Clinical Study Protocol

A RANDOMIZED, PHASE 1, PLACEBO-CONTROLLED, DOUBLE-BLIND, SINGLE-DOSE STUDY TO EVALUATE THE SAFETY, TOLERABILITY AND PHARMACOKINETICS OF SUBCUTANEOUSLY AND INTRAVENOUSLY DELIVERED ANIFROLUMAB IN HEALTHY SUBJECTS

PAREXEL Study No.:	
Sponsor Study Code:	
IND No.:	
Study Type:	PK Study
Test Product:	Anifrolumab
Therapeutic Indication:	Systemic Lupus Erythematosus, Lupus Nephritis
Pharmacological Class:	Human immunoglobulin G1 kappa (IgG1κ) monoclonal antibody (mAb)
Development Phase:	Phase 1
Sponsor:	AstraZeneca AB 151 85 Södertälje Sweden
Study Center:	PAREXEL Early Phase Clinical Unit Baltimore

Date of Protocol:	Final 1.0, 08 October 2015
Protocol Amendment No. 1	Final 1.0, 05 January 2016

This clinical study will be conducted according to the protocol and in compliance with Good Clinical Practice, with the most current version of the Declaration of Helsinki and with other applicable regulatory requirements.

PROTOCOL AMENDMENTS

Protocol Amendment No. 1, dated 05 January 2016

The following changes were made to the Final 1.0 version of the clinical study protocol, dated 08 October 2015.

- Corrected a footnote formatting error in the Schedule of Assessments (Table 1).
- Clarified that for Cohort 2 only, a blood sample for anifrolumab will be collected 5 minutes after the completion of the intravenous (IV) infusion (including the saline flush) in the Schedule of Assessments (Table 1).
- Updated Section 5.5, Previous Clinical Experience, with an anifrolumab study.
- Clarified what is meant by clinical laboratory assessments in the Schedule of Assessments (Table 1) and in Section 7.5.6, Total Blood Volume (Table 2)
- Added viral serology to the IV dosing section of Section 7.5.6, Total Blood Volume (Table 2) and adjusted the blood volume total.
- Adjusted Volumes per sampling, Numbers and Total columns in Section 7.5.6, Total Blood Volume (Table 2) (both SC and IV dosing).
- Corrected language replacing “pain” with “itching” in Section 9.3.2, Local injection site pruritus.
- Clarified the restriction period for blood or plasma/serum donation in Section 7.4, Restrictions During the Study.
- Clarified reproductive restrictions in Section 7.4, Restrictions During the Study.
- Corrected where samples retained for further use will be registered in Section 9.4.3, Chain of custody of biological samples.
- Clarified in Section 11.9.2, Derivation of pharmacokinetic data, that for Cohort 3 subjects, actual administered dose after correction for amount left over in the dosing equipment may be used for PK analyses.
- Corrected typographical errors and inconsistencies.

PROTOCOL SYNOPSIS

Title of the study
A RANDOMIZED, PHASE 1, PLACEBO-CONTROLLED, DOUBLE-BLIND, SINGLE-DOSE STUDY TO EVALUATE THE SAFETY, TOLERABILITY AND PHARMACOKINETICS OF SUBCUTANEOUSLY AND INTRAVENOUSLY DELIVERED ANIFROLUMAB IN HEALTHY SUBJECTS

Principal Investigator (PI)
Dr. Ronald Goldwater

Study center
This study will be conducted at a single study center.

PAREXEL Early Phase Clinical Unit Baltimore

Study rationale
This study will be conducted to evaluate the safety, tolerability and pharmacokinetics (PK) of delivering 2 doses of anifrolumab via the subcutaneous (SC) route of administration (ROA) and 1 dose of anifrolumab via intravenous (IV) route in healthy subjects. Developing a SC ROA for anifrolumab will provide patients more flexibility in their dosing options and may improve accessibility and compliance. Inclusion of an IV arm will allow for a comparison of the PK in healthy subjects with subjects with systemic lupus erythematosus (SLE), in whom SC doses of anifrolumab have never been tested before.

Number of subjects planned
Thirty subjects will be randomized in 3 cohorts of 10 subjects.

- Cohort 1: The first 10 subjects will be randomized to receive a single dose of either anifrolumab 300 mg or placebo (6 subjects anifrolumab 300 mg and 4 subjects placebo; delivered as 2 separate 1 mL SC injections administered serially).
- Cohort 2: The following 10 subjects will be randomized to receive a single dose of either anifrolumab 300 mg or placebo (6 subjects anifrolumab 300 mg and 4 subjects placebo; delivered as an IV infusion over 30 minutes).
- Cohort 3: After $\geq$ 6 subjects in Cohort 1 have been observed on the study for one week and the PI has deemed an acceptable safety profile, 10 subjects will be randomized to receive a single dose of either anifrolumab 600 mg or placebo (6 subjects anifrolumab 600 mg and 4 subjects placebo; delivered as 4 mL SC by infusion pump).

Study period

Estimated date of first subject enrolled:	November 2015 (signing of informed consent)
Estimated date of last subject completed:	April 2016

Study objectives
Primary objectives:

- To evaluate the PK of a single administration of 2 doses of subcutaneously and 1 dose of intravenously dosed anifrolumab in healthy subjects.
- To evaluate the safety and tolerability of subcutaneously and intravenously dosed anifrolumab in healthy subjects.

Secondary objectives:

- To evaluate the immunogenicity of subcutaneously and intravenously dosed anifrolumab in healthy subjects.

Study design

This study will be a Phase 1, single-center, double-blind, randomized, placebo-controlled study to evaluate the safety, tolerability and PK of 2 dose levels of SC administered and 1 dose level of IV administered anifrolumab in healthy subjects.

The study will comprise:

- A screening period of maximum 28 days;
- One treatment period during which subjects will be resident prior to the evening meal the night before dosing with anifrolumab or placebo (Day -1) until at least 48 hours after dosing; discharged on the morning of Day 3;
- Follow-up visits on Days 5, 8, 11, 15, 22, 29, 42 and 57 with a final visit on Day 85.

Subjects will receive a single dose of anifrolumab or placebo on 1 occasion.

Expected duration of the study

Each subject will be involved in the study for approximately 16 weeks.

Targeted study population

This study will be conducted in male and female subjects, 18 to 55 years of age.

Investigational medicinal products

IMP:	Anifrolumab	Placebo
Supplier:	AstraZeneca	AstraZeneca
Formulation:	Concentration for solution for SC injection or IV infusion	Concentration for solution for SC injection or IV infusion
Strength/concentration:	150 mg/mL	Not applicable
Dose:	300 mg or 600 mg	Not applicable
Route of administration:	SC (abdomen[a]) or IV	SC (abdomen[a]) or IV
Specific device for drug administration, if applicable:	For Cohort 1 (300 mg): 27G ½" needle For Cohort 2(300 mg): Latex-free IV infusion bags of normal 0.9% saline (100 mL size). Infusion lines should contain a low protein-binding 0.2 µm or 0.22 µm in-line filter For Cohort 3 (600 mg): Syringe pump	For Cohort 1 (300 mg): 27G ½" needle For Cohort 2(300 mg): Latex-free IV infusion bags of normal 0.9% saline (100 mL size). Infusion lines should contain a low protein-binding 0.2 µm or 0.22 µm in-line filter. For Cohort 3 (600 mg): Syringe pump
Regimen:	Single-dose	Single-dose
Special handling requirements:	The total in-use storage time from needle puncture for dose preparation to start of administration should not exceed 4 hours at room temperature or 24 hours at 2°C to 8°C (36°F to 46°F).	The total in-use storage time from needle puncture for dose preparation to start of administration should not exceed 4 hours at room temperature or 24 hours at 2°C to 8°C (36°F to 46°F).
Availability of the IMP:	IMP will be shipped after regulatory approval	NA

IMP = Investigational medicinal product; SC = Subcutaneous; IV = intravenous; mg = milligrams; mL = milliliters

[a] Avoid 5 cm radius around umbilicus

Outcome endpoints

Pharmacokinetic endpoints:

Where possible, the following PK parameters will be assessed for anifrolumab using serum concentrations.

- Primary PK parameters: C_{max}, $AUC_{(0\text{-}last)}$, AUC_{inf}
- Secondary PK parameters: t_{max}, λ_z, CL/F*, CL, V_z V_z/F* (*SC only)

Additional PK parameters may be determined where appropriate.

Safety and tolerability endpoints:

Safety and tolerability variables will include:

- Local injection site pain assessment (Visual Analog Scale [VAS]) (SC dosing only)
- Local injection site pruritus assessment (VAS) (SC dosing only)
- Local injection site reaction assessment (including erythema and induration) (SC dosing only)
- Adverse events (AEs)
- Vital signs (systolic and diastolic blood pressure [BP], pulse rate and oral temperature)
- 12-lead electrocardiograms (ECGs)
- Physical examination
- Laboratory assessments (hematology, clinical chemistry and urinalysis)

Viral serology, urine drugs of abuse and serum alcohol will be assessed for eligibility. Follicle-stimulating hormone (FSH) (post-menopausal females only), pregnancy testing (females of childbearing potential only), Pap smear results (females only, if needed) and use of concomitant medication will also be assessed and reported.

Immunogenicity endpoints:

Immunogenicity will be assessed by the measurement of anti-drug antibody (ADA).

Statistical methods

Presentation and analysis of pharmacokinetic data:

A listing of PK blood sample collection times, as well as derived sampling time deviations will be provided. Serum concentrations and PK parameters of anifrolumab will be summarized by treatment (dose level of anifrolumab) using descriptive statistics. Where possible, the following descriptive statistics will be presented: n, geometric mean, geometric CV, arithmetic mean, arithmetic SD, arithmetic CV, median, minimum and maximum. For t_{max}, only n, median, minimum and maximum will be presented.

Data from subjects excluded from the PK analysis set will be included in the data listings, but not in the descriptive statistics.

Individual serum concentrations versus actual time will be plotted in linear and semi logarithmic scale with separate plots for each subject. Combined individual serum concentration versus actual times will be plotted in linear and semi logarithmic scale. Plots will be grouped by dose level of anifrolumab and ROA.

Arithmetic mean serum concentration (± SD) versus nominal sampling time will be plotted in linear and semi logarithmic (no SD presented) scale with each dose level of anifrolumab and ROA overlaid on the same figure.

Scatter plots showing the individual PK parameters and geometric mean versus dose level/ROA will be presented for C_{max} and AUC.

Presentation and analysis of safety and eligibility data:

Subject disposition will be listed and summarized include the number of withdrawals and the primary reason for withdrawal. Subjects excluded from any analysis sets will be listed including the reasons for exclusions.

All safety data will be listed for each subject and summarized appropriately. Adverse events will be coded using MedDRA and summarized by system organ class and preferred term. Additional summaries by severity and causality will be presented.

All clinical safety laboratory data, vital signs measurements and ECGs will be listed and summarized including changes from baseline where appropriate. Any out of range laboratory measurements will be flagged in the listings.

The results of the assessment of local injection site reactions will be listed and summarized by treatment as appropriate.

Presentation and analysis of immunogenicity data:

The results of the ADA assessments will be listed for each subject and time point. This will include the classification of the response (positive/negative) and the measured titers where appropriate. Summary tables will be presented, by treatment (dose of anifrolumab/ROA or pooled placebo), for the number and percentage of subjects with positive/negative results at each time point, based on the safety analysis set.

In addition, the ADA titers (n, median, minimum and maximum) will be summarized by treatment (dose of anifrolumab/ROA or pooled placebo) for all subjects with a positive confirmatory assay at each time point; this tabulation will include a summary of the highest titer across all time points for each subject.

Determination of sample size

The sample size is not based on statistical considerations. With a sample size of 6 subjects treated with active treatment there is 80% probability to observe at least one event of an adverse event (AE) that occurs with an incidence of 24% in the studied population.

1. TABLE OF CONTENTS

1.1. List of Tables

1.2. List of Figures

2. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation or special term	Explanation
ADA	Anti-drug antibody
AE	Adverse event (see definition in Section 12.1.1)
AESI	Adverse event of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANOVA	Analysis of variance
AST	Aspartate aminotransferase
AUC_{inf}	Area under serum concentration-time curve from time zero extrapolated to infinity
$AUC_{(0\text{-}last)}$	Area under the serum concentration-curve from time zero to time of last quantifiable concentration
beta-hCG	Beta human chorionic gonadotropin
BLQ	Below the limit of quantification
BMI	Body mass index
BP	Blood pressure
bpm	Beats per minute
CI	Confidence interval
CL	Systemic clearance for parent drug estimated as dose divided by AUC
C_{last}	Drug concentration at last observed time point
CL/F	Apparent total body clearance after extravascular administration estimated as dose divided by AUC
	PAREXEL's electronic source data capturing and information management system
C_{max}	Observed maximum serum concentration
CRF	Case report form
CRO	Contract research organization
CRP	C-reactive protein
CSR	Clinical study report
C-SSRS	Columbia-Suicide Severity Rating Scale
CV	Coefficient of variation
DAE	Adverse event leading to the discontinuation of IMP
DCF	Data clarification form

Abbreviation or special term	Explanation
DES	Data Entry Site – where serious adverse event reports from AstraZeneca Clinical studies are entered onto the AstraZeneca Patient Safety database by Tata Consultancy Services
dECG	Digital electrocardiogram
DMP	Data management plan
DNA	Deoxyribonucleic acid
DVS	Data validation specification
ECG	Electrocardiogram User-interactive, modular computer-based system for dECG data processing, analysis and measurement of ECG intervals and wave amplitudes, exports and reports, used by the AstraZeneca ECG Centre
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	Gamma glutamyl transpeptidase (transferase)
GI	Gastrointestinal
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GRand	Global randomization system
Hb	Hemoglobin
HBsAg	Hepatitis B surface antigen
HCT	Hematocrit
HIV	Human immunodeficiency virus
IATA	International Airline Transportation Association
ICD	Informed Consent Document
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IFN	Interferon
IFNAR	Type I interferon receptor
IFNAR1	Subunit 1 of the type I interferon receptor
IgG1κ	Immunoglobulin G1 kappa
IGRA	Interferon Gamma Release Assay

Abbreviation or special term	Explanation
INR	International normalized ratio
IMP	Investigational medicinal product
IRB	Institutional Review Board
ISRB	Investigational Medicines Safety Review Board
kel	Elimination rate constant
λ_z	Terminal elimination rate constant
LC-MS/MS	Liquid chromatography with tandem mass spectrometry
LLN	Lower limit of normal
LLOQ	Lower limit of quantification
mAb	Monoclonal antibody
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MDT	Mean dissolution time
MedDRA	Medical Dictionary for Regulatory Activities
n	Number of subjects
NIMP	Non-investigational medical products
NA	Not applicable
ND	Not determined
NOAEL	No-observed-adverse-effect-level
NR	No result
OAE	Other significant adverse events
OTC	Over-the-counter
$\%AUC_{extr}$	Percentage of AUC obtained by extrapolating the area under the serum concentration-time curve to infinity from the time of the last quantifiable concentration using λ_z
PD	Pharmacodynamics
PDF	Portable Document Format
PDS	Protocol deviation specification (document)
PHL	Potential Hy's Law
PI	Principal Investigator
PK	Pharmacokinetics
PR(PQ)	ECG interval measured from the onset of the P wave to the onset of the QRS complex
QP	Qualified Person

Abbreviation or special term	Explanation
QRS	ECG interval measured from the onset of the QRS complex to the J point
QT	ECG interval measured from the onset of the QRS complex to the end of the T wave
QTcB	QT interval corrected for heart rate using Bazett's formula
QTcF	QT interval corrected for heart rate using Fridericia's formula
R&D	Research and Development
RBC	Red blood cell
ROA	Route of administration
RR	The time between corresponding points on 2 consecutive R waves on ECG
Rsq_adj	Regression coefficient adjusted for λ_z, N, Goodness of fit statistic for calculation of λ_z
SAE	Serious adverse event (see definition in Section 12.1.2).
SAP	Statistical Analysis Plan
SD	Standard deviation
SLE	Systemic lupus erythematosus
SOC	System Organ Class
SOP	Standard operating procedure
SRC	Safety Review Committee
SSc	Systemic Sclerosis
SUSAR	Suspected unexpected serious adverse reaction
TB	Tuberculosis
TCA	Tricyclic anti-depressant
TCS	Tata Consultancy Services – an AstraZeneca partner who conduct data entry into the safety database, Sapphire
TEAE	Treatment-emergent adverse event
t_{last}	Time of last quantifiable serum concentration
t_{max}	Time to reach maximum serum concentration
TSH	Thyroid-stimulating hormone
UK	United Kingdom
ULN	Upper limit of normal
USA	United States of America
V_z	Apparent volume of distribution during the terminal phase after intravenous administration

Abbreviation or special term	Explanation
Vz/F	Apparent volume of distribution during the terminal phase after extravascular administration
WAD	Windows Allowance Document
WBC	White blood cell

3. ETHICAL AND REGULATORY REQUIREMENTS

3.1. 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), Good Clinical Practice (GCP) and the AstraZeneca policy on Bioethics and Human Biological Samples.

3.2. Subject Data Protection

The Informed Consent Document (ICD) will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation.

All clinical study findings and documents will be regarded as confidential. The investigator and members of his/her research team must not disclose such information without prior written approval from the sponsor.

The anonymity of participating subjects must be maintained. Subjects will be specified in outputs and other documents containing subject data by their subject number, not by name. Documents that identify the subject (e.g., signed ICD) will be maintained in confidence by the investigator.

Study data will be stored in accordance with local and global data protection laws.

3.3. Ethics and Regulatory Review

The study will be submitted to the national regulatory agency for review and approval, by PAREXEL in accordance with local regulatory procedures.

The study will be submitted to the Independent Ethics Committee (IEC)/Institutional Review Board (IRB) for ethical review and approval, by PAREXEL in accordance with local procedures.

All safety update reports will be prepared by AstraZeneca.

PAREXEL will provide the IEC/IRB, and if applicable the Principal Investigator (PI), with safety updates/reports according to local requirements, and will track compliance information for the latter according to the tracker provided in the agreed Safety Reporting and Management Process.

AstraZeneca will provide the national regulatory authority with safety updates and/or reports, in accordance with local requirements, including suspected unexpected serious adverse reactions (SUSARs), where relevant. The PI will provide the IEC/IRB with reports of any serious and unexpected adverse drug reactions from any other study conducted with the investigational medicinal product (IMP). AstraZeneca will provide this information to the PI to meet these reporting requirements.

Compensation will be reasonable and related to the nature and degree of inconvenience and discomfort as a result of participation in the study. Information on how participants will be compensated is contained in the ICD.

3.4. Insurance

The sponsor has covered this clinical study by means of an insurance of the clinical study according to national requirements. The name and address of the relevant insurance company, the certificate of insurance, the policy number and the sum insured are provided in the Investigator's Site File.

3.5. Informed Consent

The subjects shall be informed of the nature, significance, implications and risks of the trial, and informed consent will be freely given and evidenced in writing, dated and signed, or otherwise marked, by the subject as evidence to indicate his/her free informed consent, prior to the start of the study.

In conformance with the law, the nature of the informed consent will comply with the appropriate version of the Declaration of Helsinki, the current requirements of GCP (CPMP/ICH/135/95) and local regulation which ever affords the greater subject protection.

3.6. Changes to the Protocol and Informed Consent Document

Study procedures will not be changed without the mutual agreement of the investigator and AstraZeneca.

If there are any substantial changes to the study protocol, then these changes will be documented in a study protocol amendment and where required in a new version of the study protocol. The amendment should be approved by the IEC/IRB and the national regulatory authority, before implementation, as appropriate. Local requirements should be followed for revised protocols.

If a protocol amendment requires a change to the ICD, the IEC/IRB should approve the revised ICD before the revised form is used.

If local regulations require, any administrative change will be communicated to or approved by the IEC/IRB.

4. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

Sponsor:	AstraZeneca AB 151 85 Södertälje Sweden
Sponsor's Lead Physician:	Raj Tummala
Sponsor's Biostatistician:	Tomas Rouse
Sponsor's Pharmacologist:	Balaji Agoram
Principal Investigator (PI):	Ronald Goldwater, MD
Contract Research Organization (CRO):	PAREXEL Early Phase Clinical Unit Baltimore

Clinical Laboratory:	Harbor Hospital Laboratory
Analytical Laboratory:	MedImmune Nancy Lee
Adverse Event Reporting:	AstraZeneca Patient Safety Data Entry Site Tata Consultancy Services

A list and contact details of investigators and other key study team members are provided in the Project Plan in the electronic Investigator's Site File. A list of all participating investigators will be provided in the clinical study report (CSR).

5. INTRODUCTION

5.1. Background Information

Anifrolumab is a human immunoglobulin G1 kappa (IgG1κ) monoclonal antibody (mAb) directed against subunit 1 of the type I interferon receptor (IFNAR1). It is composed of 2 identical light chains and 2 identical heavy chains, with an overall molecular weight of approximately 148 kDa. Anifrolumab inhibits binding of type I interferon (IFN) to type I interferon receptor (IFNAR) and inhibits the biologic activity of all type I IFNs. It lacks any agonist activity and was specifically engineered to be devoid of complement-activating activity via C1q, which is multivalent for attachment to the complement fixation sites of immunoglobulin, for complement-dependent cytotoxicity (CDC). Anifrolumab is also engineered to be lacking in the binding activity via Fc gamma receptor I/IIA/IIB/IIIA (FcγRI, FcγRIIA, FcγRIIB and FcγRIIIA, respectively). Therefore, it does not mediate antibody-dependent cell-mediated cytotoxicity (ADCC). In spite of its Fc modification, anifrolumab retains the binding activity to Fc gamma neonatal receptor (FcRn) similar to a wild-type immunoglobulin G1 (IgG1) and, thus, maintains its physiological recycling by vascular endothelial cells. With the growing evidence that type I IFNs play an important role in autoimmune diseases such as systemic sclerosis (SSc), systemic lupus erythematosus (SLE) and myositis, inhibition of the biological activity of type I IFNs with anifrolumab may, therefore, be a novel therapy for the treatment of these diseases with significant unmet medical need.

Anifrolumab binds with high affinity to IFNAR1. Anifrolumab blocks the binding of type I IFN to the receptor and also induces receptor internalization. Anifrolumab binds equally well to both human and cynomolgus monkey IFNAR1 on peripheral blood mononuclear cells (PBMCs). In contrast, it does not inhibit the effect of mouse type I IFN. Therefore, cynomolgus monkey is the relevant model for pharmacokinetic (PK) and toxicology studies. Anifrolumab effectively inhibits the activating effects of recombinant type I IFNs on IFNAR1-bearing target cells. It blocks the induction of type I IFN-inducible gene expression by sera from patients with SLE. In an accelerated NZB/W F1 mouse model of lupus induced by overexpression of murine IFN-α-5a using adenoviral delivery, treatment with an anti-mouse surrogate, anti-IFNAR1 mAb 5A3 effectively protected mice from disease development and proteinuria as compared to isotype-matched control mAb. In a scleroderma model using RAG2/-2 mice, 5A3 reduced severity of dermal lesions, collagen deposition, inflammation and epithelial remodeling. The 5A3 effectively inhibited the induction of type I IFN gene signatures (IFNGSs) in both models.

5.2. Clinical Pharmacokinetics

In Study MI-CP180 (single and multiple intravenous [IV] dose safety study), the PK parameters were estimated by non-compartmental analysis. In the single-dose administration, anifrolumab exhibited nonlinear PK at lower dose levels (< 10.0 mg/kg). A dose-proportional increase in C_{max} was observed, but an increase in AUC was more than dose-proportional between 0.1- and 10.0-mg/kg. However, AUC increased dose proportionally between 10.0-and 20.0-mg/kg single dose. Systemic clearance decreased from 40.8 to 4.68 mL/kg/day when the dose was increased from 0.1- to 20.0-mg/kg, which was attributed to receptor-mediated clearance by IFNAR1. Anifrolumab $t_{½}$ was more prolonged in higher dose cohorts. At the highest dose level investigated (20.0-mg/kg), the $t_{½}$ was approximately 12 days. In the multiple-dose administration (4 doses administered weekly), anifrolumab exposures increased more than dose proportionally between the 0.3- and 1.0-mg/kg multiple dose cohorts, and anifrolumab exposures increased dose proportionally between the 1.0- and 5.0-mg/kg multiple dose cohorts. The PK nonlinearity between 0.3- and 1.0-mg/kg is likely due to the antigen-sink effect (target receptor-mediated clearance) .

5.3. Study Rationale

The purpose of this study is to evaluate the safety, tolerability and PK of delivering 2 doses of anifrolumab via the subcutaneous (SC) route of administration (ROA) and 1 dose of anifrolumab via IV route in healthy subjects. One of the doses to be studied is a large volume SC injection, to obtain early information on the feasibility of developing a large volume SC device for the anifrolumab program that could support less frequent administration. Developing a SC ROA for anifrolumab will provide patients more flexibility in their dosing options and may improve accessibility and compliance. Inclusion of an IV arm will allow for a comparison of the PK in healthy subjects with subjects with SLE, in whom SC doses of anifrolumab have never been tested before.

5.4. Dose Rationale

The following doses have been selected for this study: 300 mg IV, 300 and 600 mg SC doses. In the phase 2 study of anifrolumab in patients with moderate to severe SLE, the 300 mg and 1000 mg doses met the primary endpoint of achieving a SLE responder index (SRI) 4 (SRI4) response and reduction of corticosteroid dose to ≤ 7.5 mg/day at day 169. These results were consistent across multiple measures of efficacy including British Isles Lupus Assessment Group (BILAG)-based Combined Lupus Assessment (BICLA) response, Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) in patients who had a CLASI score>10 at baseline, and reduction in flare rate. Although numbers were small, there were more patients who developed herpes zoster in the 1000 mg group than in the

300 mg group, therefore the 300 mg dose was selected as the preferred dose for further study. Although there is currently no PK data available in normal subjects, the PK of anifrolumab was similar in 2 different patient populations (SSc and SLE) and in several racial groups (Japanese subjects). The sponsor expects that the PK in normal subjects will be similar to PK data obtained previously.

Developing a SC dose is expected to offer flexibility in meeting patients' dosing needs. PKPD model-based simulations have indicated that doses of 150-300 mg SC administered every 2 weeks and 300-600 mg SC administered every 4 weeks will result in equivalent reduction in gene signature PD marker compared to the target dose of 300 mg IV. Based on these simulations, doses of 300 and 600 mg SC have been selected for PK evaluation in this study. A dose of 300 mg represents the highest feasible syringe injection dose and a dose of 600 mg represents a large volume injection.

5.5. Previous Clinical Experience

A phase 3 program with anifrolumab IV in patients with moderate to severe SLE was initiated 3Q2015. A phase 2 program with anifrolumab IV in patients with active proliferative Lupus Nephritis was initiated 4Q2015. The clinical experience from 4 prior MedImmune/AstraZeneca-sponsored clinical studies (Study MI-CP180, CD-IA-MEDI-546-1013, CD-IA-MEDI-546-1145, and) in adult subjects with SSc or SLE are summarized below:

- The first clinical study of anifrolumab was a Phase 1, multicenter, open-label, dose-escalation study to evaluate the safety and tolerability of single and multiple IV doses of anifrolumab in adult patients with SSc who had skin thickening in an area suitable for repeat biopsy (Study MI-CP180). A total of 34 patients were evaluated in the study: 21 patients received 1 of 6 single IV doses of anifrolumab (0.1, 0.3, 1.0, 3.0, 10.0, or 20.0 mg/kg), and 13 patients received 1 of 3 multiple IV doses of anifrolumab (0.3, 1.0, or 5.0 mg/kg/dose every week × 4 doses). The most common TEAEs in Study MI-CP180 (seen in more than 10% of patients) were upper respiratory tract infection (URTI), headache, diarrhea, nausea, arthralgia, fatigue and pruritus.

- A Phase 2, randomized, double-blind, placebo-controlled, parallel group study to evaluate the efficacy and safety of anifrolumab in adult patients with chronic, moderately-to-severely active SLE with an inadequate response to standard of care treatment for SLE (Study CD-IA-MEDI-546-1013) has been completed. Three hundred and seven patients were randomized in a 1:1:1 ratio to receive a fixed IV dose of anifrolumab (300 or 1000 mg) or placebo every 4 weeks (q4wks) for 48 weeks for a total of 13 doses. The most common TEAEs in study

CD-IA-MEDI-546-1013 (seen in more than 10% of patients) were headache, URTI, nasopharyngitis and urinary tract infection.

- A Phase 2, open-label extension (OLE) study to evaluate long-term safety of anifrolumab in adults with SLE is ongoing (Study CD-IA-MEDI-546-1145). All patients who completed Study CD-IA-MEDI-546-1013 and met the OLE study criteria were enrolled. The most common AEs in Study CD-IA-MEDI-546-1145 (seen in more than 5% of patients) have been nasopharyngitis and bronchitis.

- A Phase 2, multicenter, open-label, dose-escalation study to evaluate the safety and tolerability of anifrolumab in adult Japanese patients with active SLE ( ) is ongoing. Approximately 15 patients were planned to receive a fixed IV dose of anifrolumab (100-, 300-, or 1000-mg) q4wks for 48 weeks, for a total of 13 doses, followed by a fixed IV dose of anifrolumab (300 or 1000 mg) q4wks for 104 weeks for a total of 27 doses. The most common TEAEs in Study (seen in more than 20% of patients) (stages 1 and 2) have been nasopharyngitis, upper abdominal pain URTI, headache and SLE.

Important potential risks include serious viral and bacterial infections, including viral reactivation (particularly herpes zoster) and opportunistic infections, malignancies, infusion-related reactions, severe hypersensitivity reactions, including anaphylaxis and immune complex disease/vasculitis. Potential risks include drug-drug interactions and vaccine-drug interactions.

As with the administration of any immunoglobulin, hypersensitivity reactions and acute immunoglobulin E (IgE)-mediated allergic (anaphylaxis) reactions may occur, which may be severe and may result in death. Acute allergic reactions may include hypotension, dyspnea, cyanosis, respiratory failure, urticaria, pruritus, angioedema, hypotonia, and unresponsiveness. Acute severe allergic reactions (anaphylaxis) usually occur soon after exposure, usually within 10 minutes. Subjects may experience paresthesia, hypotension, facial, laryngeal or pharyngeal angioedema, mental status changes, flushing, urticaria, pruritus, gastrointestinal symptoms, airway obstruction, bronchospasm, and wheezing.

Although anifrolumab is a human mAb, there is still a chance that humans could develop anti-drug antibodies (ADAs). The occurrence of such ADAs can result in immune complex disease (with manifestations such as arthralgia, serum sickness, and vasculitis) or altered anifrolumab levels or pharmacologic activity/efficacy. Subjects will be monitored clinically for symptoms associated with immune reactivity and for the presence of such antibodies.

Anifrolumab has been administered IV in clinical studies conducted to date. Potential risks associated with IV administration of anifrolumab are infection, redness, swelling, pain, and induration at the administration site. These types of reactions have not been reported to date.

5.6. Risk-benefit Assessment

There are no direct benefits for the subjects participating in this study.

In study CD-IA-MEDI-546-1013, anifrolumab demonstrated a clinically relevant benefit in patients with moderate to severe SLE treated with standard-of-care. The efficacy was supported by a broad range of clinical measures of global (various levels of SRI responses, BICLA) and organ-specific disease activity (CLASI, joint count). A clinically relevant increase in the proportion of patients achieving pre-specified corticosteroid reduction in the 300-mg group was also observed compared with placebo.

Anifrolumab was generally well tolerated. The proportion of patients receiving anifrolumab and experiencing herpes zoster reactivation was greater compared to placebo. A dose-related increase in the proportion of patients with uncomplicated cutaneous herpes zoster infections was also observed in patients receiving anifrolumab (either 300 mg or 1000 mg). Uncomplicated herpes zoster is considered an identified risk.

To minimize this risk for the current healthy subject study, subjects with any severe herpes infection at any time prior to dosing, including, but not limited to, disseminated herpes (ever; greater than 3 dermatomes), herpes encephalitis (ever), recurrent herpes zoster (defined as 2 episodes within 2 years) or ophthalmic herpes (ever) or any herpes zoster infection that has not completely resolved within 12 weeks prior to screening will be excluded from the study.

To date, in clinical trials of IV administration of anifrolumab, hypersensitivity events or anaphylaxis/anaphylactoid events have not occurred more frequently in patients who were treated with anifrolumab as compared to placebo, although careful monitoring for such events will continue.

Although arteritis was detected in the monkey toxicology studies, to date no signal for an increased risk of vasculitis or arteritis has been detected in human clinical studies, although this continues to be followed as an adverse event (AE) of special interest (AESI).

The administration of any foreign protein may be associated with acute allergic reactions that may be severe and may result in death. Acute allergic reactions may include hypotension, dyspnea, cyanosis, respiratory failure, urticaria, pruritus, angioedema, hypotonia and unresponsiveness. Reports of infusion-related reactions from clinical trials conducted to date

suggest that the frequency, severity and characteristics of these reactions are similar across all treatment groups.

The current study with SC administration in healthy subjects will be conducted in an experienced clinical pharmacology unit with trained staff and adequate equipment to handle any hypersensitivity events. Although there is no potential benefit for healthy subjects to receive anifrolumab, the overall safety and tolerability profile of anifrolumab support administration of a single dose to normal subjects for the purposes of assessing safety, tolerability and PK.

Although anifrolumab is a human monoclonal antibody, there is still a chance that humans could develop anti-anifrolumab antibodies. The occurrence of such ADAs can result in acute or delayed hypersensitivity reactions, including anaphylaxis or immune complex disease (with manifestations such as arthralgia, serum sickness and vasculitis) or altered anifrolumab levels or pharmacologic activity/efficacy.

In order to minimize the risk of treatment with anifrolumab, subjects with risk factors for serious infection, malignancy, or immune deficiency disorders are specifically excluded from participation in this study.

Additionally, serious infections, including non-opportunistic serious infections, opportunistic infections, anaphylaxis, malignancy, herpes zoster, tuberculosis (TB) (including latent TB), influenza vasculitis (non-SLE) and major adverse cardiovascular events (MACE) (including myocardial infarction [MI], stroke, acute coronary syndrome, or cardiovascular death) are designated as AESIs in this study.

In conclusion, AstraZeneca believes that the available nonclinical and clinical data indicate an acceptable safety profile for anifrolumab. The proposed dosing regimens for Protocol are adequately justified and the management plan for potential risks associated with anifrolumab is appropriate. The emerging safety profile has not identified any risks that would preclude continued investigation of anifrolumab. AstraZeneca believes that anifrolumab continues to demonstrate an overall positive benefit-risk balance to support its further clinical evaluation.

AstraZeneca will immediately notify the investigator of important safety data that becomes available during the study.

6. STUDY OBJECTIVES

6.1. Primary Objectives

- To evaluate the PK of a single administration of 2 doses of subcutaneously and 1 dose of intravenously dosed anifrolumab in healthy subjects.
- To evaluate the safety and tolerability of subcutaneously and intravenously dosed anifrolumab in healthy subjects.

6.2. Secondary Objective

- To evaluate the immunogenicity of subcutaneously and intravenously dosed anifrolumab in healthy subjects.

Refer to Section 11.9.1 for PK parameters and Section 9.3 for safety variables.

7. OVERALL DESIGN AND PLAN OF THE STUDY

7.1. Overall Study Design

This study will be a Phase 1, single-center, double-blind, randomized, placebo-controlled study to evaluate the safety, tolerability and PK of 2 dose levels of SC administered and 1 dose level of IV administered anifrolumab in healthy subjects.

The study will comprise:

- A screening period of maximum 28 days;
- One treatment period during which subjects will be resident prior to the evening meal the night before dosing with anifrolumab or placebo (Day -1) until at least 48 hours after dosing; discharged on the morning of Day 3;
- Follow-up visits on Days 5, 8, 11, 15, 22, 29, 42 and 57 with a final visit on Day 85.

7.1.1. End of study

The end of study is defined as the last subject's last visit to the clinical unit.

7.1.2. Interim analyses

No interim analyses will be performed in this study.

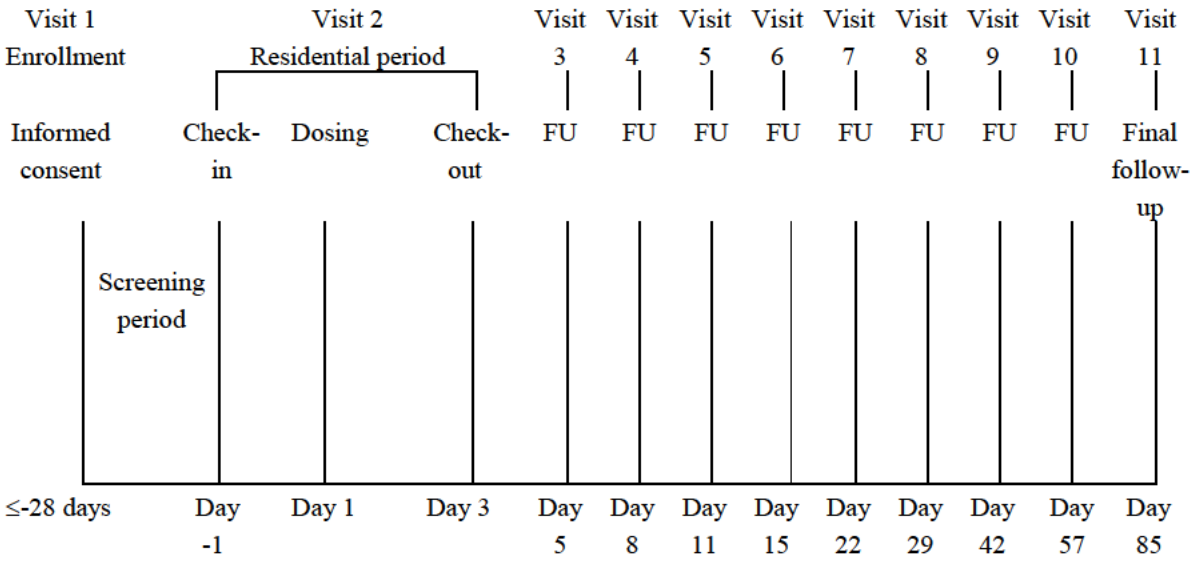
7.1.3. Expected duration of the study

Each subject will be involved in the study for approximately 16 weeks.

7.2. Study Flow Chart and Schedule of Assessments

The flow of events is illustrated in Figure 1 for all treatments, depending on the subject's assigned randomization (refer to Section 8.9.2).

Figure 1 Study Flow Chart



FU = Follow-up

The Schedule of Assessments displaying assessments/tasks and time points is presented in Table 1.

Table 1 Schedule of Assessments

Study Plan	Visit 1	Visits 2		Visits 3 to 10	Visit 11
	Screening	Day -1	Dosing Session Days 1 to 3	Follow-up visits[a]	Final Follow-up Visit (Day 85 ± 2 days)
Informed consent	X				
Inclusion/exclusion criteria	X	X			
Demographic data	X				
Weight, height, BMI	X	X (weight)			
Medical history	X				
Concomitant medication	X	X	X	X[a]	X
Urinary drug screen	X	X			
Viral Serology	X				
Pregnancy and FSH (females only)	X	X[b]			X[b]
Pap smear (females only)	X[c]				
IGRA (QuantiFERON-TB GOLD)	X				
Serum alcohol screen	X	X			
Randomization			X		
Study residency:					
Check-in		X			
Check-out			Day 3 (48h post-dose)		
Non-residential visit	X			X[a]	X
IMP administration:			Day 1 (0h)		
Pharmacokinetics:					
Blood samples for Anifrolumab			Pre-dose, at 5 minutes after end IV infusion[d] and at 24 and 48 hours post-dose	X[a]	X
Safety and tolerability:					
Local injection site pain (VAS) assessment[e]			Immediately after dosing, at 10, 20 and 30 minutes and at 1, 2, 4, 8, 24 and 48 hours after injection		
Local injection site pruritus (VAS) assessment[e]			Immediately after dosing, at 10, 20 and 30 minutes and at 1, 2, 4, 8, 24 and 48 hours after injection		

Study Plan	Visit 1	Visits 2		Visits 3 to 10	Visit 11
	Screening	Day -1	Dosing Session Days 1 to 3	Follow-up visits[a]	Final Follow-up Visit (Day 85 ± 2 days)
Local injection site reaction (erythema, induration) assessment[e]			Immediately after dosing, at 10, 20 and 30 minutes and at 1, 2, 4, 8, 24 and 48 hours after injection		
Adverse event questioning	Only SAEs	X	X	X[a]	X
Physical examination	X (full)	X (brief)			X (full)
Blood pressure, pulse rate and oral temperature	X	X	Pre-dose and at 48 hours post-dose	X	X
12-lead Safety ECG	X	X	Pre-dose and at 48 hours post-dose		X
Clinical laboratory assessments[h]	X	X		X[f]	X
Immunogenicity:					
ADA			Pre-dose	X[g]	X

[a] Days 5, 8, 11, 15, 22, 29, 42 and 57. The follow-up visits should all be performed at approximately the same time of day based off of Day 1 dosing (± 1 day for Days 5, 8, 11 and 15 and ± 2 days for Days 22, 29, 42 and 57).

[b] Pregnancy screen

[c] Pap smear allowed anytime during the screening period as long as result is back prior to randomization.

[d] For Cohort 2 only, a sample should be drawn 5 minutes after the completion of IV infusion (including the saline flush)

[e] Only in subjects who receive dose subcutaneously (Cohorts 1 and 3). Will be followed until event is resolved, if applicable.

[f] Day 29

[g] Days 5 and 29

[h] Includes hematology, serum clinical chemistry and urinalysis. See Section 9.3.8.

7.3. Order of Assessments

It is important that PK sampling occurs as close as possible to scheduled time. In order to achieve this, other assessments scheduled at the same time may be initiated prior to the time point.

The sequence at a particular time point is:

1. ECGs
2. Vital signs (systolic and diastolic blood pressure [BP], pulse rate, oral temperature)

3. PK blood sampling (will be drawn at the specified time point)
4. Immunogenicity sampling
5. Clinical laboratory assessments
6. Local injection site pain, pruritus and reaction assessments (SC dosing only)

7.4. Restrictions During the Study

The following restrictions apply for the specified times during the study period:

1. Subjects should not engage in any strenuous activity from 72 hours prior to dosing on Day 1 and prior to each visit until after their final follow-up visit.
2. Subjects should abstain from alcohol for 72 hours prior to admission and each visit. During the follow-up period, subjects should consume no more than 2 units of alcohol per day and should abstain from alcohol for 72 hours before their final follow-up visit.
3. During in-house stay, subjects will receive a standard diet, which excludes all alcohol and grapefruit-containing products. No additional food or beverages must be consumed whilst in the clinical unit.
4. During the subjects' outpatient periods, subjects should abstain from consuming high energy drinks (e.g.,), and food containing poppy seeds (e.g., specialty breads and muffins) and any over-the-counter (OTC) medication or herbal preparations until after their final follow-up visit has been completed.
5. Subjects will be required to abstain from blood or plasma/serum donation until after the final follow-up visit (Day 85).
6. Medication restrictions

Refer to Section 8.7.

7. Reproductive restrictions

   - Female subjects

     Women of childbearing potential must use 2 effective methods of avoiding pregnancy, one of which is a barrier method from screening until after the final follow-up visit (Day 85), unless the subject is surgically sterile (i.e., bilateral tubal ligation, bilateral oophorectomy, or complete hysterectomy), has a sterile male partner, is 1 year postmenopausal, or practices abstinence. Cessation of birth control after this period should be discussed with a responsible physician.

- Sustained abstinence is an acceptable practice; however, periodic abstinence, the rhythm method and the withdrawal method are not acceptable methods of contraception.
- Postmenopausal is defined as at least 12 months since last menses and the subject has an elevated follicle-stimulating hormone (FSH) level greater than the clinical laboratory value of post-menopausal at screening.

Methods of birth control:

- Barrier methods
  - Male condom plus spermicide*
  - Cap (with spermicide cream or jelly*)
  - Diaphragm (with spermicide cream or jelly*)

    *Where commercially available
- Intrauterine Device methods
  -
  -
- Hormonal methods
  - Implants
  - Hormone shot or injection
  - Combined pill
  - Minipill
  - Patch

- Male subjects
  - Nonsterilized males who are sexually active with a female partner of childbearing potential must use a condom with spermicide (where commercially available) from Day 1 until after the final follow-up visit (Day 85).

- Sperm donation

  Male subjects should not donate sperm for the duration of the study (Day 1 until after the final follow-up visit [Day 85]).

- Pregnancy

  Subjects will be instructed that if their partner becomes pregnant during the study, this should be reported to the investigator. The investigator should also be notified of pregnancy occurring during the study but confirmed after completion of the study. In the event that a subject's partner is subsequently found to be pregnant after the subject is included in the study, then consent will be sought from the partner and if granted any pregnancy will be followed and the status of mother and/or child will be reported to the sponsor after delivery.

  A pregnancy notification form and follow-up will be completed. Any SAE associated with the pregnancy, delivery or termination of the pregnancy will be reported as an SAE.

7.5. Selection of Study Population

The investigator should keep a subject screening log of all potential subjects who consented and were subjected to screening procedures.

Subjects who fail to meet the inclusion criteria or meet any exclusion criterion should not, under any circumstances, be randomized into the study. There can be no exceptions to this rule.

This study will be conducted in male and female subjects.

7.5.1. Inclusion criteria

For inclusion in the study, subjects should fulfill the following criteria:

1. Provision of signed and dated, written informed consent prior to any study specific procedures.
2. Healthy male and/or female subjects aged 18 – 55 years with suitable veins for cannulation or repeated venipuncture.
3. Females must have a negative pregnancy test at screening and on admission to the unit and must not be lactating.

   If of non-childbearing potential, it must be confirmed at screening by fulfilling 1 of the following criteria:

Post-menopausal defined as amenorrhea for at least 12 months or more following cessation of all exogenous hormonal treatments and FSH levels in the post-menopausal range as per the clinical laboratory for this study.

Documentation is needed for irreversible surgical sterilization by hysterectomy, bilateral oophorectomy, bilateral salpingectomy, bilateral tubal occlusion or bilateral tubal ligation.

4. Females with an intact cervix must have documentation of a Pap smear with no documented malignancy (e.g., cervical intraepithelial neoplasia grade III [CIN III], carcinoma in situ [CIS], or adenocarcinoma in situ [AIS]) within 2 years prior to Day 1) (see Appendix 15.4 for guidance on abnormal Pap smear results).
5. Have a body mass index (BMI) between 18 and 32 kg/m^2, inclusive, and weigh at least 50 kg.
6. Must have adequate abdominal adipose tissue for SC injection, as judged by the investigator.
7. No history of latent or active TB prior to screening.
8. No signs or symptoms suggestive of active TB from medical history or physical examination, including a negative IGRA test at screening.

   Note: If the IGRA result is reported as indeterminate, then the test can be repeated once. If the repeat test result is reported as indeterminate, then the subject will not be included in the study.
9. No recent contact with a person with active TB.
10. A chest radiograph with no evidence of current active infection (e.g., TB) or old active TB, malignancy, or clinically significant abnormalities obtained during the screening period or anytime within 6 months prior to screening.

7.5.2. Exclusion criteria

Subjects will not enter the study if any of the following exclusion criteria are fulfilled:

1. History of any clinically significant disease or disorder which, in the opinion of the Investigator, may either put the subject at risk because of participation in the study, or influence the results or the subject's ability to participate in the study.
2. History or presence of hepatic or renal disease, or any other condition known to interfere with absorption, distribution, metabolism, or excretion of drugs.

3. Any clinically significant illness, medical/surgical procedure, or trauma within 8 weeks of the first administration of IMP.
4. Any clinically significant chronic infection (i.e., osteomyelitis, bronchiectasis, etc.) within 8 weeks prior to screening (chronic fungal nail infections are allowed).
5. Any infection requiring hospitalization or treatment with IV anti-infectives not completed at least 4 weeks prior to screening.
6. Any infection requiring oral anti-infectives (including antivirals) within 2 weeks prior to Day 1.
7. History of cancer, apart from squamous or basal cell carcinoma of the skin treated with documented success of curative therapy ≥ 3 months prior to dosing.
8. Any clinically significant abnormalities in clinical chemistry, hematology, or urinalysis results at screening and Check-in, as judged by the investigator, including:
   - Aspartate aminotransferase (AST) > 1.0 × upper limit of normal (ULN);
   - Alanine aminotransferase (ALT) > 1.0 × ULN;
   - Total bilirubin > ULN (unless due to Gilbert' s syndrome);
   - Serum creatinine > ULN at clinical laboratory;
   - Neutrophil count < lower limit of normal (LLN);
   - Platelet count < LLN; and
   - Hemoglobin < LLN.

   Note: Abnormal screening laboratory tests may be repeated ONCE on a separate sample before subject is declared a screen failure.
9. Any clinically significant abnormal findings in vital signs at screening and Check-in, as judged by the investigator.
10. Any clinically significant abnormalities on 12-lead ECG at screening and Check-in, as judged by the investigator.
11. Known history of a primary immunodeficiency or an underlying condition such as human immunodeficiency virus (HIV) infection or splenectomy that predisposes the subject to infection.
12. Any positive result on screening for serum hepatitis B surface antigen (HBsAg), hepatitis B core total antibodies, hepatitis C antibody and HIV antibody.

13. Known or suspected history of drug abuse within 1 year of dosing, as judged by the investigator.
14. Any severe herpes infection at any time prior to dosing, including, but not limited to, disseminated herpes (ever), herpes encephalitis (ever), recurrent *herpes zoster* (defined as 2 episodes within 2 years) or ophthalmic herpes (ever).
15. Any *herpes zoster* infection that has not completely resolved within 12 weeks prior to screening.
16. Opportunistic infection requiring hospitalization or parenteral antimicrobial treatment within 3 years of randomization.
17. Has received another new chemical entity (defined as a compound which has not been approved for marketing) within 4 weeks or 5 half-lives of administration of IMP in this study.

    Note: Subjects consented and screened, but not randomized in this study or a previous phase I study, are not excluded.
18. Spontaneous or induced abortion, still or live birth, or pregnancy $\leq$ 4 weeks prior to screening (females only).
19. Plasma/serum donation within 1 month of screening or any blood donation/loss more than 500 mL during the 3 months prior to screening.
20. Previous receipt of:
    - Anifrolumab;
    - B cell-depleting therapy (including but not limited to epratuzumab, ocrelizumab, or rituximab) $\leq$ 52 weeks prior to screening.
21. History of severe allergy/hypersensitivity or ongoing allergy/hypersensitivity, as judged by the investigator or history of hypersensitivity to drugs with a similar chemical structure or class to anifrolumab or to any human gamma globulin therapy.
22. Any live or attenuated vaccine within 8 weeks prior to screening (administration of killed vaccines is acceptable, the Sponsor recommends investigator to ask if subjects are up-to-date on required vaccinations, including influenza [inactivated/recombinant] vaccine prior to study entry) (up-to-date vaccinations are recommended but not required for study participation).
23. Receipt of Bacillus Calmette-Guerin (BCG) vaccine within 1 year of screening.

24. Positive screen for drugs of abuse and positive screen for alcohol at screening and on admission to the study center.
25. Known or suspected history of alcohol or drug abuse or excessive intake of alcohol as judged by the investigator.
26. Use of any prescribed or non-prescribed medication including antacids, analgesics (other than paracetamol/acetaminophen), herbal remedies, megadose vitamins (intake of 20 to 600 times the recommended daily dose) and minerals during the 2 weeks prior to the administration of IMP or longer if the medication has a long half-life.

    Note: Hormonal replacement therapy is allowed for females.
27. Involvement of any AstraZeneca, PAREXEL or study site employee or their close relatives.
28. Judgment by the investigator that the subject should not participate in the study if they have any ongoing or recent (i.e., during the screening period) minor medical complaints that may interfere with the interpretation of study data or are considered unlikely to comply with study procedures, restrictions and requirements.
29. Vulnerable subjects, e.g., kept in detention, protected adults under guardianship, trusteeship, or committed to an institution by governmental or juridical order.
30. History of vasculitis.

7.5.3. Discontinuation of subject, individual stopping criteria and withdrawal from the study

Subjects may be discontinued from the study in the following situations:

- Healthy subject decision. The healthy subject is at any time free to discontinue treatment, without prejudice to further treatment.
- Adverse event.
- Severe noncompliance to study protocol.
- Any significant and clinically relevant changes in the safety parameters (e.g., AEs, BP, pulse, ECG and laboratory assessments) making continuation in the study unjustified.

7.5.4. Premature termination of the study and stopping criteria

The study may be terminated prematurely if:

- The PI and the sponsor assess that the number and/or severity of AEs justify discontinuation of the study. For instance when there is at least 1 case of fatal SAE or

2 cases of other SAEs, in both situations considered related to the IMP by the investigator and the sponsor.

- The sponsor decides to discontinue the study.
- Data not known before become available and raise concern about the safety of IMP so that continuation would pose potential risks to the subjects.
- Premature termination of the study must be mutually agreed upon by the PI and the sponsor and must be documented. However, study results will be reported according to the requirements outlined in this clinical study protocol as far as applicable.

7.5.5. Replacement of subjects

Subjects who are withdrawn from the study will be replaced if the sponsor's responsible physician and the PI agree it is safe to do so.

Where a subject, who does not meet the selection criteria, is randomized in error and this is identified before IMP administration, the subject should be withdrawn from the study. If a subject is withdrawn prior to IMP administration, the subject will be replaced.

If a subject, who does not meet the selection criteria, has been dosed before the error is identified, the subject should be advised to continue safety assessments to ensure their safety. The PI will inform the AstraZeneca Lead Physician of the error and a joint decision will be made as to whether the subject should be replaced.

7.5.6. Total blood volume

The approximate total amount of blood to be collected from each subject in this study, excluding repeat samples, is summarized in Table 2.

Table 2 Total Blood Volume

SC dosing	Volume per sampling	Number	Total
PK samples	4 mL	12	48 mL
ADA samples	4 mL	4	16 mL
Clinical Laboratory assessments*	6.5 mL	4	26 mL
Viral Serology	3.5 mL	1	3.5 mL
IGRA (QuantiFERON-TB GOLD)	3 mL	1	3 mL
Total			**96.5 mL**

PK = pharmacokinetic; ADA = anti-drug antibody; IGRA = Interferon Gamma Release Assay
*Includes hematology, serum clinical chemistry and urinalysis. See Section 9.3.8.

IV dosing	Volume per sampling	Number	Total
PK samples	4 mL	13	52 mL
ADA samples	4 mL	4	16 mL
Clinical Laboratory assessments*	6.5 mL	4	26 mL
Viral Serology	3.5 mL	1	3.5
IGRA (QuantiFERON-TB GOLD)	3 mL	1	3 mL
Total			**100.5 mL**

PK = pharmacokinetic; ADA = anti-drug antibody; IGRA = Interferon Gamma Release Assay
*Includes hematology, serum clinical chemistry and urinalysis. See Section 9.3.8.

Repeat blood samples may be collected for safety reasons. The maximum volume to be drawn from each subject must not exceed 500 mL.

8. TREATMENTS

8.1. Identity of the Investigational Medicinal Product

Details on the identity of the IMP are presented in Table 3.

Table 3 Identity of the Investigational Medicinal Product

IMP:	Anifrolumab	Placebo
Supplier:	AstraZeneca	AstraZeneca
Formulation:	Concentrate for solution for SC injection or IV infusion	Concentrate for solution for SC injection or IV infusion
Strength/concentration:	150 mg/mL	Not applicable
Dose:	300 mg or 600 mg	Not applicable
Route of administration:	SC (abdomen[a]) or IV	SC (abdomen[a]) or IV
Specific device for drug administration, if applicable:	For Cohort 1 (300 mg): 27G ½" needle For Cohort 2 (300 mg): Latex-free IV infusion bags of normal 0.9% saline (100 mL size). Infusion lines should contain a low protein-binding 0.2 µm or 0.22 µm in-line filter. For Cohort 3 (600 mg): Syringe pump	For Cohort 1 (300 mg): 27G ½" needle For Cohort 2 (300 mg): Latex-free IV infusion bags of normal 0.9% saline (100 mL size). Infusion lines should contain a low protein-binding 0.2 µm or 0.22 µm in-line filter. For Cohort 3 (600 mg): Syringe pump
Regimen:	Single-dose	Single-dose
Special handling requirements:	The total in-use storage time from needle puncture for dose preparation to start of administration should not exceed 4 hours at room temperature or 24 hours at 2°C to 8°C (36°F to 46°F).	The total in-use storage time from needle puncture for dose preparation to start of administration should not exceed 4 hours at room temperature or 24 hours at 2°C to 8°C (36°F to 46°F).
Availability of the IMP:	IMP will be shipped after regulatory approval	NA

IMP = Investigational medicinal product; SC = Subcutaneous; IV = intravenous; mg = milligrams; mL = milliliters

[a] Avoid 5 cm radius around umbilicus

AstraZeneca will provide detailed preparation, storage and handling instructions for each product and treatment. Details of the batch numbers will be included in the Trial Master File and the final CSR, as applicable.

8.2. Supply of Investigational Medicinal Product

The IMP will be manufactured in accordance with Good Manufacturing Practice (GMP) and will be supplied by AstraZeneca.

All drug products will be labelled in a double-blind fashion. Anifrolumab (MEDI-546) 150 mg and Placebo kits will be provided containing 2 vials/kit. Two vials of 150 mg or

2 vials of placebo. The vials will be labelled with a single panel label. Two labelled vials will be placed into an insert and into a carton labelled with a single panel label.

AstraZeneca will provide Anifrolumab (MEDI-546) and placebo vials. PAREXEL will provide IV infusion bags and labels to apply to IV bags after dose preparation.

If applicable, a technical agreement between PAREXEL and AstraZeneca will be in place to cover all pharmacy related activities, detailing roles and responsibilities prior to receipt of the IMP at the clinical unit.

If applicable, a release document signed by a legally authorized Qualified Person (QP) at PAREXEL will be placed in the appropriate section of the Trial Master File to document labeling.

8.3. Storage and Handling Procedures

The IMP will be stored in a secure facility under appropriate storage conditions. Details of storage conditions will be provided by AstraZeneca.

AstraZeneca will be permitted upon request to audit the supplies, storage, dispensing procedures and records.

8.4. Labelling

Labels will be prepared in accordance with GMP and local regulatory guidelines. The labels will fulfill GMP Annex 13 requirements and medical device directive for labelling.

8.5. Drug Accountability, Dispensing and Destruction

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

In accordance with GCP, the clinical unit will account for all supplies of the IMP. Details of receipt, storage, assembly/dispensing and return will be recorded.

All used and unused supplies of the IMP will be destroyed by PAREXEL at the end of the study. The certificate of delivery and destruction must be signed, in accordance with instruction by AstraZeneca. Destruction must not take place unless the responsible person at AstraZeneca has approved it.

8.6. Dose and Treatment Regimens

Subjects will receive a single dose of anifrolumab or placebo.

- Cohort 1: The first 10 subjects will be randomized to receive a single dose of either anifrolumab 300 mg or placebo (6 subjects anifrolumab 300 mg and 4 subjects placebo; delivered as 2 separate 1 mL SC injections).
- Cohort 2: The following 10 subjects will be randomized to receive a single dose of either anifrolumab 300 mg or placebo (6 subjects anifrolumab 300 mg and 4 subjects placebo; delivered as an IV infusion over 30 minutes).
- Cohort 3: After ≥ 6 subjects in Cohort 1 have been observed on the study for one week and the PI has deemed an acceptable safety profile, 10 subjects will be randomized to receive a single dose of either anifrolumab 600 mg or placebo (6 subjects anifrolumab 600 mg and 4 subjects placebo; delivered as 4 mL SC by infusion pump).

Restrictions are described in Section 7.4. Data of subjects may be excluded from the PK analysis set as described in Section 11.3.2.

Subcutaneous dosing will be given in the anterior abdominal wall, specifically avoiding the 5 cm radius around umbilicus.

The date and time of dosing will be recorded in the CRF, together with the location of the injection site for SC dosing. For IV dosing, the volume of the infusion together with the start and stop time will be recorded.

8.7. Concomitant Medication

Apart from paracetamol/acetaminophen, no concomitant medication or therapy will be allowed. The subjects should be instructed that no other medication is allowed, including herbal remedies, vitamin supplements and OTC products, without the consent of the investigator.

For females, hormonal replacement therapy is allowed.

Medication, which is considered necessary for the subject's safety and well-being, may be given at the discretion of the investigator during the residential period.

When any medication is required, it should be prescribed by the investigator. Following consultation with AstraZeneca Lead Physician, the investigator must determine whether or not the subject should continue in the study.

8.8. Treatment Compliance

Dosing will take place at the PAREXEL Early Phase Clinical Unit. Compliance will be assured by direct supervision and witnessing of study drug administration

Administration of IMP will be recorded in .

8.9. Randomization

8.9.1. Subject enrollment and randomization

The PI will ensure:

- Signed informed consent is obtained from each potential subject before any study specific procedures are performed.
- Each potential subject is assigned a unique enrollment number at screening upon signing the ICD.
- The eligibility of each subject is in accordance with the inclusion and exclusion criteria.
- Each eligible subject is assigned a unique randomization code (subject number).

Randomization must occur the morning of dosing.

Refer to Section 8.6 (Dose and Treatment Regimens) for order of randomization.

[redacted]

If a subject withdraws his/her participation in the study, then his/her enrollment/randomization code cannot be reused.

8.9.2. Procedures for randomization

Upon completion of the randomization request form, the randomization will be produced by AstraZeneca using the global randomization system (GRand).

Subjects will be assigned a randomization number for dosing in consecutive order per the randomization list.

Once a randomization number has been allocated to 1 subject, it may not be assigned to another subject. If subjects withdraw prematurely from the study and are replaced under the direction of the sponsor, then a new randomization number will be assigned. The replacement subjects will be assigned to the same treatment as the discontinued subject using the next available randomization number that corresponds to the specific treatment.

The randomization list will contain sufficient numbers such that two sets of replacements are available i.e., there will be 30 randomization numbers per cohort.

8.10. Blinding

8.10.1. Methods for ensuring blinding

This study is double-blind with regard to treatment (anifrolumab or placebo) within each cohort.

The randomization list should be kept in a secure location until the database is locked or equivalently, clean file is declared. The following personnel will have access to the randomization list:

- The pharmacy personnel preparing study drug at the clinical unit
- The personnel performing the bioanalyses of the serum PK samples

8.10.2. Methods for unblinding the study

Other than for the personnel listed in Section 8.10.1 who have access to the randomization list, the treatment code should not be broken except in medical emergencies when the appropriate management of the subject requires knowledge of the treatment randomization. The investigator should document and report the action to AstraZeneca, without revealing the treatment given to subjects to the AstraZeneca staff. An adequate procedure (e.g., code break envelopes) should be followed to maintain the blinding or allow breaking the blind for non-emergency reasons.

In the event of a medical emergency when management of a subject's condition requires knowledge of the trial medication, the treatment received may be revealed by personnel authorized by the PI. If possible, such emergencies are to be discussed with AstraZeneca prior to disclosure of the treatment allocation. Reasons for breaking a code will be clearly explained and justified in the subject's CRF and reported in the CSR. The time and date on which the code was broken together with the identity of the person responsible will also be documented.

9. MEASUREMENTS AND METHODS OF ASSESSMENTS

9.1. Appropriateness of Measurements

Standard measures to assess PK, safety and tolerability apply during the study. For the single doses of anifrolumab planned to be given during this study, no safety issues are expected.

For timing of assessments refer to Table 1.

9.2. Pharmacokinetics

9.2.1. Sample collection and handling

Blood samples for the determination of serum concentrations of anifrolumab will be collected as listed in the Schedule of Assessments Table 1.

Samples will be collected, handled, labelled, stored and shipped as detailed in the Laboratory Manual. Serum samples will be analyzed for anifrolumab using a validated assay.

9.2.2. Pharmacokinetic drug assays

Blood samples for determination of anifrolumab concentrations in plasma will be analyzed using a validated assay.

Full details of the analytical method and analyses performed will be described in a separate Bioanalytical Report.

9.2.3. Disposal of pharmacokinetic samples

Pharmacokinetic samples will be disposed of after finalization of the Bioanalytical Report or 6 months after issuance of the draft Bioanalytical Report (whichever is earlier), unless requested for future analyses.

Pharmacokinetic samples may be disposed of or destroyed and anonymized by pooling. Additional analyses may be conducted on the anonymized, pooled PK samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately from the CSR.

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples. The results from the evaluation will be reported separately in a Bioanalytical Report appended to the final CSR.

9.3. Safety, Tolerability and Eligibility Measurements

Safety and tolerability variables will include:

- Local injection site pain assessment (VAS) (SC dosing only)
- Local injection site pruritus assessment (VAS) (SC dosing only)
- Local injection site reaction assessment (including erythema and induration) (SC dosing only)
- AEs
- Vital signs (systolic and diastolic BP, pulse rate and oral temperature)
- ECG
- Physical examination
- Laboratory assessments (hematology, clinical chemistry and urinalysis).

Viral serology, urine drugs of abuse and serum alcohol, as well as height, weight and BMI will be assessed for eligibility. FSH (post-menopausal females only), pregnancy testing (females of childbearing potential only), Pap smear results (female only) and use of concomitant medication will also be assessed and reported.

9.3.1. Local injection site pain

Tolerability will be measured by local injection site pain intensity assessed immediately and at 10, 20 and 30 minutes and then at 1, 2, 4, 8, 24 and 48 hours post-injection within each SC cohort. A 100 mm patient rated VAS (0 - 100 ungraduated scale, where 0 = "no pain" to 100 = "worst imaginable pain") for injection-site pain assessments will be used. These will not be recorded as an AE unless subject complains at a time other than the scheduled collection times.

9.3.2. Local injection site pruritus

Tolerability will be measured by local injection site pruritus assessed immediately and at 10, 20 and 30 minutes and then at 1, 2, 4, 8, 24 and 48 hours post-injection within each SC cohort. A 100 mm patient rated VAS (0 - 100 ungraduated scale, where 0 = "no itching" to 100 = "worst imaginable itching") for injection-site pruritus assessments will be used. These will not be recorded as an AE unless subject complains at a time other than the scheduled collection times.

9.3.3. Local injection site reaction

Local injection site reactions (including erythema and induration) assessed immediately and at 10, 20 and 30 minutes and then at 1, 2, 4, 8, 24 and 48 hours post injection within each SC cohort. Assessments should continue until resolved, if applicable. Measurements will be obtained and recorded. These will not be recorded as AEs unless subject complains at a time other than the scheduled collection times.

Erythema: Either none (0) or a mm measurement. This should be the largest diameter across the needle site

Induration: Either none (0) or a mm measurement. This should be the largest diameter across the needle site.

9.3.4. Adverse events

Refer to Section 12.2.3.

9.3.5. Vital signs

The following variables will be collected after the subject has rested in the supine position for at least 5 minutes and prior to any invasive procedures, i.e., blood draws:

- Systolic BP (mmHg)
- Diastolic BP (mmHg)
- Pulse rate (beats per minute [bpm])
- Temperature (degrees Celsius)

The measurement of vital signs will be carried out according to the relevant PAREXEL standard operating procedures (SOPs).

9.3.6. Resting 12-lead electrocardiogram

A 12-lead ECG will be obtained after the subject has rested in the supine position for at least 10 minutes at each of the time points specified in the schedule of assessments (Table 1) and prior to any invasive procedures, i.e., blood draws.

At each time point, the investigator will judge the overall ECG as normal or abnormal and this evaluation will be reported in ClinBase. If abnormal, it will be decided as to whether or not the abnormality is clinically significant by the investigator. For all abnormalities (regardless of clinical significance) the specific type and nature of the abnormality will be

documented in ClinBase. Clinically significant findings should also be documented on the AE page of the CRF if applicable (Section 12.2).

The investigator may add extra 12-lead resting ECG safety assessments if there are any abnormal findings or if the investigator considers it is required for any other safety reason. These assessments should be entered as an unscheduled assessment.

All ECG readings will be digitally stored as source documents.

9.3.7. Physical examination

Full

The complete physical examinations will include an assessment of the general appearance, skin, cardiovascular, respiratory, abdomen, head and neck (including ears, eyes, nose and throat), lymph nodes, thyroid, musculoskeletal and neurological systems.

Brief (Abbreviated)

The brief physical examinations will include an assessment of the general appearance, skin, cardiovascular system, respiratory and abdomen.

9.3.8. Laboratory assessments

9.3.8.1. Hematology

White blood cell (WBC) count
Red blood cell (RBC) count
Hemoglobin (Hb)
Hematocrit (HCT)
Mean corpuscular volume (MCV)
Mean corpuscular hemoglobin (MCH)
Mean corpuscular hemoglobin concentration (MCHC)
Neutrophils absolute count
Lymphocytes absolute count
Monocytes absolute count
Eosinophils absolute count
Basophils absolute count
Platelets
Reticulocytes absolute count

9.3.8.2. Serum clinical chemistry

Sodium
Potassium
Urea
Creatinine
Albumin
Calcium
Phosphate
Glucose(fasting)
C-reactive protein (CRP)
Follicle-stimulating hormone (FSH) (post-menopausal women only) (screening only)
Alkaline phosphatase (ALP)
Alanine aminotransferase (ALT)*
Aspartate aminotransferase (AST)*
Gamma glutamyl transpeptidase (GGT)
Total bilirubin*
Unconjugated bilirubin
Conjugated bilirubin
T4 (screening only)
Thyroid-stimulating hormone (TSH) (screening only)

* In case a subject shows an AST or ALT ≥ 3xULN or total bilirubin ≥ 2xULN please refer to Appendix 15.3 'Actions required in cases of combined increase of Aminotransferase and Total Bilirubin – Hy's Law', for further instructions.

9.3.8.3. Urinalysis

Glucose
Protein
Blood
Microscopy (if positive for protein or blood)

9.3.8.4. Pregnancy testing

Serum beta human chorionic gonadotropin (beta-hCG) (females of childbearing potential only)

9.3.8.5. Viral serology

Human immunodeficiency virus (HIV) I and II
Hepatitis B surface antigen (HBsAg)
Hepatitis C virus antibody
Hepatitis B core total antibodies

9.3.8.6. Drugs of abuse and alcohol screen

Amphetamine / Ecstasy
Cannabinoids
Cocaine
Opiates
Tricyclic anti-depressants (TCA)
Alcohol (Serum collection)
Benzodiazepines
Methadone metabolites
Barbiturates
Phencyclidine
Urine creatinine

Drugs of abuse screen will be done via a urine sample. Alcohol screen will be done via a serum sample.

9.3.8.7. QuantiFERON-TB GOLD

The IGRA test (QuantiFERON-TB GOLD) will be performed at the screening visit to identify those subjects who have had TB or may have active or latent TB. Results of this test will be reported as positive, negative, or indeterminate. Subjects with a positive test result will not be included in the study. If the result is reported as indeterminate, then the test can

be repeated once. If the repeat test result is reported as indeterminate, then the subject will not be included in the study.

9.3.9. Pap smear

Most cases of cervical cancer appear to be related to infection with papilloma virus. Because of the potential for viral reactivation due to blockade of the interferon pathway, we are assessing cervical dysplasia in this study, although to date there has been no signal in the anifrolumab studies. A Pap smear is required at screening in women who have not had their cervix surgically removed. If a Pap smear was performed within 2 years prior to screening with no documented malignancy (e.g., CIN III, CIS, or AIS), it does not need to repeated. Subjects with abnormal Pap smear results of atypical squamous cells of undetermined significance (ASC-US), atypical squamous cells where high-grade squamous intraepithelial lesion (HSIL) cannot be ruled out (ASC-H), atypical glandular cells (AGC), or CIN grades I and II (CIN I and II) will be allowed to enter the study; please refer to Appendix 15.4 for guidance.

9.3.10. Concomitant medication

Refer to Section 8.7.

9.3.11. Immunogenicity

Instructions for immunogenicity (ADA) sample collection, processing, storage and shipment can be found in the separate laboratory manual.

9.3.11.1. Anti-drug Antibodies

The serum samples to measure presence of ADA will be collected according to the schedule of assessments (Table 1). The presence or absence of ADA will be determined in the serum samples using validated bioanalytical methods.

9.4. Procedures for Handling of Biological Samples

9.4.1. Storage and destruction of biological samples

Samples will be disposed of, on instruction from AstraZeneca, after the CSR has been finalized, unless samples are retained for additional or future analyses.

9.4.1.1. Pharmacokinetic samples

For disposal of PK samples, refer to Section 9.2.3.

9.4.2. Labelling and shipment of biohazard samples

Samples will be labelled and shipped in accordance with the Laboratory Manual and the Biological Substance, Category B regulations (materials containing or suspected to contain infectious substances that do not meet Category A criteria) (for International Airline Transportation Association [IATA] guidance, see Appendix 15.2 of this clinical study protocol).

Any samples identified as Infectious Category A materials will not be shipped and no further samples will be taken from the subject unless agreed with AstraZeneca and appropriate labelling, shipment and containment provisions are approved.

9.4.3. Chain of custody of biological samples

A full chain of custody will be maintained for all samples throughout their life cycle.

The PI will ensure full traceability of collected biological samples from the subjects while in storage at the clinical unit until shipment and will keep documentation of receipt of arrival.

The sample receiver will keep full traceability of samples while in storage and during use, until used, disposed of, or until further shipment or disposal (where appropriate) and will keep documentation of receipt of arrival.

Samples retained for further use will be registered in the MedImmune bio-bank system during the entire life cycle.

9.4.4. Withdrawal of informed consent for donated biological samples

If a subject withdraws consent to the use of donated biological samples, the samples will be disposed if not already analyzed and the action documented. As collection of donated biological samples is an integral part of the study, consent withdrawal implies that the subject is withdrawn from further study participation.

AstraZeneca ensures the laboratory holding the samples is informed about the withdrawn consent immediately and that samples are disposed of or destroyed, the action documented and the signed document returned to the clinical unit.

10. DATA QUALITY ASSURANCE AND DATA MANAGEMENT

10.1. Quality Control and Source Data Verification

Source data verification will be conducted with due regard to subject confidentiality.

The clinical unit will allow the study monitor and sponsor representative direct access to all study documents, medical files and source documents to enable verification of the study data, whilst maintaining the anonymity of the subject and confidentiality of the data.

Internal quality control will be performed at all stages of the study by the clinical unit.

10.2. Audit/Inspections

The clinical unit facilities and all study data/documentation may be audited/inspected by independent auditor/inspector/any representatives of regulatory authorities. The investigator must allow the applicable persons access to all relevant facilities and data/documents. The investigator must be available to discuss any findings/issues.

If an audit was performed, the audit certificate will be included in the CSR.

10.3. Study Monitoring

The conduct of the study will be monitored by an independent PAREXEL monitor or a subcontracted monitor to ensure compliance with applicable regulatory requirements and GCP. The summary of the documentation of the monitoring visits will form part of the study documentation and will be archived as such.

10.4. Data Collection

The ClinBase system is an electronic source data capturing and information management system. The system combines all aspects of source data capturing with process control and clinical study management. All clinical and laboratory data, except those which are paper-based or provided by external vendor, will be collected in ClinBase. Only paper-based data will be subject to data entry. For electronic source data, no data entry will be performed.

The responsible study monitor will check data at the monitoring visits to the clinical unit. The investigator will ensure that the data collected are accurate, complete and legible. Data will be monitored within ClinBase by the study monitor before being exported. Any changes made during monitoring will be documented with a full audit trail within ClinBase.

10.4.1. Case report forms and source documents

All data obtained using paper collection methods during the clinical study will be recorded in ClinBase. All source documents from which ClinBase entries are derived should be placed in the subject's personal records.

The original ClinBase entries for each subject will be checked against source documents by the study monitor. Instances of missing or uninterpretable data will be discussed with the investigator for resolution.

10.4.2. Access to source documents

During the course of the clinical study, a study monitor will make clinical unit visits to review protocol compliance, compare ClinBase entries and individual subject's personal records, assess IMP accountability and ensure that the clinical study is being conducted according to pertinent regulatory requirements. ClinBase entries will be verified against source documents. The review of medical records will be handled confidentially to ensure subject anonymity.

Checking of the ClinBase entries for completeness and clarity and verifying with source documents, will be required to monitor the clinical study for compliance with GCP and other regulations. Moreover, regulatory authorities of certain countries, IECs/IRBs may wish to carry out source data inspections on-site, and the sponsor's clinical quality assurance group may wish to carry out audits. Direct access to source data will be required for these inspections and audits; they will be carried out giving due consideration to data protection and subject confidentiality. The investigator assures the sponsor of the necessary support at all times.

10.5. Data Management

PAREXEL will utilize standardized and validated procedures and systems to collect, process and file the clinical data of this study. Any system used will be compliant with FDA 21 CFR Part 11 requirements.

A data management plan (DMP) will be prepared to describe the processes and data-flow within the clinical study. Timelines, versions for the computer systems and the coding will be defined in the DMP, and if applicable, sponsor specific requests will also be documented within. The DMP will be finalized before first dose where possible but before database lock.

A data validation specification (DVS) will be created to outline the validation checks to be performed during the study. The DVS must be finalized before data validation.

After the data has been monitored by the responsible study monitor all data received will be reviewed, logged and filed.

The raw data intended for further processing will be checked by standard routines or according to the DVS and queries will be generated and sent to the investigator for review and resolution. Corrections resulting from these queries will be confirmed on the data clarification forms (DCFs). This process will be repeated until no further discrepancies are found. The data will then be declared as clean. Applicable documentation will be stored in the study files.

Only trained study staff will have access to the clinical database and every change in data will have a full audit trail.

11. STATISTICAL METHODS

11.1. Overview

The statistical methodology below describes the statistical analysis as it is foreseen when the study is being planned.

If circumstances should arise during the study rendering the analysis inappropriate, or if in the meantime improved methods of analysis should come to light, different analyses may be performed. A separate statistical analysis plan (SAP) will not be written for the study. Any deviations from the statistical methodology defined in this protocol, reasons for such deviations and all alternative/additional statistical analyses that may be performed will be described in the CSR. Such changes to analyses may be written into an abbreviated SAP, if appropriate.

11.2. General Statistical Methodology

All original and derived parameters as well as demographic and disposition data will be listed and described using summary statistics. All safety data (scheduled and unscheduled) will be presented in the data listings.

Demographic and baseline data will be summarized by treatment (dose of anifrolumab/ROA or placebo) and overall. Pharmacokinetic data will be summarized by dose of anifrolumab and ROA. Safety and tolerability data will be summarized by treatment, if applicable. For the purpose of the analyses the subjects receiving placebo will be pooled across cohorts, unless otherwise stated.

Frequency counts (number of subjects [n] and percentages) will be made for each qualitative variable. Descriptive statistics (n, mean, standard deviation [SD], median, minimum and maximum) will be calculated for each quantitative variable (unless otherwise stated). Descriptive statistics will only be presented if $n \geq 3$.

The following rules will apply to any repeated safety assessments:

- If the repeated measurement of a specific parameter occurs prior to IMP administration (Day 1), then the last obtained value prior to dosing will be used in the descriptive statistics and in the calculation of changes from baseline;
- If the repeated measurement of a specific parameter occurs after IMP administration (Day 1), then the first (non-missing) value after dosing will be used in descriptive statistics and in the calculation of changes from baseline.

The planned sequence for measurement of multiple assessments at the same time point is described in Section 7.3.

All statistical analyses and production of tables, figures and listings will be performed using .

11.2.1. Missing Data

Missing dates and times in the AE data will be handled as described in Section 11.11.1. Concentrations that are below limit of quantification (BLQ) in the PK data will be handled as described in Section 11.9.2.

There will be no imputations of other missing data. All subjects will be included into the safety analyses as far as the data permit.

11.3. Study populations

11.3.1. Safety analysis set

The safety analysis set will include all subjects who received at least 1 dose of IMP (anifrolumab or placebo) and for whom any safety post-dose data are available.

Unless otherwise stated the safety analysis set will be used for the presentation of all demographic and disposition data, as well as all safety, tolerability and immunogenicity analyses. Exposure to IMP will also be presented using the safety analysis set.

11.3.2. Pharmacokinetic analysis set

The PK analysis set will consist of all subjects in the safety analysis set for whom at least 1 of the primary PK parameters can be calculated, and who have no major protocol deviations thought to impact on the analysis of the PK data.

The exclusion of any subjects or time points from the calculation of the PK parameters will be documented by the PK Scientist including the reason(s) for exclusion.

The available concentration data and PK parameter data for any subjects excluded from the PK analysis set will be listed only. Concentration data for subjects excluded from the PK analysis set will be presented in the individual subject figures of concentration versus time plots.

11.4. Determination of Sample Size

The sample size is not based on statistical considerations. With a sample size of 6 subjects treated with active treatment there is 80% probability to observe at least one event of an AE that occurs with an incidence of 24% in the studied population.

11.5. Protocol Deviations

Protocol deviations are considered any deviation from the clinical study protocol relating to a subject, and include the following:

- Inclusion/exclusion criteria deviations
- Dosing deviations (e.g., incorrect treatment received, injection was not administered correctly)
- Time window deviations for safety and/or PK assessments, if applicable
- Subjects receiving prohibited concomitant medications
- Other procedural and study conduct deviations recorded by the clinical unit on a protocol deviation log

The criteria for the assessment and reporting of protocol deviations will be stipulated in a separate study-specific protocol deviation specification (PDS) document. This will include a Windows Allowance Document (WAD) which stipulates tolerance windows for safety and PK assessments. Measurements performed within these tolerance windows will not be considered as protocol deviations and will not be reported.

All protocol deviations will be discussed at the data review meeting prior to database hard lock in order to define the analysis sets for the study.

Important protocol deviations will be listed by subject.

Protocol deviations will be handled in accordance with PAREXEL SOPs.

For handling of protocol amendments, see Section 3.6.

11.6. Subject Disposition

A randomization listing will be presented and include the following: each subject's randomization number, the subject's full enrolment number, the treatment to which the subject has been randomized and the country where the study center is located.

Subjects and/or data excluded from the PK analysis set will be listed including the reason for exclusion. Subject disposition will be summarized by treatment (dose of anifrolumab/ROA

or pooled placebo) and will include the following information: number of subjects randomized and dosed, number and percentage of subjects completing the study and the number and percentage of subjects who were withdrawn (including reasons for withdrawal). Disposition data will be presented based on all subjects randomized.

Subject discontinuations will be listed including the date of study exit, duration of treatment (time [in days] since dosing) and reason for discontinuation. A listing of informed consent response will also be presented.

11.7. Demographic and Baseline Data

Demographic variables (age, gender, race, ethnicity, height, weight and BMI) will be listed by subject. Demographic characteristics (age, gender, race and ethnicity) and subject characteristics (height, weight and BMI) will be summarized separately, by treatment and overall, for all subjects in the safety analysis set. The denominator for percentages will be the number of subjects in the safety analysis set for each treatment or for all subjects as applicable.

Medical history data will be listed by subject including visit, description of the disease/procedure, Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC), MedDRA Preferred Term, start date and stop date (or ongoing if applicable).

11.8. Prior and Concomitant Medication and Drug Administration

11.8.1. Prior and concomitant medication

Prior medications are those that started and stopped prior to dosing with IMP; all medications taken after IMP dosing are considered as concomitant (including medications that started prior to dosing and continued after).

Prior and concomitant medication will be listed by subject and will include the following information: reported name, Preferred Term, the ROA, dose, frequency, start date/time, flag for whether the medication is prior or concomitant, duration and indication. Prior and concomitant medication will be coded according to the sponsor's drug dictionary.

The duration will be calculated as:

Duration = end date/time – start date/time

The duration may be presented in hours or days in the listing depending on the applicability to the emerging data. For medications with partial or completely missing start date/times and/or end date/times, the duration will not be calculated.

Medications with missing or partial start date/time and/or end date/time such that it is not possible to classify as prior or concomitant will be considered as concomitant in the listings.

11.8.2. Drug administration

Drug administration dates and times will be listed for each subject, including the location of the injection site for SC dosing and including the infusion volume, start and stop time for IV dosing. Any interruptions in the IV infusion will also be included in the listing.

11.9. Pharmacokinetic analysis

11.9.1. Pharmacokinetic parameters

Where possible, the following PK parameters will be assessed for anifrolumab on plasma concentrations.

Primary PK parameters

AUC	Area under serum concentration-time curve from time zero extrapolated to infinity
$AUC_{(0-t)}$	Area under the serum concentration-time curve from time zero to time of last quantifiable concentration
C_{max}	Observed maximum serum concentration

Secondary PK parameters

t_{max}	Time to reach maximum plasma concentration
λ_z	Terminal elimination rate constant
CL	Total body clearance after intravenous administration
CL/F*	Apparent total body clearance after extravascular administration estimated as dose divided by AUC
V_z	Apparent volume of distribution during the terminal phase after intravenous administration
V_z/F*	Apparent volume of distribution during the terminal phase after extravascular administration

* After SC administration only

The following diagnostic parameters for serum PK analysis will be listed, but not summarized:

λ_z upper and lower	The time interval (h) of the log-linear regression to determine $t_{½}$
λ_z, N	Number of data points included in the log-linear regression analysis
Rsq_adj	Regression coefficient adjusted for λ_z, N, Goodness of fit statistic for calculation of λ_z
$\%AUC_{extr}$	Percentage of AUC obtained by extrapolating the area under the serum concentration-time curve to infinity from the time of the last quantifiable concentration using λ_z

Additional PK parameters may be determined where appropriate.

11.9.2. Derivation of pharmacokinetic parameters

The calculation of the PK parameters will be performed by Quantitative Clinical Development, PAREXEL.PK parameters will be derived using non-compartmental methods with , or higher and/or , or higher. All descriptive and inferential statistical computations will be performed using , or higher.

PK analysis will, where possible, be carried out using actual times recorded in the raw data. If actual times are missing, nominal times will be used.

For Cohort 3 subjects, actual administered dose after correction for amount left over in the dosing equipment may be used for PK analyses.

Serum concentrations which are BLQ prior to the first quantifiable concentration will be set to a value of zero. After the first quantifiable concentration, any BLQ serum concentrations will be set to missing for all concentration profiles. Where 2 or more consecutive concentrations are BLQ at the end of a profile, the profile will be deemed to have terminated and therefore any further quantifiable concentrations will be set to missing for the calculation of the PK parameters.

If an entire concentration-time profile is BLQ, the profile will be excluded from the PK analysis.

Terminal elimination half-life is estimated as $(\ln 2)/\lambda_z$, where λ_z refers to the terminal elimination rate constant, estimated by log-linear least squares regression of the terminal part of the concentration-time curve. For the determination of λ_z, the start of the terminal elimination phase for each subject will be defined by visual inspection and will be the first point at which there is no systematic deviation from the log linear decline in plasma

concentrations. A minimum of 3 data points will be used in calculating λ_z, and the duration of time over which PK blood samples were collected will be at least twice the subsequently estimated terminal half-life. Where an elimination half-life is estimated to be more than half of the PK collection interval, it will be flagged, commented upon in the study report and interpreted with caution. AUC is estimated by $AUC_{(0-t)} + C_{last}/\lambda_z$ where C_{last} is the observed last quantifiable drug concentration. The AUC values where the percentage extrapolation is greater than 20% will be listed but excluded from summary statistics.

AUCs (including AUC and $AUC_{(0-t)}$) will be calculated using the linear trapezoidal method when concentrations are increasing and the logarithmic trapezoidal method when concentrations are decreasing.

The minimum requirement for the calculation of AUC will be the inclusion of at least 3 consecutive serum concentrations above the lower limit of quantification (LLOQ), with at least 1 of these concentrations following C_{max}.

11.9.3. Presentation of pharmacokinetic data

A listing of PK blood sample collection times, as well as derived sampling time deviations (where applicable) will be provided. Serum concentrations and PK parameters of anifrolumab will be summarized by treatment (dose level of anifrolumab and ROA) using appropriate descriptive statistics. Where possible, the following descriptive statistics will be presented: n, geometric mean, geometric CV, arithmetic mean, arithmetic SD, arithmetic CV, median, minimum and maximum. For t_{max}, only n, median, minimum and maximum will be presented.

The geometric mean is calculated as the exponential of the arithmetic mean calculated using log-transformed data.

The CV% is calculated as $100 \cdot \sqrt{(\exp(s^2)-1)}$ where s is the SD of the log-transformed data.

The following rules will apply to presentation of PK data:

- For PK concentration data, the listings will be presented to the same number of significant figures as the data received from the bioanalytical laboratory; for PK parameters, the listings will be presented according to the following rules:
  - C_{max} – will be presented to the same number of significant figures as received from the bioanalytical laboratory
  - t_{max}, λ_z lower and upper time limit – will be presented as received in the data, usually to two decimal places

- AUC, $AUC_{(0-t)}$, CL/F, CL, V_z, V_z/F, R squared adjusted will be presented to three significant figures
- λ_z – will be presented to four significant figures
- λ_z, N will be presented as an integer (no decimals)
- %AUC extrapolated will be presented to two decimal places

- For PK concentration data all descriptive statistics will be presented to four significant figures with the exception of the minimum and maximum which will be presented to three significant figures
- For PK parameter data the descriptive statistics will be presented according to the following rules:
  - C_{max}, AUC, $AUC_{(0-t)}$, CL/F, CL, V_z, V_z/F – all descriptive statistics will be presented to four significant figures with the exception of the minimum and maximum which will be presented to three significant figures
  - λ_z – all descriptive statistics will be presented to five significant figures with the exception of the minimum and maximum which will be presented to three significant figures
  - t_{max} – all descriptive statistics will be presented as received in the data, usually to two decimal places

Serum concentrations that are BLQ or if there are missing values (e.g., no result [NR]) will be handled as follows:

- Where there is NR, these will be set to missing.
- At a time point where less than or equal to 50% of the values are BLQ, all BLQ values will be set to the LLOQ, and all descriptive statistics will be calculated.
- At a time point where more than half of the values are BLQ, the mean, SD, geometric mean and CV% will be set to Not Determined (ND). The maximum value will be reported from the individual data, and the minimum and median will be set to BLQ.
- If all values are BLQ at a time point, no descriptive statistics will be calculated for that time point. Not applicable (NA) will be written in the field for standard deviation and CV% and BLQ will be written in fields for mean, geometric mean, minimum, median and maximum.
- The number of BLQ values (n below LLOQ) will be reported for each time point.

Data from subjects excluded from the PK analysis set will be included in the data listings, but not in the descriptive statistics.

Individual serum concentrations versus actual time will be plotted in linear and semi logarithmic scale with separate plots for each subject.

Combined individual serum concentration versus actual times will be plotted in linear and semi logarithmic scale. Plots will be grouped by dose level of anifrolumab and ROA.

Arithmetic mean serum concentration (± SD) versus nominal sampling time will be plotted in linear and semi logarithmic (no SD presented) scale with each dose level of anifrolumab and ROA overlaid on the same figure.

For mean plots, BLQ values will be handled as described for the summary tabulations; for individual plots serum concentrations which are BLQ prior to the first quantifiable concentration will be set to a value of zero (linear plots only). After the first quantifiable concentration, any BLQ serum concentrations will be regarded as missing. All combined individual and mean plots will be based on the PK analysis set. Individual subject plots will be based on the safety analysis set (excluding any subjects receiving placebo).

Finally, scatter plots showing the individual PK parameters and geometric mean versus dose level/ROA will be presented for C_{max} and AUC.

11.9.4. Statistical analysis of pharmacokinetic data

No inferential statistical analysis of the PK data will be performed. All PK data will be summarized using descriptive statistics only.

11.10. Analysis of Immunogenicity Data

The results of the ADA assessments will be listed for each subject and time point. This will include the confirmatory assay (positive/negative) and the measured titers where appropriate. Summary tables will be presented, by treatment (dose of anifrolumab/ROA or pooled placebo), for the number and percentage of subjects with positive/negative results at each time point, based on the safety analysis set.

In addition, the ADA titers (n, median, minimum and maximum) will be summarized by treatment (dose of anifrolumab/ROA or pooled placebo) for all subjects with a positive confirmatory assay at each time point; this tabulation will include a summary of the highest titer across all time points for each subject.

11.11. Analysis of Safety Data

Safety data (scheduled and unscheduled) will be presented in the data listings. Continuous variables will be summarized by treatment (dose level of anifrolumab/ROA or pooled placebo, unless otherwise stated) using descriptive statistics (n, mean, SD, minimum, median, maximum). Categorical variables will be summarized in frequency tables (frequency and percentage) by treatment (dose level of anifrolumab/ROA or pooled placebo, unless otherwise stated). The analysis of the safety variables will be based on the safety analysis set.

11.11.1. Adverse events

All AEs will be coded using MedDRA vocabulary, and will be listed for each subject. A treatment-emergent AE (TEAE) is defined as an AE with onset (start date/time) after dosing on Day 1.

Adverse events with missing start dates/times will be handled as follows for classification as treatment-emergent:

- If the start date is completely missing but the end date is known and shows that the AE ended on or after the date of dosing, then the start date will be imputed as the date of dosing; if the end date is known and shows that the AE ended before the date of dosing, then the screening date will be used for the start date. If the end date is non-informative (i.e., is missing or does not contain enough information), the start date will be imputed as the date of dosing;
- If only the start day is missing the day will be imputed as the date of dosing if the known month is the same month as dosing occurred. If the end date is known and shows that the AE ended before dosing occurred the date will be imputed as 01. If the end date is non-informative (i.e., is missing or does not contain enough information), the start date will be imputed as the date of dosing in the known month. If the month is not the same as the month of dosing the date will be imputed as 01;
- If the start day and month are missing the date will be imputed as the date of dosing in the known year unless the end date is known and shows that the AE ended before dosing; in which case the start day and month will be imputed as 01Jan or with the date of screening if this is later. If the end date is non-informative (i.e., is missing or does not contain enough information), the start date will be imputed as the date of dosing in the known year. If the year is not the year of dosing then the date will be imputed as 01Jan or with the date of screening if this is later.
- Missing times will be imputed as 00:00 h or with the time of dosing for events starting on the dosing day.

Adverse events will be summarized by treatment, SOC and Preferred Term, including tabulations by causality and severity (mild, moderate and severe). A separate tabulation will be presented for AEs of special interest. Listings of SAEs, AEs that led to discontinuation (DAEs) and AEs that led to death will also be presented.

The following information will be included in the listings: verbatim term, SOC, PT and lowest level term, start date/time, end date/time, time from dosing, causality, action taken, whether the AE was classified as serious and the outcome.

All tabulations will include the number and percentage of subjects and will be presented by dose level of anifrolumab/ROA or placebo. Placebo subjects will be presented separately for each corresponding dose level/ROA and pooled for all the tabulations. In addition a separate tabulation will be presented showing the number of events by treatment and PT.

Finally an overview of all AEs will be presented, separately for the number and percentage of subjects and the number of events. This will include categories for any AE, AEs with outcome of death and SAEs.

11.11.2. Vital signs

The results of the vital signs measurements will be listed by subject and time point including the date/time of the assessment, changes from baseline and repeat/unscheduled measurements. The baseline for vital signs measurements will be the pre-dose assessment on Day 1. Descriptive statistics will be presented by treatment and time point for both observed values and changes from baseline.

11.11.3. Resting 12-lead electrocardiogram

12-Lead ECG results will be listed for each subject. This will include the Investigator assessment and details of any abnormalities as appropriate.

11.11.4. Physical examination

The results of the physical examination will be listed by body system for each subject.

Body weight will be listed by subject and time point.

11.11.5. Laboratory assessments

Hematology and clinical chemistry values will be listed by subject and time point including changes from baseline and repeat/unscheduled measurements. Summary tabulations will be presented by treatment and time point for the safety analysis set. The baseline for the measurements will be the last pre-dose assessment performed on Day -1. Changes from

baseline will be calculated and presented for all post-baseline time points. Shift tables will also be presented.

The listings will include the following information: test name, date of measurement, reference range, result and flags for any measurements that are outside the reference range (e.g., AstraZeneca, program, or laboratory ranges).

Additional listings will be presented for the following:

- Urinalysis (macroscopic and microscopic, if applicable)
- Pregnancy testing (including FSH)
- QuantiFERON-TB GOLD testing
- Pap smear

The results of the viral serology, drugs of abuse screen, and alcohol screen will not be listed in the CSR.

11.11.6. Additional safety variables

11.11.6.1. Injection Site Pain and Pruritus

The assessment of pain and pruritus at the injection site will be performed using separate 100 mm VAS. The VAS scores will be listed by subject and time point. Descriptive statistics (including n, mean, median, SD, minimum and maximum) will be presented by treatment (dose level of anifrolumab or corresponding placebo*) and time point for each parameter.

*Placebo subjects will be presented separately for each corresponding dose level of anifrolumab i.e., placebo subjects will not be pooled across SC doses for the injection site analyses.

11.11.6.2. Injection Site Reactions

The results of the injection site reaction assessments (erythema and induration) will be listed for each subject and time point including the size of the reaction (in mm) where appropriate.

Descriptive statistics (including n, mean, median, SD, minimum and maximum) will be presented by treatment (dose level of anifrolumab or corresponding placebo*) and time point for the reaction size for each parameter. For any time point where the reaction is 'none' the result will be imputed as 0 mm for the tabulation.

In addition, frequency tabulations will be presented by treatment showing the number and percentage of subjects with presence/absence of erythema and induration at each time point. For the purposes of this tabulation subjects with a result of 'none' will be counted as having an absence of response and subjects with a measured diameter of > 0 mm will be counted as having a response of 'present'.

*Placebo subjects will be presented separately for each corresponding dose level of anifrolumab i.e., placebo subjects will not be pooled across SC doses for the injection site analyses.

12. ADVERSE EVENTS

12.1. Definitions

12.1.1. 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 (e.g., nausea, chest pain), signs (e.g., tachycardia, enlarged liver) or the abnormal results of an investigation (e.g., ECG, laboratory findings).

In clinical studies, an AE can include an undesirable medical condition occurring at any time after the subject has signed informed consent, including run-in or washout periods, even if no specific treatment has been administered.

The term AE is used generally to include any AE whether serious or non-serious.

12.1.2. Definitions of serious adverse event

A SAE is an AE occurring during any study phase (i.e., run-in, treatment, washout, follow-up), that fulfills 1 or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the subject or may require medical intervention to prevent 1 of the outcomes listed above

For further guidance on the definition of a SAE, see Appendix 15.1 of this clinical study protocol.

12.1.3. Definitions of Adverse Events of Special Interest

An AESI is an AE of scientific and medical concern specific to understanding biologics and requires close monitoring and rapid communication by the Investigator to the Sponsor/Sponsor's delegate. An AESI may be serious or non-serious.

Adverse Events of Special Interest in this protocol will be assessed at each visit in the CRF. The events of interest are serious infections, including non-opportunistic serious infections, opportunistic infections, anaphylaxis, malignancy, herpes zoster, TB (including latent TB), influenza, vasculitis, and MACE (including stroke, acute coronary syndrome, MI, or cardiovascular death).

An AESI that meets 1 of the seriousness outcomes listed in Section 12.1.2 will be categorized as an SAE for the purposes of follow-up responsibility and safety reporting. A non-serious AESI will be categorized as an AE. For reporting of AESIs, see Section 12.3.

12.1.3.1. Non-opportunistic serious infection

A non-opportunistic serious infection is any infection requiring hospitalization and/or parenteral antibiotic administration and will be categorized as serious and reported as an SAE. It is expected that the results of all cultures, diagnostic or therapeutic procedures and outcomes on a subject experiencing a serious non-opportunistic infection will be provided as an SAE update.

12.1.3.2. Opportunistic infection

An opportunistic infection is an invasive infection caused by microorganisms that are normally non-pathogenic or rarely pathogenic in individuals with normal immune function or cause an infection of a type or severity not seen in the normal host. Opportunistic infections are categorized as serious and reported as an SAE.

Examples of opportunistic infections that may occur include: herpes zoster meningoencephalitis, Salmonella bacteremia, Pneumocystis jiroveci pneumonia or progressive multifocal leukoencephalopathy (PML). It is expected that the results of all cultures, diagnostic or therapeutic procedures and outcomes on a subject experiencing an opportunistic infection will be provided as an SAE update.

12.1.3.3. Anaphylaxis

Anaphylaxis is a severe, potentially fatal, systemic allergic reaction that occurs suddenly after contact with an allergy-causing substance, such as investigational product. For the purposes of this study, the definition detailed in Appendix 15.5 is provided as a simple and rapid

means to make the diagnosis of anaphylaxis during infusion with investigational product. This definition was a product of a symposium convened by the National Institute of Allergy and Infectious Diseases and Food Allergy and Anaphylaxis Network [3].

12.1.3.4. Malignancy

Malignancy is a neoplasm characterized by cells with abnormal features, uncontrolled rapid growth with invasive and/or metastatic tendencies diagnosed based on pathologic and clinical standards. When possible a biopsy of the malignancy should be obtained and a biopsy report should be provided with the SAE report.

12.1.3.5. Herpes zoster

Herpes zoster is a viral infection characterized by a cutaneous vesicular eruption on an erythematous base presenting along dermatome(s) and usually associated with prodromal pain. Herpes zoster results from the reactivation of varicella-zoster virus; multiple dermatomes may be involved (> 3 dermatomes indicates disseminated disease) and organ or systemic infection may occur (invasive; therefore an opportunistic infection). Polymerase chain reaction (PCR) testing of samples from vesicles or biopsy specimens may confirm the presence of varicella-zoster virus.

For additional information regarding Herpes zoster, refer to the Investigator Brochure. As this is an event of special interest, the Sponsor will collect information on whether or not subjects have received vaccination for Herpes zoster. History of Herpes zoster vaccination will be captured in the appropriate sections of the CRF.

12.1.3.6. Tuberculosis

Tuberculosis is a mycobacterial infectious disease generally presenting as cough with systemic symptoms of infection diagnosed by skin test (purified protein derivative), blood test (IFN-gamma release assay), radiographic imaging, body fluid and tissue sampling; presentation may include disseminated or latent disease. An infection may be new (at least conversion of a TB test to positive) or reactivation of dormant disease (new active disease in a previously TB test positive subject without prior evidence of active disease).

- A bacteriologically confirmed TB case is a case where a biological specimen is positive by smear microscopy, culture or rapid diagnostic such as PCR or nucleic acid amplification test (Xpert MTB/RIF).
- A clinically diagnosed TB case is a case where the subject does not fulfil the criteria for bacteriological confirmation, but has been diagnosed with active TB by a clinician or other medical practitioner who has decided to give the subject a full course of TB

treatment. This definition includes cases diagnosed on the basis of X-ray abnormalities or suggestive histology and extra-pulmonary cases without laboratory confirmation. Clinically diagnosed cases subsequently found to be bacteriologically positive (before or after starting treatment) should be reclassified as bacteriologically confirmed.

Bacteriologically confirmed or clinically diagnosed cases of TB are also classified according to: anatomical site of disease; history of previous treatment; drug resistance; HIV status (World Health Organization, 2014).

12.1.3.7. Influenza

Influenza is a severe viral infection that includes the following symptoms: temperature greater than 100.8°F (38.2°C), and malaise, headache or myalgia. It is often accompanied by nausea, vomiting and diarrhea, and at least 1 of the following respiratory symptoms: cough, sore throat, or shortness of breath.

Laboratory criteria for influenza include at least 1 of the following: isolation of influenza virus from a clinical specimen, detection of influenza virus nucleic acid in a clinical specimen, identification of influenza virus antigen by direct fluorescent antibody test in a clinical specimen OR influenza-specific antibody response.

A confirmed case of influenza meets the clinical and laboratory criteria for the viral illness. Laboratory confirmation should be done using locally available, rapid, commercial tests approved by Regulatory Agencies and sampling respiratory specimens.

Not all upper respiratory viral infections or gastrointestinal viral infections are influenza. In the case where a subject reports a viral infection severe enough to be considered, in the opinion of the Investigator, influenza, a viral test should be performed (if possible) to confirm the diagnosis. Whether or not a test to confirm the diagnosis has been performed, if, in the opinion of the Investigator, the subject has had influenza (the specific viral infection), this should be reported as an AESI. If the subject has had a viral infection that is less severe, then this should be reported as an AE only.

12.1.3.8. Vasculitis

Vasculitis is defined as an inflammatory disorder of blood vessels involving arteries and/or veins and characterized by characteristic clinical signs/symptoms and diagnosed by biopsy, imaging such as angiography or blood tests such as findings of antineutrophil cytoplasmic antibodies consistent with the diagnosis. Underlying causes should be identified, such as medications including study drug, infections or systemic inflammatory syndromes, wherever possible.

12.1.3.9. Major acute cardiovascular events (MACE)

MACE events for this study are defined as stroke, acute coronary syndrome, MI, or cardiovascular death.

12.1.4. Other significant adverse events

During the evaluation of the AE data, an AstraZeneca medically qualified expert will review the list of AEs that were not reported as SAEs or AEs leading to withdrawal. Based on the expert's judgment, significant AEs of particular clinical importance may, after consultation with the Global Safety Physician, be considered other significant AEs (OAEs) and reported as such in the CSR. A similar review of other data from vital signs, ECGs, laboratory assessments and other safety assessments will be performed for identification of OAEs.

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

12.2. Recording of Adverse Events

12.2.1. Time period for collection of adverse events

Serious AEs will be collected from the signing of informed consent and AEs from randomization until the final visit.

12.2.2. Follow-up of unresolved adverse events

Any AEs that are unresolved at the subject's last visit in the study are followed up by the investigator for as long as medically indicated, but without further recording in the ClinBase. Thereafter, follow-up findings from subjects with SAEs will be reported to the DES based on the established standard reporting process.

AstraZeneca retains the right to request additional information for any subject with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

12.2.3. Variables

The following variables will be collected for each AE:

- AE diagnosis/description
- The date and time when the AE started and stopped
- Intensity
- Whether the AE is serious or not

- Investigator causality rating against the IMP (yes or no)
- AE caused subject's withdrawal from study (yes or no)
- Outcome

Additional variables (e.g., action taken with study drug) will be collected for all SAEs including treatment given for the event.

The following intensity ratings will be used:

1. Mild (awareness of sign or symptom, but easily tolerated)
2. Moderate (discomfort sufficient to cause interference with normal activities)
3. Severe (incapacitating, with inability to perform normal activities)

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 12.1.2.

An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be an SAE.

12.2.4. Causality collection

The investigator will assess causal relationship between IMP 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 investigational product?"

For SAEs, causal relationship will also be assessed for study procedures and other medication, if applicable. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as "yes".

A guide to the interpretation of the causality question is found in Appendix 15.1 of this clinical study protocol.

12.2.5. Adverse events based on symptoms and signs

All AEs spontaneously reported by the subject or reported in response to the open question from the study personnel: *"Have you had any health problems since you were last asked?"*, or revealed by observation will be collected and recorded in ClinBase.

When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of symptoms and signs. However, if a diagnosis is known and there are other symptoms

or signs that are not generally part of the diagnosis, the diagnosis and each symptom or sign will be recorded separately.

12.2.6. Adverse events based on examinations and tests

The results from protocol-mandated safety assessments will be summarized in the CSR. Deterioration as compared to baseline in protocol-mandated safety assessments should therefore only be reported as AEs if they fulfill any of the SAE criteria or, if applicable, they are the reason for discontinuation of treatment with the IMP.

If deterioration in vital sign or a laboratory value is associated with clinical symptoms and/or signs, the symptom or sign will be reported as an AE and the associated vital sign or laboratory result will be considered as additional information.

Wherever possible the reporting investigator should use the clinical, rather than the laboratory term (e.g., anemia versus low hemoglobin value).

In the absence of clinical symptoms or signs, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE.

12.2.7. Hy's Law

Cases where a subject shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT $\geq$ 3xULN together with total bilirubin $\geq$ 2xULN may need to be reported as SAEs. Please refer to Appendix 15.3 for further instruction on cases of increases in liver biochemistry and evaluation of Hy's Law.

12.3. Reporting of adverse events of special interest

Adverse Events of Special Interest will be assessed by the Investigator for severity, relationship to the investigational product, possible etiologies, and whether the event also meets criteria of an SAE. All AESIs (serious or non-serious) will be recorded on the AE CRF (using a recognized medical term or diagnosis that accurately reflects the event). AESIs that are assessed as serious will also be reported to the DES on the standard SAE reporting form.

The reporting period for AESIs is the period immediately following the time that written informed consent is obtained through the end of subject participation in the study. Detection of an AESI (serious or non-serious), is required to be reported within 24 hours of knowledge of the event to the appropriate AstraZeneca representative.

12.4. Reporting of serious adverse events

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

If any SAE occurs in the course of the study, then investigators or other clinical unit personnel will inform appropriate AstraZeneca representatives immediately, or **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative will work with the investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety Data Entry Site **within 1 calendar day** of initial receipt for fatal and life-threatening events and **within 5 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up will be undertaken immediately.

Investigators or other clinical unit personnel will inform AstraZeneca representatives of any follow-up information on a previously reported SAE immediately, or **no later than 24 hours** of when he or she becomes aware of it.

In addition to recording of SAEs in ClinBase, the AstraZeneca Serious Adverse Event Report – Clinical Study form for reporting an SAE to the Data Entry Site (DES) will also be used.

All information provided for the SAE sent into the DES will be in English.

The following CRF modules will be completed for each SAE report:

- Demography
- Dosing
- AE (including start and stop date/time for the AE, the investigator's causality assessment to study drug, action taken with study drug, severity and outcome)
- SAE (including serious criteria, causality assessment to study procedure any investigations, the symptoms and course of the event and any treatments given)
- Medical history
- Concomitant medications
- LIVERRF (risk factors), LIVERSS (signs and symptoms) and LIVERDI (additional diagnostic with results) for all SAEs with a reported term of 'Potential Hy's Law' or 'Hy's Law' will be provided in a narrative form by the PI

- Any additional supporting information, e.g., vital signs, ECG assessments, laboratory test results

The 'AstraZeneca first aware date' for all SAEs reported is the date that any member of the Provider or AstraZeneca first become aware of the SAE and for regulatory reporting purposes this is the 'clock start date'.

Each SAE (as Portable Document Format [PDF]) should be sent to the DES Tata Consultancy Services (TCS) preferably via secure e-mail using the mailbox e-mail address:

The e-mail should contain the following information in the e-mail header:

Subject Title: New SAE; <study code>, <SAE text>, <Country>, <Center No>, <Enrollment code>, <Randomization code>

The message in the e-mail itself should contain the following:

A NEW serious adverse event has been reported for the following subject:

Study Code:

Country: <country>

Center No: <study site number>

Enrollment Code: <SUBJECT>

Randomization Code: <SUBJECT>

SAE Description:

Seriousness Criteria:

Study Drug Causality/Additional Med Causality/other Med Causality/Study Procedure Causality

Date SAE met criteria for serious:

AstraZeneca (= PAREXEL investigator) first aware date:

13. LEGAL AND ADMINISTRATIVE ASPECTS

13.1. Archiving of Study Documents

All source documents generated in connection with the study will be retained in the limited access file storage area, respecting the privacy and confidentiality of all records that could identify the subjects. Direct access is allowed only for authorized people for monitoring and auditing purposes. Source documents will be handled, stored and archived according to in house procedures.

Investigator specific essential documents will be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the IMP. These documents could be retained for a longer period however, if required by the regulatory requirements or by an agreement with AstraZeneca. It is the responsibility of AstraZeneca to inform the investigator as to when these documents no longer need to be retained.

Study documentation will be archived by the contract research organization (CRO) for 15 years.

13.2. Publication of Study Results

All of the study information and data collected during the study are confidential and the property of AstraZeneca. After completion of the study, the investigator may prepare a joint publication with AstraZeneca. The investigator must undertake not to submit any part of the individual data from this clinical study protocol for publication without prior consent of AstraZeneca at a mutually agreed time.

13.3. Clinical Study Report

An integrated CSR will be prepared in accordance with the standards of the ICH guideline for structure and content of clinical study reports (ICH E3). Copies of the CSR will be provided to the IEC/IRB and the national regulatory authority in accordance with regulatory requirements and PAREXEL SOPs. In the event of premature termination of the study or other conditions specified in ICH E3, an abbreviated CSR may be prepared.

14. REFERENCE LIST

1.

2. Wang B, Higgs BW, Chang L, Vainshtein I, Liu Z, Streicher K, et al. Pharmacogenomics and translational simulations to bridge indications for an anti-interferon-α receptor antibody. Clin Pharmacol Ther. 2013 Jun;93(6):483-92.

3. Sampson et al, Second symposium on the definition and management of anaphylaxis: summary report--Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol. 2006 Feb;117(2):391-7.

4. FDA Guidance for Industry 'Drug-induced liver injury: Premarketing clinical evaluation'. July 2009. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

15. APPENDICES

15.1. Additional Safety Information

FURTHER GUIDANCE ON THE DEFINITION OF A SERIOUS ADVERSE EVENT

Life-threatening

'Life-threatening' means that the subject was at immediate risk of death from the 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 (e.g., hepatitis that resolved without hepatic failure).

Hospitalization

Outpatient treatment in an emergency room is not in itself a SAE, although the reasons for it may be (e.g., bronchospasm, laryngeal edema). 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 judgment 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, hospitalization, disability or incapacity but may jeopardize the subject or may require medical intervention to prevent 1 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 judgment 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-acetyl cysteine.
- Intensive treatment in an emergency room or at home for allergic bronchospasm.
- Blood dyscrasias (e.g., neutropenia or anemia requiring blood transfusion) or convulsions that do not result in hospitalization.

- Development of drug dependency or drug abuse.

A GUIDE TO INTERPRETING THE CAUSALITY QUESTION

The following factors should be considered when deciding if there is a "reasonable possibility" that an AE may have been caused by the investigational medicinal product (IMP).

- **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 other etiology 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?

  Note: 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 1 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 recognized 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.

15.2. International Airline Transportation Association (IATA) 6.2 Guidance Document

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

International Airline Transportation Association (IATA) classifies bio hazardous 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

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. Category A pathogens are for example, Ebola and Lassa Fever viruses. Category A pathogens:

Are to be packed and shipped in accordance with IATA Instruction 602.

CATEGORY B

Category B Infectious Substances are infectious substances that do not meet the criteria for inclusion in Category A. Category B pathogens are for example, hepatitis A, B, C, D and E viruses, and HIV types 1 and 2. They are assigned the following UN number and proper shipping name:

- UN 3373 – Biological Substance, Category B

Category B pathogens:

- Are to be packed in accordance with UN3373 and IATA Instruction 650.

EXEMPT

Exempt refers to all other materials with minimal risk of containing pathogens.

- Clinical trial samples will fall into Category 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. Packing should be done by an IATA certified person, as applicable.
- 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.

15.3. Actions Required in Cases of Combined Increase of Aminotransferase and Total Bilirubin - Hy's Law

1. INTRODUCTION

During the course of the study, the investigator will remain vigilant for increases in liver clinical chemistry. The investigator is responsible for determining whether a subject/patient meets potential Hy's Law (PHL) criteria at any point during the study.

The investigator participates, together with AstraZeneca clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether Hy's Law (HL) criteria are met. The HL criteria are met if there is no alternative explanation for the elevations in liver clinical chemistry other than Drug Induced Liver Injury (DILI) caused by the investigational medicinal product (IMP).

The investigator is responsible for recording data pertaining to PHL/HL cases and for reporting AEs and SAEs according to the outcome of the review and assessment in line with standard safety reporting processes.

2. DEFINITIONS

Potential Hy's Law (PHL)

- Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥ 3x upper limit of normal (ULN) **and** total bilirubin (TBL) ≥ 2x ULN at any point during the study irrespective of an increase in alkaline phosphatase (ALP)
- The elevations do not have to occur at the same time or within a specified time frame

Hy's Law (HL)

- AST or ALT ≥ 3x ULN **and** TBL ≥ 2x ULN, where no other reason, other than the IMP, can be found to explain the combination of increases, e.g., elevated ALP indicating cholestasis, viral hepatitis, another drug
- The elevations do not have to occur at the same time or within a specified time frame

3. IDENTIFICATION OF POTENTIAL HY'S LAW CASES

In order to identify cases of PHL it is important to perform a comprehensive review of laboratory data for any subject/patient who meets any of the following identification criteria in isolation or in combination:

- ALT ≥ 3x ULN
- AST ≥ 3x ULN

- TBL ≥ 2x ULN

The investigator will review without delay each new laboratory report and if the identification criteria are met will:

- Notify the AstraZeneca representative
- Determine whether the subject/patient meets PHL criteria (see Section 2 of this Appendix for definition) by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory case report form (CRF)

4. FOLLOW-UP

4.1 Potential Hy's Law Criteria not met

If the subject/patient does not meet PHL criteria the investigator will:

- Inform the AstraZeneca representative that the subject/patient has not met PHL criteria
- Perform follow-up on subsequent laboratory results according to the guidance provided in the clinical study protocol

4.2 Potential Hy's Law Criteria met

If the subject/patient does meet PHL criteria the investigator will:

- Notify the AstraZeneca representative who will then inform the central study team.

  The study physician contacts the investigator, to provide guidance, discuss and agree an approach for the study subjects'/patients' follow-up and the continuous review of data.

Subsequent to this contact the investigator will:

- Monitor the subject/patient until liver clinical chemistry variables and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated.
- Investigate the etiology of the event and perform diagnostic investigations as discussed with the study physician.
- Complete the 3 Liver CRF Modules as information becomes available.

If at any time (in consultation with the study physician) the PHL case meets serious criteria, report it as an SAE using standard reporting procedures.

5. REVIEW AND ASSESSMENT OF POTENTIAL HY'S LAW CASES

The instructions in this section should be followed for all cases where PHL criteria were met.

No later than 3 weeks after the clinical chemistry abnormality was initially detected, the study physician contacts the investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the IMP. The AstraZeneca Medical Science Director and Global Safety Physician will also be involved in this review together with other subject matter experts as appropriate.

According to the outcome of the review and assessment, the investigator will follow the instructions below.

If there is an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for an SAE:

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate CRF
- If the alternative explanation is an AE/SAE, record the AE /SAE in the CRF accordingly and follow the AstraZeneca standard processes

If it is agreed that there is **no** explanation that would clarify the ALT or AST and TBL elevations other than IMP causality:

- Report an SAE (report term 'Hy's Law') according to AstraZeneca standard processes.
  - The 'Medically Important' serious criterion should be used if no other serious criteria apply
  - As there is no alternative explanation for the HL case, a causality assessment of 'related' should be assigned

If, there is an unavoidable delay, of over 3 weeks, in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Report an SAE (report term 'Potential Hy's Law') applying serious criteria and causality assessment as per above
- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are met. Update the SAE report according to the outcome of the review [4].

15.4. Guidance for abnormal Pap smear results

Pap Smear Result	Abbreviation	Also Known As	Suggested Action
Atypical squamous cells–undetermined significance	ASC–US	—	Permitted to enter study
Atypical squamous cells–cannot exclude HSIL	ASC–H	—	Permitted to enter study
Atypical glandular cells	AGC	—	Permitted to enter study
Low-grade squamous intraepithelial lesion	LSIL	Mild dysplasia Cervical intraepithelial neoplasia–1 (CIN–1)	Permitted to enter study
High-grade squamous intraepithelial lesion	HSIL	Moderate dysplasia CIN-2 / CIN II	Permitted to enter study
High-grade squamous intraepithelial lesion	HSIL	CIN–3 / CIN III Carcinoma in situ (CIS)	**Exclude/discontinue subject**
Endocervical adenocarcinoma in situ	AIS	—	**Exclude/discontinue subject**

15.5. Anaphylaxis

In adults, anaphylaxis is highly likely when any 1 of the following 3 criteria is fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips, tongue and/or uvula)

AND AT LEAST ONE OF THE FOLLOWING:

- Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)
- Reduced BP (see number 3 below for definition) or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)

2. Two or more of the following that occur rapidly after exposure to a likely allergen for that subject (minutes to several hours):
    - Involvement of the skin-mucosal tissue (e.g., generalized hives, itch, flush, swollen lips, tongue and/or uvula)
    - Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)
    - Reduced BP (see number 3 below for definition) or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence)
    - Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)
3. Reduced BP after exposure to known allergen for that subject (minutes to several hours); for adults a systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline BP (taken at or immediately prior to start of the infusion), whichever BP is lower.

The following definitions are provided for the purposes of this study:

Hypersensitivity reaction: an acute onset of an illness with involvement of the skin, mucosal tissue, or both during infusion of investigational product (but does not meet the definition of anaphylaxis described above).

Infusion-related reaction: any other reaction occurring during infusion of investigational product or felt to be temporally related to the infusion within 24 hours of investigational product administration.

To assist with the mitigation of these AEs, see Table 4, which categorizes reactions by severity of symptoms, proposes severity-specific treatment and offers guidance on management of investigational product. Final treatment is at the discretion of the Investigator and should reflect local SOC.

Table 4 An Approach to Management of Anaphylactic, Hypersensitivity, and Infusion-Related Reactions

Severity of symptoms	Treatment	Investigational product
Mild reactions (infusion and hypersensitivity) Mild infusion-related reactions such as headache, nausea, non-pruritic rash, or mild hypersensitivity reactions including localized cutaneous reactions such as mild pruritus, flushing, rash, dizziness, headache, ≤20 mmHg change in systolic BP from pre-infusion measurement	Evaluate subject, including close monitoring of vital signs At the discretion of the Investigator, treat subject, for example, with: - Normal saline (~500 to 1000 mL/hour IV) and/or - Diphenhydramine 50 mg IV or equivalent and/or - Acetaminophen 500 to 650 mg or equivalent dose of paracetamol and/or - Topical antihistamines and/or low-potency topical corticosteroid preparations and/or - Anti-nausea medication, as needed	Stop investigational product infusion immediately Option 1: do not resume investigational product infusion; OR at the discretion of the Investigator, resume current investigational product infusion under observation and complete investigational product infusion at no more than half the planned infusion rate Option 2: discontinue any further administration of investigational product; OR at the discretion of the Investigator, continue future investigational product administrations and consider slowing infusion rate and pretreating subject 1.5 to 0.5 hours prior to investigational product administration, for example with: - Diphenhydramine 50 mg IV or equivalent - Acetaminophen 500 to 650 mg or equivalent dose of paracetamol
Moderate reactions (infusion) Infusion-related reaction such as those listed above under mild reactions but excluding moderate hypersensitivity reactions (see below)	Evaluate subject, including close monitoring of vital signs Treat subject, for example, with: - Normal saline (~500 to 1000 mL/hour IV) and/or - Diphenhydramine 50 mg IV or equivalent and/or - Acetaminophen 500 to 650 mg or equivalent dose of paracetamol and/or - Anti-nausea and/or antiemetic intramuscular, as needed	Stop investigational product infusion immediately Option 1: do not resume investigational product infusion; OR based on risk/benefit evaluation, at the discretion of the Investigator, resume current investigational product infusion under observation and at no more than half the planned infusion rate after treatment of current signs and symptoms as suggested (e.g., normal saline and/or and/or topical antihistamines)

Severity of symptoms	Treatment	Investigational product
		Additional Options for Future Administration of investigational product Discontinue any further administrations of investigational product; OR Further investigational product infusions, at the discretion of the Investigator, continue investigational product administration and consider slowing infusion rate and pretreating subject 0.5 to 1.5 hours prior to investigational product administration, for example with: - Diphenhydramine 50 mg IV or equivalent - Acetaminophen 500 to 650 mg or equivalent dose of paracetamol - Anti-nausea and/or antiemetic by mouth Prior to next administration of investigational product administration, consider initiating at a slower infusion rate and pretreating subject 0.5 to 1.5 hours prior to next administration of investigational product, for example, with - Diphenhydramine 50 mg IV or equivalent - Acetaminophen 500 to 650 mg or equivalent dose of paracetamol If moderate event recurs in the same subject, discontinue further investigational product administration

Severity of symptoms	Treatment	Investigational product
Moderate hypersensitivity reactions Infusion related reactions which may include generalized rash or urticaria, palpitations, chest discomfort, shortness of breath, hypo- or hypertension with >20 mmHg change in systolic BP from pre-infusion measurement	Evaluate subject, including close monitoring of vital signs Treat subject, for example, with: - Normal saline (~500 to 1000 mL/hour IV) and/or - Diphenhydramine 50 mg IV or equivalent and/or - Acetaminophen 500 to 650 mg or equivalent dose of paracetamol and/or - IV corticosteroids, such as hydrocortisone 100 mg or methylprednisolone 20 to 40 mg	Stop investigational product infusion immediately DO NOT resume current infusion Discontinue any further administrations of investigational product Consider need for additional oral antihistamine administration or oral corticosteroid administration to prevent reoccurrence of symptoms over subsequent 2 to 3 days
Severe Above plus fever with rigors, hypo- or hypertension with ≥40 mmHg change in systolic BP, signs of end organ dysfunction (e.g., symptomatic hypotension such as hypotonia, syncope, incontinence, seizure) from pre-infusion measurement, or wheezing, angioedema, or stridor OR **Life-threatening** Defined as a reaction that is life-threatening and requires pressor and/or ventilator support or shock associated with acidemia and impairing vital organ function due to tissue hypoperfusion	Evaluate subject, including close monitoring of vital signs Maintain airway, oxygen if available Treat subject immediately, for example with: - Normal saline (~500 to 1000 mL/hour IV) - Epinephrine for bronchospasm, hypotension unresponsive to IV fluids, or angioedema. Dose and route as per local SOC, example, epinephrine 1:1000, 0.5 to 1.0 mL administered SC for mild cases and intramuscular for more severe cases - IV corticosteroids, such as hydrocortisone 100 mg or methylprednisolone 20 to 40 mg - Diphenhydramine 50 mg IV or equivalent - Acetaminophen 500 to 650 mg or equivalent dose of paracetamol Call emergency medical transport for transport to emergency hospital based on judgment of the Investigator Grade 3 wheezing, hypotension or angioedema is unresponsive to single dose of epinephrine Grade 4 event At the discretion of the Investigator	Stop investigational product infusion immediately Do not resume current infusion Permanently discontinue investigational product administration Consider need for additional oral antihistamine administration or oral corticosteroid administration to prevent reoccurrence of symptoms over subsequent 2 to 3 days