

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) =			

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

AstraZeneca

Clinical Study Protocol: Appendix G

Drug Substance	AZD9773
Study Code	D0620C00005
Appendix Edition Number	2
Appendix Date	[redacted]

Appendix G
Sequential Organ Failure Assessment (SOFA) Score

[redacted]

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

1. SEQUENTIAL ORGAN FAILURE ASSESSMENT (SOFA) SCORE

	SOFA Score				
	0	**1**	**2**	**3**	**4**
Respiration					
PaO_2/FiO_2 (torr) [c]	>400	≤400	≤300	≤200 With respiratory support	≤100 With respiratory support
SpO_2/FiO_2 (torr) [a, c]	≥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 [c]	No hypotension	MAP <70 mm Hg	Dopamine ≤5 or dobutamine (any dose)[b]	Dopamine >5 or epi ≤0.1 or norepi ≤0.1[b]	Dopamine >15 or epi >0.1 or norepi >0.1 [b]
Central Nervous System					
Glasgow Coma Score [d]	15	13-14	10-12	6-9	<6
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] Data on file

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

[redacted]

[c] The worst blood pressure 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 or the last available (if within 48 hours). On days when laboratory results are unavailable, values will be extrapolated from the previous available values.

[d] Glasgow Coma Score must be recorded at the same timepoints as for the SOFA score (to allow the calculation of the SOFA score)

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.

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

[redacted]

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

Clinical Study Protocol: Appendix H

Drug Substance	AZD9773
Study Code	D0620C00005
Appendix Edition Number	2
Appendix Date	[redacted]

Appendix H
Ventilator Weaning Protocol

[redacted]

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

1. VENTILATOR WEANING

1.1 Ventilator procedures

A modified, simplified version of the Acute Respiratory Distress Syndrome (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 (6 mL/kg Predicted Body Weight [PBW] ± 2 mL/kg) may be used, provided the V_T 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 tidal volume (V_T).

2. V_T goal = 6 mL/kg PBW.

3. Measure and record inspiratory plateau pressure (P_{plat}) according to intensive care unit (ICU) routine (at least every 4 hours and after changes in V_T and positive end expiratory pressure [PEEP] recommended).

4. If P_{plat} greater than 30 cm H_2O, reduce V_T to 5 mL/kg and then to 4 mL/kg PBW if necessary to decrease P_{plat} to less than or equal to 30.

5. If V_T less than 6 mL/kg PBW and P_{plat} less than 25, raise V_T 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 V_T to 7 or 8 mL/kg PBW if P_{plat} remains below 30. If P_{plat} exceeds 30 on 7 or 8 mL/kg PBW, then revert to lower V_T and consider more sedation.

7. If pH less than 7.15, V_T may be raised and P_{plat} limit suspended (not required).

8. Oxygenation target: PaO_2 = 55-80 mmHg 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 (Table 1) represents a consensus approach

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

developed by investigators in 1995. The higher PEEP/lower FiO_2 table (Table 2) yielded equivalent results in a randomised trial (Brower, 2003) and would be acceptable and perhaps 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 the following weaning readiness criteria each day between 06:00 and 10:00. If a patient procedure, test, or other extenuating circumstance prevents assessment for these criteria between 06:00 and 10:00, 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).

[redacted]

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

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 (= 5 microgram/kg/min dopamine or doubutamine will not be considered a vasopressor).

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. Continuous positive airway pressure (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 measured.

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

   - Heart rate greater than or equal to 120% of the 06:00 rate (less than or equal to 5 min at greater than 120% may be tolerated).
   - Marked use of accessory muscles.
   - Abdominal paradox.
   - Diaphoresis.
   - 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 PEEP and FiO_2 = previous settings and reassess

[redacted]

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.

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 to 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.

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

Clinical Study Protocol: Appendix I

Drug Substance	AZD9773
Study Code	D0620C00005
Appendix Edition Number	2
Appendix Date	[redacted]

Appendix I
Recommendations for Immunosuppressive Agents

[redacted]

1. RECOMMENDATIONS FOR IMMUNOSUPPRESSIVE AGENTS

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

Immunosuppressive Agent[a]	Upper limit dosage use
1. Corticosteroid	• If for 7 days within 8 weeks prior to screening, 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 hydrocortisone, will be an allowed exception to this restriction. Steroids, other than hydrocortisone, with greater anti-inflammatory effects (such as predisone or equivalent) are not the preferred steroid preparation for adrenal replacement therapy in this study.** **Once on study drug, >40 mg or >0.5 mg/kg prednisone or a steroid with equivalent activity for ≥2 days is prohibited. See below for the equivalent dose of steroids compared to prednisone.**
Equivalent Dose	
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)	Acceptable if being used as monotherapy.
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.

[redacted]

Immunosuppressive Agent[a]	Upper limit dosage use
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.
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 – Entanercept (Enbrel) – Adalimumab (Humira) – Infliximab (Remicade)	Patients receiving anti-TNF agents within the last 8 weeks are excluded.
(b) Interleukin-1 Receptor Antagonist (IL-1 RA) (Kineret)	Patients receiving IL-1 RA within the last 8 weeks are excluded.

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

Immunosuppressive Agent[a]		Upper limit dosage use
(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 of ATG)	
(d)	**Anti-CD52**	
	– Alemtuzumab (Campath)	Patients receiving this drug within the last 2 years are excluded.
	– Alefacept (AMEVIVE)	Patients receiving this drug in the last 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.

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

Clinical Study Protocol: Supplement A

Drug Substance	AZD9773
Study Code	D0620C00005
Supplement Edition Number	2.0
Supplement Date	[redacted]

Supplement A
Investigators and Study Administrative Structure

[redacted]

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

STAFF AT STUDY SITES

Centre No.	Centre address	Name (First name, Last name)	Qualifications	Present position	Role in the study
[redacted]			M.D.	Associate professor of Department of Traumatology and Critical care medicine Intensive Care Unit	Principal investigator
			M.D.	Sub Director, Anesthesiologists	Principal investigator
			M.D.	Director,Critical Care and Emergency Center Iwate Medical University Hospital	Principal investigator
			M.D.	Director of Emergency and Critical Care Center	Principal investigator

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

Centre No.	Centre address	Name (First name, Last name)	Qualifications	Present position	Role in the study
[redacted]			M.D.	Professor, Specific Intensive Care Division	Principal investigator
			M.D.	Director of Emergency Diagnosis and Treatment Department	Principal investigator
			M.D.	Director of Critical Care Medical Centre	Principal investigator

[redacted]

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

Centre No.	Centre address	Name (First name, Last name)	Qualifications	Present position	Role in the study
[redacted]			M.D.	Director of Emergency and Critical Care Medicine	Principal investigator

[redacted]

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

PAREXEL AND ASTRAZENECA STUDY PERSONNEL

Address	Name (First name, Last name)	Qualifications	Present Position	Role in the study
[redacted]			Clinical Lead Clinical Development	Monitor
			Senior CRA Clinical Development	Monitor
			Clinical Development	Monitor

[redacted]

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

Address	Name (First name, Last name)	Qualifications	Present Position	Role in the study
[redacted]			Clinical Development	Monitor
			Clinical Development	Monitor
			Clinical Development	Monitor
		M.D.	Associate project leader	Medical monitor: Japan

[redacted]

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

Address	Name (First name, Last name)	Qualifications	Present Position	Role in the study
[redacted]		M.D.	Senior Medical Director	Medical monitor: Global
		M.D.	Medical Director	Medical monitor: Global
		BSc	**Senior Biostatistician**	**Biostatistician**
		BSc	Senior Clinical Data Analyst	Data Management

[redacted]

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

Address	Name (First name, Last name)	Qualifications	Present Position	Role in the study
[redacted]			Project Leader Clinical Development	Study responsible in AstraZeneca KK
		M.D., MHS	Senior Medical Director Cytofab CPT Physician	Global Project Physician
			Senior Medical Director	Japan Project Physician
			Early Phase Development	PK analysis
			Patient Safety Department	Collection of SAE reports

[redacted]

Address	Name (First name, Last name)	Qualifications	Present Position	Role in the study
[redacted]			Patient Safety Department	Collection of SAE reports
			Compliance Advice & Assurance Department	Auditor
			Compliance Advice & Assurance Department	Auditor
			Compliance Advice & Assurance Department	Auditor
			Compliance Advice & Assurance Department	Auditor

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

[redacted]

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

Address	Name (First name, Last name)	Qualifications	Present Position	Role in the study
[redacted]			Compliance Advice & Assurance Department	Auditor
			Compliance Advice & Assurance Department	Auditor
			Compliance Advice & Assurance Department	Auditor
			Compliance Advice & Assurance Department	Auditor

[redacted]

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

SAFETY REVIEW COMMITTEE

Committee name and address	Member name (First name, Last name)	Present Position	Role in committee
Safety review Committee	[redacted]	Senior Medical Director Cytofab CPT Physician	Global Project Physician Member
		Senior Statistician	Member
		Global Drug Safety Physician	Member
		Senior Director of Clinical Research	Member

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

Committee name and address	**Member name** (First name, Last name)	**Present Position**	**Role in committee**
	[redacted]	Professor Emeritus	Member
		Senior Medical Director	Japan Project Physician Member

[redacted]

THIS IS A PRINTED COPY OF AN ELECTRONIC DOCUMENT. PLEASE CHECK ITS VALIDITY BEFORE USE.

OTHER PARTICIPANTS

Organisation and address	Role in study
[redacted]	Clinical Coordinating Centre
	Randomisation system
	Central laboratory for electrocardiograms
	Central laboratory handling samples for centralised laboratory analyses

[redacted]