CLINICAL STUDY PROTOCOL

ALX0061-C201

A Phase IIb Multicenter, Randomized, Double-blind, Placebo-Controlled Dose-Range Finding Study of ALX-0061 Administered Subcutaneously in Combination with Methotrexate, in Subjects with Moderate to Severe Rheumatoid Arthritis Despite Methotrexate Therapy

Short Title:	A Phase IIb Dose-Range Finding Study for ALX-0061 Combination Therapy in Subjects with Rheumatoid Arthritis
Study Drug:	ALX-0061
EudraCT n°:	2014-003033-26
Sponsor Protocol Code:	ALX0061-C201
Sponsor:	Ablynx NV Technologiepark 21 9052 Zwijnaarde, Belgium
Contract Research Organization:	[redacted]
Phase of Development:	Phase IIb
Indication:	Rheumatoid arthritis (RA)
Protocol Date:	July 9, 2015
Protocol Version:	2.0
Protocol Status:	Final

This study will be performed in compliance with the Clinical Study Protocol, the principles of Good Clinical Practice (GCP), and the applicable regulatory requirement(s).

CONFIDENTIALITY STATEMENT

The information contained in this document, especially unpublished data, is the property of Ablynx NV (or under its control), and therefore provided to you in confidence as an Investigator, potential Investigator, or consultant, for review by you, your study staff, and an applicable Independent Ethics Committee (IEC) / Institutional Review Board (IRB). It is understood that this information will not be disclosed to others without written authorization from Ablynx NV, except to the extent necessary to obtain informed consent from those persons to whom the study drug may be administered.

APPROVAL OF CLINICAL STUDY PROTOCOL

The Sponsor and the Investigator(s) agree to conduct the study as outlined in this Clinical Study Protocol. Any modification of the Clinical Study Protocol must be agreed upon by the Sponsor and the Investigator(s), and must be documented in writing.

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Signature – Date: 07/10/2015

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Investigator:

I have read Clinical Study Protocol ALX0061-C201 and agree to personally conduct or supervise the clinical study in accordance with the Clinical Study Protocol.

I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that site staff receives the appropriate information throughout the study.

I confirm that the study team and I will not implement any changes to the Clinical Study Protocol without agreement of Ablynx NV, except where necessary to eliminate an immediate hazard to the patients.

I confirm that I am thoroughly familiar with the appropriate use of the study drug, as described in the Clinical Study Protocol and any other information provided by Ablynx NV.

I confirm that I am aware of and will comply with GCP.

Hence, I agree to supply Ablynx NV with any necessary information regarding the ownership interest and financial ties, to promptly update this information if any relevant changes occur during the course of the study, and that Ablynx NV may disclose any available information about such ownership interests and financial ties to regulatory authorities.

Signature – Date:

Primary Investigator Name:

Degree/Function:

Site Details/Address:

CONTACT INFORMATION

Serious adverse event (SAE) contact information and other contact details of the Sponsor and third parties are available in the "Investigator Site File".

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LIST OF ABBREVIATIONS

ACR	American College of Rheumatology
ADA	Anti-drug antibodies
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
CA	Competent Authority
CCP	Cyclic citrullinated peptide
CD20	Cluster of differentiation 20
CDAI	Clinical Disease Activity Index
CHF	Congestive heart failure
CL	Total body clearance
CRO	Contract research organization
CRP	C-reactive protein
CTCAE	Common Terminology Criteria for Adverse Events
CTD	Clinical trial directive
CXCL13	C-X-C Motif Chemokine 13
CYP450	Cytochrome P450
DAS28	Disease Activity Score using 28 joint counts
DMARD	Disease modifying anti-rheumatic drug
DNA	Deoxyribonucleid acid
DSMB	Data safety monitoring board
EC_{50}	Half maximal effective concentration
ECG	Electrocardiogram
(e)CRF	(Electronic) Case report form
ELISA	Enzyme-linked immunosorbent assay
ESR	Erythrocyte sedimentation rate
EULAR	European League Against Rheumatism
FACIT-Fatigue	Functional Assessment of Chronic Illness Therapy-Fatigue
GCP	Good Clinical Practice
GH	VAS Patient Global Assessment of Disease Activity
GLP	Good Laboratory Practice
gp130	Glycoprotein 130
HAQ-DI	Health Assessment Questionnaire-Disability Index
HDL	High-density lipoprotein
HIV	Human immunodeficiency virus
HSA	Human serum albumin
i.a.	Intra articular

ICF	Informed Consent Form
ICH	International Conference on Harmonization
ID	Identification
IEC	Independent Ethics Committee
Ig	Immunoglobulin
IGRA	Interferon-gamma release assay
IL-1	Interleukin 1
IL-6	Interleukin 6
IL-6R	Interleukin-6 receptor
i.m.	Intramuscular(ly)
INR	International normalized ratio
IRB	Institutional review board
ITT	Intent-to-treat
i.v.	Intravenous(ly)
IWRS	Interactive web response system
JAK	Janus kinase
LDL	Low-density lipoprotein
MAD	Multiple ascending dose
mIL-6R	Membrane-bound interleukin-6 receptor
MMP-3	Matrix metalloproteinase 3
MTX	Methotrexate
nAbs	Neutralizing antibodies
NSAID	Non-steroidal anti-inflammatory drug
OLE	Open-label extension
PD	Pharmacodynamic
PIP	Proximal interphalangeal
PK	Pharmacokinetic
PP	Per protocol
q2w	Every 2 weeks
q4w	Every 4 weeks
QTc	QT interval corrected for heart rate
QTcB	QT interval corrected for heart rate according to Bazett's formula; QTcB = $QT/\sqrt{RR}$
QTcF	QT interval corrected for heart rate according to Fridericia's formula; $QTcF = QT/\sqrt[3]{RR}$
RA	Rheumatoid arthritis
RNA	Ribonucleid acid
SAD	Single ascending dose
SAE	Serious adverse event
SAP	Statistical analysis plan

SC	Sternoclavicular joint
s.c.	Subcutaneous(ly)
SDAI	Simplified Disease Activity Index
SF-36	Short Form (36) Health Survey
sIL-6R	Soluble interleukin-6 receptor
SJC	Swollen joint count
SLE	Systemic lupus erythematosus
SUSAR	Suspected Unexpected Serious Adverse Reaction
TB	Tuberculosis
TCZ	Tocilizumab
TEAE	Treatment-emergent adverse event
TJC	Tender joint count
TK	Toxicokinetics
TMJ	Temporomandibular joint
TNF α	Tumor necrosis factor alpha
ULN	Upper limit of normal
VAS	Visual analogue scale
VASPA	Visual analogue scale, patient assessment of disease activity
VASPHA	visual analogue scale, physician assessment of disease activity
VH	Heavy chain variable region
WHO	World Health Organization
WMA	World Medical Association

CHANGES COMPARED TO PREVIOUS VERSION(S)

Original section	Change/Rationale
Version 2.0 (dated July 9, 2015) compared to Version 1.0 (dated October 17, 2014)	
Version n° and date were adapted throughout the document (incl. headers and footers). Section "Changes compared to previous version(s)" was completed.	
Table of Contents	Page numbers have been updated.
List of Abbreviations, Synopsis, Schedule of Assessments, Sections 3.4.4.1., 3.4.4.2., and 3.4.7	Assessment of C-telopeptide pyridinoline crosslinks of Type 1 collagen (ICTP) has been removed as the commercially available ELISAs for ICTP are not adequate.
Synopsis and Section 3.2.1.	The inclusion criterion on active RA has been updated to allow inclusion of subjects with C-reactive protein (CRP) > 1.0 x upper limit of normal (ULN) at screening.
Synopsis and Section 3.2.2.	The exclusion criterion on previously received approved or investigational biological or targeted synthetic DMARD therapies for RA has been updated to add additional details with regard to subjects who previously received rituximab.
Synopsis	Completion of list of safety assessments.
Schedule of Assessments and Section 3.4.5.2.	A clarification has been added to reflect that pregnancy testing applies to women of childbearing potential only.
Schedule of Assessments and Section 3.4.8.	Order of assessments has been simplified.
Section 1.2.5.	As the study report of Study ALX0061-C102 has been finalized, the word "preliminary" has been removed from the description of the results of this study.
Schedule of Assessments , Sections 3.1.1., 3.3.6., 3.4.1.1., and 3.4.7.	A typographical error has been corrected.
Sections 3.1.2. and 3.4.5.2.	Specified that results of CRP or fibrinogen will be unblinded in case of alert and at screening, which is needed to assess subject's eligibility for randomization.
Section 3.2.1.	Inclusion criterion 8 has been updated to add details with regard: - to inclusion of subjects with latent tuberculosis (TB) who have positive IGRA test and who have completed appropriate treatment. - to clarify that appropriate treatment should have been completed before first administration of study drug instead of screening.
Section 3.2.2.	Exclusion criterion 11 has been updated to correct an inconsistency between the synopsis and the body text of the protocol. In addition, exclusion criterion 17 to correct a typographical error.
Section 3.2.3.2.	Wording has been updated for clarification purpose and to correct use of an incorrect word.
Sections 3.3.2., 3.4.1.2., and 3.6.5.	A crossreference has been corrected.
Section 3.3.3.	Wording has been updated to reflect a correction according to the procedure for IMP destruction.

Section 3.3.6.	The prohibited medications high-potency opioid analgesics have been further specified.
Section 3.4.1.2.	Specification with regard to route of administration of MTX has been deleted.
Sections 3.4.2.6., 3.4.2.13., and 3.4.2.18.	Details have been added with regard to use of unit of CRP for a specific assessment.
Section 3.4.2.7.	Additional text has been added to explain the role of the independent person performing the assessment of erythrocyte sedimentation rate (ESR) analysis.
Sections 3.4.3.1., 3.4.4.1., and 3.4.6.1.	A sentence has been updated to reflect that exact time of blood sampling will not be captured in the case report form (CRF) (but in the requisition form).
Section 3.4.5.2.	It has been specified that additional pregnancy testing is allowed according to local guidelines; however, this additional pregnancy testing is not part of and cannot replace the protocol specific procedures.
Section 3.4.5.2.	Wording has been added to clarify that the IGRA test also detects latent TB.
Section 3.4.5.2.	Details with regard to allowing retesting of samples have been added.
Section 3.4.5.3.	Wording has been updated with regard to options to measure body temperature.
Section 3.5.1.1.	The text on adverse events (AEs) severity has been updated to reflect that for assessment of severity of AEs related to laboratory abnormalities, the Investigator should refer to the CTCAE v4.0 criteria.
Section 3.5.5.	Wording with regard to follow-up of AEs was updated to clarify that all AEs will be followed until satisfactory outcome.
Section 3.5.6.1.	Information with regard to pregnancies should be reported using the pregnancy form (and not the pregnancy report CRF page).
Section 3.6.4.	More clear specification of sensitivity analysis on primary endpoint using per-protocol population has been added.
Section 4.2.	Details with regard to specific version of guidelines has been removed.
Section 4.3.	Wording with regard to signing of the informed consent form (ICF) has been updated according to the ICH E6 guideline.
Section 6.	As the contract research organization (CRO) will not insure subjects separately against damage resulting from accidents that may occur during the study, but that are not directly related to the study, this statement has been deleted.

PROTOCOL SYNOPSIS

Protocol Title:

A Phase IIb Multicenter, Randomized, Double-blind, Placebo-Controlled Dose-Range Finding Study of ALX-0061 Administered Subcutaneously in Combination with Methotrexate, in Subjects with Moderate to Severe Rheumatoid Arthritis Despite Methotrexate Therapy

Protocol Short Title:

A Phase IIb Dose-Range Finding Study for ALX-0061 Combination Therapy in Subjects with Rheumatoid Arthritis

Study Drug:

ALX-0061, a Nanobody directed towards the Interleukin-6 receptor (IL-6R)

EudraCT n°:

2014-003033-26

Sponsor Protocol Code:

ALX0061-C201

Sponsor:

Ablynx NV
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9052 Zwijnaarde, Belgium

Phase of Development:

Phase IIb

Indication:

Rheumatoid arthritis (RA)

Objectives:

Primary objective:

- To assess the efficacy and safety of dose regimens of ALX-0061 administered subcutaneously (s.c.) in combination with methotrexate (MTX) to subjects with active RA despite MTX therapy, compared with placebo.

Secondary objective:

- To assess the effects of ALX-0061 on quality of life, pharmacokinetics (PK), pharmacodynamics (PD), and immunogenicity of ALX-0061, and to define the optimal dose regimen for ALX-0061, based on safety and efficacy, for further clinical development.

Study Type and Treatments Administered:

This is a multicenter, randomized, double-blind, placebo-controlled dose-range finding Phase IIb study of ALX-0061 administered s.c. in combination with MTX to subjects with active RA despite MTX therapy.

Treatment Arms

Eligible subjects will be randomly assigned in a 1:1:1:1:1 ratio to 1 of the treatment groups listed below. As the highest dose of ALX-0061 will be administered via 2 injections every 2 weeks (q2w), subjects in Groups 1-4 will also be administered 2 injections q2w, with 1 or both syringes containing placebo depending on the assigned treatment group, to maintain the blind:

Group 1 (N=66) Placebo
Placebo s.c. injections (2 syringes [0.5 and 1.0 mL]) at Week 0 and q2w thereafter up to and including Week 22.

Group 2 (N=66) 75 mg every 4 weeks (q4w)
ALX-0061 75 mg s.c. injections (1 syringe [0.5 mL]) at Week 0 and q4w thereafter up to and including Week 20. To maintain the blind, subjects in this group will also receive placebo s.c. up to and including Week 22 (1 placebo syringe [1.0 mL] at Week 0 and q4w thereafter in combination with the ALX-0061 injection; 2 placebo syringes [0.5 and 1.0 mL] at Week 2 and q4w thereafter).

Group 3 (N=66) 150 mg q4w
ALX-0061 150 mg s.c. injections (1 syringe [1.0 mL]) at Week 0 and q4w thereafter up to and including Week 20. To maintain the blind, subjects in this group will also receive placebo s.c. up to and including Week 22 (1 placebo syringe [0.5 mL] at Week 0 and q4w thereafter in combination with the ALX-0061 injection; 2 placebo syringes [0.5 and 1.0 mL] at Week 2 and q4w thereafter).

Group 4 (N=66) 150 mg q2w
ALX-0061 150 mg s.c. injections (1 syringe [1.0 mL]) at Week 0 and q2w thereafter up to and including Week 22. To maintain the blind, subjects in this group will also receive placebo s.c. q2w up to and including Week 22 (1 placebo syringe [0.5 mL]).

Group 5 (N=66) 225 mg q2w
ALX-0061 225 mg s.c. injections (2 syringes [0.5 and 1.0 mL]) at Week 0 and q2w thereafter up to and including Week 22. These subjects will not receive placebo injections.

Efficacy Discontinuation Criteria at Week 12, 16, or 20:

Any subject with < 20% improvement from baseline in both swollen and tender joint count (SJC and TJC; 66/68 counts) at any of the visits at week 12, 16 or 20 will discontinue from the trial, but remain blinded to study drug assignment. The visit at which subjects will meet the efficacy discontinuation criteria, is defined as the Early Termination Visit for these patients. Following this Early Termination Visit, any future care will then be provided (outside of the study) at the discretion of the treating physician as part of usual clinical practice.

The blind will be maintained until the last enrolled subject completes the final evaluations and the database is locked.

In countries where open-label extension (OLE) study ALX0061-C203 is approved, subjects who complete the 24-week assessment period of the current study will be invited to roll-over. Details on the open-label extension (OLE) study are described in Clinical Study Protocol ALX0061-C203.

Study Population:

Subjects with active RA despite MTX therapy

Number of Subjects:

Up to approximately 330 subjects in 5 treatment arms, randomized in a 1:1:1:1:1 ratio.

Inclusion criteria:

The main criteria for inclusion include the following:

- Man or woman ≥ 18 years and < 75 years of age at the time of signing the informed consent form.

- Diagnosis of RA (according to the 2010 European League Against Rheumatism [EULAR]/American College of Rheumatology [ACR] classification criteria) for at least 6 months prior to screening, and ACR functional class I-III.
- Treated with and tolerating MTX according to the following criteria:
  a. Minimum treatment duration of 4 months prior to screening.
  b. Stable dose of MTX of ≥ 12.5 mg/week to ≤ 25 mg/week for at least 6 consecutive weeks prior to screening.
  c. Expected to maintain that stable dose throughout the study as described in section "Concomitant Medication".
- Active RA as defined, for the purpose of this study, by persistent disease activity with at least 6 swollen and 6 tender joints (66/68-joint count), at the time of screening and baseline, and C-reactive protein (CRP) > 1.0 x upper limit of normal (ULN) at screening.

Exclusion criteria:

The main criteria for exclusion include the following:

- Have been treated with disease modifying anti-rheumatic drugs (DMARDs)/systemic immunosuppressives (e.g., oral or parenteral gold, sulfasalazine, azathioprine, cyclosporine, mycophenolate mofetil, hydroxychloroquine, chloroquine) other than MTX during 4 weeks, or 12 weeks for leflunomide (except when an adequate wash-out procedure for leflunomide was completed) prior to first administration of study drug.
- Have received approved or investigational biological or targeted synthetic DMARD therapies for RA (including tumor necrosis factor alpha-inhibitors, abatacept, rituximab, or Janus kinase [JAK]-inhibitors) less than 6 months prior to screening. For subjects who received prior rituximab, subjects with an inadequate recovery of B cells should be excluded regardless of when they received rituximab.
- Have a history of toxicity, non-tolerance, primary non-response or inadequate response to a biological therapy, or targeted synthetic DMARDs (including JAK inhibitors), for RA.
- Have received prior therapy blocking the interleukin-6 (IL-6) pathway, such as but not limited to ALX-0061, sirukumab, sarilumab, clazakizumab, olokizumab, tocilizumab at any time.

A complete list of selection criteria can be found in the body of the Clinical Study Protocol.

Study Drug, Comparator, Dose, Mode of Administration:

- Study Drug:
  - Active substance: ALX-0061 Nanobody.

- Route and volume of administration: s.c. injections at a volume of 0.5 mL and/or 1.0 mL.

- Placebo:
  - Substance: placebo.
  - Route and volume of administration: s.c. injections at a volume of 0.5 mL and/or 1.0 mL.

At all visits, study drug is to be administered under supervision while the subject is at the study site.

- Concomitant Medication: stable dose and route of MTX (12.5-25.0 mg weekly) maintained during the 6 consecutive weeks prior to screening and for the duration of the study. Commercially available MTX will be used in this study and will not be provided by the Sponsor.

Study Duration:

- The anticipated study duration is a maximum of 34 weeks after randomization:
  - Subjects who will not participate in the OLE study will be followed for efficacy up to and including Week 24, and for safety up to and including Week 34.
  - Subjects who will participate in the OLE study will be followed until Week 24, at which time they will switch to the OLE.

  The end of study is defined as the time of the last visit of the last subject participating in the study.

- Screening period:
  - Subjects will be screened to confirm eligibility for participation in this study within 3 weeks prior to first dosing.

- Treatment and assessment period:
  - All eligible subjects will receive treatment from Week 0, up to and including Week 22. Subjects will return for 13 ambulatory visits planned on Weeks 0, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, and 24.

- End of Treatment Visit (Week 24) (or Early Termination Visit for subjects who discontinue early)/Follow-up Visit:
  - Subjects who are eligible to participate in the OLE study will have the End of Treatment Visit in Study ALX0061-C201 at Week 24.
  - Subjects who are not eligible to participate in the OLE study will have the End of Treatment Visit at Week 24 and should return for a Follow-up Visit 12 weeks after last study drug administration.

- For subjects who will discontinue study participation for fulfilling the **efficacy** discontinuation criteria (see section 3.2.3.2) at weeks 12, 16, or 20, the visit at which subjects will meet these discontinuation criteria is defined as the Early Termination Visit. These subjects should return for a Follow-up Visit 12 weeks after last study drug administration.
- Subjects who have to discontinue early for reasons other than the efficacy discontinuation criteria, but are not withdrawing consent for post-treatment follow-up, should return for an Early Termination Visit 2 weeks after the last study drug administration (unless they discontinue during a study visit, in which case that becomes their Early Termination Visit). Subjects should also return for a Follow-up Visit 12 weeks after last study drug administration.
- Subjects who terminate study participation for reasons of lost to follow-up, informed consent withdrawal, or death will not have any follow-up assessments.

Assessments:

Efficacy Evaluation:

- Primary endpoint:
  - Reduction of signs and symptoms of RA will be evaluated by calculating the proportion of subjects achieving an ACR20 response at Week 12.

- Secondary endpoints include:
  - ACR20, ACR50, and ACR70 response over time.
  - Disease activity: Disease Activity Score using 28 joint counts (DAS28 using CRP and erythrocyte sedimentation rate [ESR]), Simplified Disease Activity Index (SDAI), Clinical Disease Activity Index (CDAI).
  - EULAR DAS28 response (good, moderate, or no response).
  - Remission using disease remission parameters: DAS28, SDAI, CDAI, Boolean.
  - Health Assessment Questionnaire-Disability Index (HAQ-DI).
  - Physical and mental component scores of Short Form Health Survey (SF-36).
  - Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue).

Pharmacokinetics:

- Determination of ALX-0061 serum levels.

Pharmacodynamics:

- Determination of biomarker levels, including total soluble IL-6 receptor (sIL-6R), matrix metalloproteinase 3 (MMP-3), and C-X-C motif chemokine 13 (CXCL13).

Safety:

- Safety assessments will include:
  - Physical examinations.
  - Vital signs measurements (diastolic and systolic blood pressure, temperature, pulse rate).
  - 12-lead electrocardiogram (ECG; at screening only).
  - Clinical laboratory assessments will include blood chemistry, hematology, urinalysis, coagulation and the acute phase proteins (CRP, ESR, and fibrinogen) as well as change from baseline in these laboratory parameters.
  - Adverse events (including serious adverse events, infections, injection site, and hypersensitivity reactions).

Immunogenicity:

- Determination of anti-ALX-0061 antibodies (ADA) and potentially further characterization by modified ADA assay (mADA) and neutralizing antibody assay (nAb).

Statistical Methods:

Sample Size and Power

Up to approximately 330 subjects in 5 treatment arms randomized in a 1:1:1:1:1 ratio.

Simulations were performed to evaluate the power for detecting a significant trend effect in the different ALX-0061 doses versus placebo. Assuming Week 12 ACR20 response rates of 25%, 30%, 45%, 55%, and 55% for placebo, ALX-0061 75 mg q4w, ALX-0061 150 mg q4w, ALX-0061 150 mg q2w, and ALX-0061 225 mg q2w respectively, a sample size of 66 subjects per arm will provide more than 90% power using the Cochran Armitage test for trend at significance level of 0.05 (2-sided).

Primary Efficacy Endpoint Evaluation:

For the descriptive statistics and trend test on the primary efficacy endpoint (primary efficacy analysis), data will be analyzed according to the intent-to-treat principle; thus, subjects will be analyzed according to the treatment for which they were assigned. Subjects with missing ACR20 response at Week 12 will be treated as non-responders (non-responder imputation approach).

Additionally, exploratory comparisons of each separate dose versus placebo will be conducted using a Chi^2 or Fisher exact test (or other test if deemed more relevant). The study is only powered for testing the trend of the primary endpoint. All other p-values are exploratory and no correction for multiple testing is foreseen.

Primary efficacy endpoint evaluation will also be performed using the per-protocol population as a sensitivity analysis.

All Other Evaluations:

For continuous secondary efficacy endpoints (including DAS28, CDAI, SDAI), summary statistics, such as mean with standard deviation and median and associated 95% confidence intervals will be determined. For categorical efficacy endpoints the point estimate together with the 95% confidence interval will be calculated. Summary statistics will be provided by treatment group.

All safety, PD and immunogenicity analyses will be performed using the safety population of all subjects who received at least 1 dose of study drug. Analyses will be performed using the treatment that the subject actually received.

All these data will be summarized using descriptive statistics as appropriate.

PK/PD modelling will be performed to characterize the relationship between ALX-0061 exposure and the efficacy endpoints. The results of this exploratory analysis will be presented in a separate report.

SCHEDULE OF ASSESSMENTS [A]

Study Period	Screening (Days)	Baseline (Week/ Day)	Treatment and Assessment period (Weeks)												Early Termination[C] (Weeks)	Follow-up[D] (Weeks)
Study Visit [B]	**-21 to -1**	**0**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24**	**2 (after last study drug dosing)**	**12 (after last study drug dosing)**
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**		**15**
Ambulatory visit	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Written informed consent	X															
Demographics and medical history	X															
Physical examination	X	X						X		X		X		X	X	X
Vital signs [E]	X	X	X	X	X	X	X	X		X		X		X	X	X
Interferon-gamma release assay (IGRA) test	X															
Serology (hepatitis B, hepatitis C, human immunodeficiency virus [HIV])	X															
Chest radiograph [F]	X															
Tuberculosis (TB) evaluation (questioning) [G]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Review of entry criteria	X	X														
Previous medication	X															
Concomitant medication	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→
12-lead electrocardiogram (ECG) [H]	X															
Randomization		X														
Routine clinical laboratory analyses [I]	X		X		X		X									X
Extended clinical laboratory analyses (including fasting serum lipids) [J]		X		X		X		X		X		X	X	X	X	
Pregnancy test (serum at screening/urine at other visits) for females of childbearing potential only	X	X						X						X	X	
Interactive web response system (IWRS) notification of tender & swollen joint counts		X						X		X		X				
Study drug administration (via IWRS) [K]		X	X	X	X	X	X	X	X	X	X	X	X			

Study Period	**Screening (Days)**	**Baseline (Week/ Day)**	**Treatment and Assessment period (Weeks)**												**Early Termination[C] (Weeks)**	**Follow-up[D] (Weeks)**
Study Visit [B]	**-21 to -1**	**0**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24**	**2 (after last study drug dosing)**	**12 (after last study drug dosing)**
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**		**15**
Morning stiffness duration	X	X						X		X		X		X	X	
Joint assessment (66/68-joint count)	X	X	X	X	X	X	X	X		X		X		X	X	
Patient Pain visual analogue scale (VAS)		X	X	X	X	X	X	X		X		X		X	X	
Health Assessment Questionnaire – Disability Index (HAQ-DI)		X	X	X	X	X	X	X		X		X		X	X	
Short Form (36) Health Survey (SF-36)		X						X		X		X		X	X	
Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-Fatigue)		X						X		X		X		X	X	
Physician and patient global assessment Disease Activity		X	X	X	X	X	X	X		X		X		X	X	
Rheumatoid factor	X															
Anti-cyclic citrullinated peptide (CCP) antibodies	X															
Adverse events (AEs) [L]	→															
Pharmacokinetic (PK) samples [M]		X	X	X	X	X	X	X		X		X		X	X	
Pharmacodynamic (PD) biomarker (total sIL-6R)[M]		X	X	X	X		X	X		X				X	X	X
Joint biomarkers (MMP-3, CXCL13) [M]	X	X	X	X				X						X		
Immunogenicity samples [M]	X	X		X		X				X				X	X	X

A. All assessments are to be completed prior to study drug administration, except for subjects who discontinue study drug injections. The order of assessments if more than 1 assessment is planned at the same time should be performed according to the following principles: vital signs should be assessed prior to blood sampling; patient reported outcomes should occur prior to the physician's joint evaluation and study drug should be dosed after all other assessments have been performed.

B. All post baseline visits may occur at the indicated week ± 3 days throughout the trial.

C. The Early Termination Visit is to be performed 2 weeks after the last study drug dosing for subjects who discontinue from the trial for other reasons than described in the efficacy discontinuation criteria (see section 3.2.3.2), unless they discontinue during a study visit, in which that becomes their Early termination Visit. For subjects who will meet the efficacy discontinuation criteria at Week 12, 16, or 20, the visit at which subjects will meet these discontinuation criteria is defined as the Early Termination Visit.

D. To be performed for each subject, except in case the subject enrolls in the open-label extension study (OLE).

E. Vital signs (assessment after 5 min in supine position) will include height, weight, blood pressure, pulse, and temperature. A height measurement is only required at the Screening Visit. In case (PK) blood sampling is to be performed at the same visit, the vital signs assessment is to be performed prior to the blood sampling.

F. Chest radiograph must be performed during the screening period, unless a report of a radiograph, documenting no evidence of malignancy, infection (including Histoplasmosis), or abnormalities suggestive of TB, within 12 weeks prior to screening is available.

G. If TB is suspected at any time during the study, chest x-ray and IGRA should be performed.

H. ECG: measurement after 5 min in supine position.

I. Samples for routine clinical laboratory analyses will be collected predose, and include blood chemistry, hematology, acute phase proteins (C-reactive protein [CRP], erythrocyte sedimentation rate [ESR], and fibrinogen) and urinalysis (urinalysis at screening and Week 24). For subjects on warfarin, international normalized ratio (INR) will be performed at Weeks 0, 4, 8, 12, 16, 20, and 24, or at the Early Termination Visit.

J. At the indicated visits, samples for extended clinical laboratory analyses will be collected predose, and include fasting serum lipids on top of the routine clinical laboratory analysis, will be performed. Extended clinical laboratory analysis samples will be taken predose after the subjects has been fasting for at least 10 h.

K. At all visits, study drug is to be administered under supervision while the subject is at the study site.

L. AEs will be recorded from the time the informed consent form is signed through the Follow-up Visit. The Investigator must follow-up on all SAEs and AEs until the events have subsided, returned to baseline, or the subject's condition has stabilized in cases of permanent impairment. **In case of acute or delayed severe/serious hypersensitivity reactions, an additional serum sample should be collected as soon as possible after the start of the event (blood volume: 5 mL)**.

M. PK, biomarker and immunogenicity samples will be taken predose. PD Biomarkers will include total soluble interleukin 6 receptor (sIL-6R), joint biomarkers will include matrix metalloproteinase 3 (MMP-3), and C-X-C Motif Chemokine 13 (CXCL13).

1. INTRODUCTION

ALX-0061 has been developed by the Sponsor as a new compound neutralizing the pro-inflammatory activity of the interleukin-6 (IL-6) pathway. Based on its mode of action, ALX-0061 is currently in development for the treatment of autoimmune diseases such as RA and systemic lupus erythematosus (SLE).

The currently proposed clinical study is intended to evaluate the efficacy and safety of different dose regimens of ALX-0061 administered subcutaneously (s.c.) to subjects with active RA despite methotrexate (MTX) therapy, compared to placebo.

1.1. RHEUMATOID ARTHRITIS

RA is a chronic systemic inflammatory autoimmune disease that affects 0.5-1% of the population and is 3-times more prevalent in women than in men [1]. It is clinically characterized by joint pain, stiffness, and swelling due to synovial inflammation, leading to joint damage, deformity, severe disability, and increased mortality. Patients may develop multiple systemic symptoms including fever, fatigue, anemia, and osteoporosis.

1.1.1. TREATMENT OF RHEUMATOID ARTHRITIS

The goal of therapy is to reduce inflammation, inhibit joint damage, prevent loss of function, decrease pain, and improve function as well as quality of life. Initial treatment options include disease-modifying anti-rheumatic drugs (DMARDs), non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, analgesics, surgery, physiotherapy, and occupational therapy.

The synthetic DMARDs most commonly used include MTX, sulfasalazine, leflunomide, hydroxychloroquine, cyclosporine A, and glucocorticoids. The therapeutic benefits of DMARDs in RA include control of signs and symptoms, improvement of functional status and of quality of life, and retardation of joint damage progression [2]. MTX administered alone or in combination with another conventional DMARD, is the recommended first-line therapy for patients with RA [3].

For patients with an inadequate response to conventional DMARDs, biological drugs may be indicated. These biological drugs block certain key molecules that are involved in the pathogenesis of the illness. These targets include tumor necrosis factor alpha (TNF α), selective T-cell costimulation molecule (such as cytotoxic T-lymphocyte-associated protein 4), cluster of differentiation 20 (CD20), interleukin-1

(IL-1), IL-6, and interleukin-6 receptor (IL-6R). The development of immune-modulating agents has offered new treatment options for patients.

Although anti-TNF α agents and other biological DMARDs have been established as effective treatment options for RA, there are reasons to study the effectiveness of new therapeutic agents. For example, there is a subset of the patient population that does not achieve a clinical response, defined as American College of Rheumatology (ACR) 20 response, and only a small proportion achieve a high level ACR response (ACR50 or ACR70) [4]. In addition, biological DMARDs have limitations with respect to safety, dosing regimen, way of administration, and immunogenicity. Thus there is the potential for new therapeutic agents to address some of these limitations and to improve the effectiveness of biological agents in treating RA.

1.1.2. ROLE OF IL-6R IN PATHOPHYSIOLOGY OF RHEUMATOID ARTHRITIS

IL-6 is a pleiotropic cytokine with a wide range of biological activities. The IL-6 pathway functions through the interaction of IL-6 with its receptor IL-6R. This cytokine-receptor complex interacts with a third partner, the adaptor molecule glycoprotein 130 (gp130), responsible for signal transduction and activation of the cell [5]. IL-6R is present not only as a membrane bound form but also as a soluble form. sIL-6R can interact with IL-6 and this complex can activate gp130-positive cells without the presence of membrane-bound (m)IL-6R on the surface of the cells. This process is called trans-signaling and implies that mIL-6R negative cells are also susceptible to activation, with soluble IL-6R acting as an agonist [5, 6].

As IL-6 is a pleiotropic cytokine, its function is highly diverse. Many studies revealed that this molecule by binding to the target IL-6R and gp130 plays a role in the immune, hematopoietic, hepatic, and neuronal systems [7, 8].

IL-6 plays also a critical role in different aspects of RA such as the transition from the acute phase of the inflammation to the chronic irreversible status [9], stimulation of B cells to produce auto-antibodies, cartilage destruction [10], or anemia [11].

High concentrations of IL-6 have been documented in the serum of RA and juvenile RA patients [12]. Several studies have shown that sIL-6R is also elevated in both RA and systemic onset juvenile RA patients [13]. Analysis of the IL-6 and sIL-6R concentrations in synovial fluid showed that the extent of joint destruction correlated with increased concentrations of both ligand and receptor [12]. However, resident cells of the joint (chondrocytes, synoviocytes, fibroblasts, endothelial cells) do not express mIL-6R, indicating that high levels of sIL-6R are likely to be

expressed by infiltrating leukocytes [13]. This indicates that sIL-6R is important in the chronic inflammatory setting of RA.

Based on the findings that the IL-6 pathway is important in chronic inflammatory diseases, drugs targeting this pathway are in development. Multiple clinical studies have demonstrated that treatment with IL-6 pathway inhibitors can improve manifestations of RA, supporting the concept that IL-6 signaling plays a key role in RA.

1.2. ALX-0061

The following paragraphs provide summary information on ALX-0061; for more detailed background information, please refer to the Investigator's Brochure.

1.2.1. GENERAL PROPERTIES

The active component in ALX-0061 solution for injection is a therapeutic protein, designated "ALX-0061 Nanobody". Nanobodies are therapeutic proteins that are derived from the smallest functional fragments of heavy chain only antibodies, which occur naturally in the *Camelidae* family. They have a high degree of homology (in terms of sequence and structure) to human immunoglobulin heavy chain variable region (VH) domains, and can be further engineered and expressed by host cells such as *Pichia pastoris*.

ALX-0061 Nanobody consists of 2 humanized and sequence-optimized variable domains derived from heavy chain-only llama antibodies:

- One domain (designated 20A11) binds to human IL-6R.
- The second domain (designated ALB11) binds to human serum albumin (HSA), as a means to improve the PK properties of the Nanobody (half-life extension).

ALX-0061 Nanobody inhibits the interaction between the IL-6 ligand and the receptor subunit, thereby preventing receptor signaling. ALX-0061 has a higher affinity for sIL-6R than for mIL-6R, and thus preferentially targets sIL-6R (the trans-signaling pathway). This target binding profile of ALX-0061 may result in a stronger engagement of the disease-driving target form (sIL-6R) [6] in a physiological situation with both forms (sIL-6R and mIL-6R) present.

The second domain of ALX-0061 was designed to improve the PK properties of the Nanobody by binding to human serum albumin. Albumin is the most abundant protein in plasma and has a half-life of approximately 19 days in humans [14]. Binding to albumin (as a carrier) has been shown to lead to retention of the bound protein in circulation, with a resident time approaching that of the carrier molecule [14].

1.2.2. MANUFACTURE

The manufacture of ALX-0061 Nanobody consists of an upstream process (i.e., fermentation of a *Pichia pastoris* strain that expresses ALX-0061 Nanobody and secretes the product into the medium), and a downstream process (essentially harvest, capture, intermediate purification, polish, and formulation of the Nanobody). Additional information on the manufacture and pharmaceutical properties of ALX-0061 is included in the Investigator's Brochure.

1.2.3. NONCLINICAL STUDIES

Pharmacology
ALX-0061 was extensively characterized *in vitro*. The *in vivo* efficacy and the PK/PD properties of ALX-0061 were examined in naive cynomolgus monkeys, in an acute cynomolgus monkey model of IL-6-induced inflammation, and in a collagen-induced arthritis model in rhesus monkey. PK was assessed during the toxicology studies in cynomolgus monkeys (toxicokinetics [TK]). Additionally, the impact of anti-drug antibodies (ADA) on the PK and PD of ALX-0061 was evaluated.

Toxicology
The toxicology program was carried out in cynomolgus monkeys, and consists of a single-dose intravenous (i.v.) dose-range finding toxicity study, a Good Laboratory Practice (GLP)-compliant 13-week repeated-dose i.v. toxicity study, a GLP-compliant 4-week repeated dose i.v./s.c. toxicity study, and a 26-week repeated-dose i.v. toxicity study.

All relevant nonclinical studies conducted with ALX-0061 are described in the Investigator's Brochure. The nonclinical data revealed no specific safety risks, based on the available safety pharmacology data, and local and systemic tolerability assessment.

1.2.4. EFFECTS IN HUMANS

A combined Phase I/II study in subjects with moderately to severely active RA, on a stable background of MTX, has been completed (study ALX-0061-1.1/10). This placebo-controlled study included 28 subjects in an initial single ascending dose (SAD) part where single i.v. doses of 0.3, 1, 3, or 6 mg/kg were administered. In a subsequent multiple ascending dose (MAD) part, 37 subjects received multiple i.v. doses of 1 or 3 mg/kg every 4 weeks (q4w), or 6 mg/kg every 8 weeks, for 24 weeks in total.

A Phase I study (Study ALX0061-C102) assessing the bioavailability of single doses of ALX-0061, administered s.c. at 3 dose levels, using 2 corresponding single i.v.

dose levels as reference, in healthy adult volunteers, has been completed. This study included 70 subjects and studied doses of 50 mg, 150 mg, and 300 mg. The PK and PD results were used to bridge from i.v. to s.c. administration, and to determine the appropriate doses for the current Phase II study.

1.2.4.1. STUDY ALX-0061-1.1/10 IN SUBJECTS WITH MODERATELY TO SEVERELY ACTIVE RHEUMATOID ARTHRITIS

The results of the SAD and MAD parts of this study are discussed in detail in the Investigator's Brochure, and are briefly summarized below.

Efficacy in the MAD part

In the MAD part of the study, all ALX-0061 treatment combinations showed rapid and long-lasting improvements in disease activity (as measured by ACR, EULAR, Disease Activity Score using 28 joint counts (DAS28) [CRP], Clinical Disease Activity Index (CDAI), and Boolean remission responses). There were high numbers of responders in all ALX-0061 treatment groups, with DAS28 remission observed in 63% of ALX-0061-treated subjects at Week 24, and none of the ALX-0061-treated subjects showed worsening of disease activity during the study period. Overall, the efficacy profile obtained at Week 12 continued to improve during the subsequent 12 weeks of ALX-0061 treatment.

Pharmacokinetics

The pharmacokinetics of ALX-0061 appear dose-dependent, suggesting target-mediated disposition of the drug. A 2-compartment disposition model with parallel first-order (linear total body clearance [CL]) and Michaelis-Menten elimination (nonlinear or concentration-dependent CL) describes well the PK behavior of the drug, and is consistent with the more than proportional increase of exposure and half-life of the drug with the increase of the dose. Similar to monoclonal antibodies, the Nanobody has a limited volume of distribution, corresponding to the plasma volume. As the PK of ALX-0061 is dose-dependent due to a different contribution of the non-linear clearance at different serum concentrations, also the terminal half-life ($t_{1/2}$) is dose-dependent. At high concentrations, when non-linear clearance becomes negligible, the apparent $t_{1/2}$ estimated from the linear clearance term only, is estimated at approximately 15 days.

Pharmacodynamics

- All ALX-0061 groups received biologically effective doses: rapid and long-lasting increases in IL-6 and sIL-6R concentrations were observed across all ALX-0061 dose groups. The PD results confirmed that sIL-6R (and IL-6) concentrations can be used as a biomarker for target engagement by ALX-0061.

- Dosing q4w at 3 mg/kg yielded the highest exposure, as indicated by the observed average trough levels (~ 10 µg/mL), strongest biomarker response (based on sIL-6R profile), and the highest clinical remission rates.

Safety

- Single and repeated administration of ALX-0061 was well tolerated in all treatment groups, with a manageable and consistent safety profile for all ALX-0061 dose combinations.
- In the MAD part, the most commonly reported AEs observed after intake of ALX-0061 included headache, increased alanine aminotransferase (ALT) and aspartate aminotransferase (AST), arthralgia, back pain, and joint swelling. Most of the events were mild or moderate and resolved during the treatment period.
- There were no clear trends in the occurrence or type of treatment-related AEs when comparing the individual ALX-0061 treatment groups, and there was no evidence to suggest that a maximum tolerated dose was reached.
- 3 subjects reported SAEs.
  - In the SAD part, 1 subject (3 mg/kg ALX-0061) experienced an acute hypersensitivity during the first infusion of ALX-0061, which was stopped immediately. The subject was successfully treated in the hospital with anti-histaminic drugs, prednisone, and salbutamol.
  - In the MAD part of the study, 1 subject (3 mg/kg q4w ALX-0061) experienced an SAE of cerebrovascular accident after having received 2 infusions of ALX-0061 in total. Although the subject recovered from the initial event, a second, more severe SAE of cerebrovascular accident occurred several days later and the subject died. Both events were considered remotely related[a] to study treatment by the Investigator.
  - One other subject with a confirmed *Helicobacter pylori* gastritis and history of short NSAID intake experienced an SAE of hemorrhagic gastritis (not related) and a linked SAE of upper gastrointestinal hemorrhage (remotely related). Both SAEs resolved before the end of the study.
- Four subjects reported treatment-emergent AEs (TEAEs) leading to withdrawal of study drug in the MAD part of the study: 1 subject with the SAE cerebrovascular accident (described above), 1 subject with rash and non-immunoglobulin (Ig) E mediated hypersensitivity reaction (probably related to the study drug), 1 subject with uncontrolled hypertension (remotely related to the study drug), and 1 subject with infected dermal cyst (remotely related to the study drug).
- Regarding laboratory abnormalities, a rapid and reversible decrease in neutrophils and platelets was seen in the majority of subjects after administration of ALX-0061. These decreases in neutrophil and platelet count seemed to be dose-related but did not reach clinically relevant levels. No AEs

[a] The relationship between AEs and study medication was to be indicated as "none", "remote", "possible", "probable" or "definite".

related to the decreases in neutrophil and platelet count (or other hematology parameters) were reported, except for 1 subject with mild leukopenia (without neutropenia).

- With the exception of individual subjects showing increases in liver parameters (mainly AST and/or ALT) beyond the normal range, there were no clinically relevant trends in mean liver or other safety-related biochemistry parameters (including lipids) across dose levels.

1.2.4.2. STUDY ALX0061-C102 IN HEALTHY VOLUNTEERS

Overall, a single s.c. dose of ALX-0061 in the dose range of 50 to 300 mg was safe and well-tolerated in a group of 70 healthy male and female subjects. The s.c. bioavailability of ALX-0061 was 82.3% as estimated by the population PK model.

There were no severe AEs, deaths, other SAEs or AEs that resulted in study drug discontinuation.

In the s.c. treatment groups, the majority of possibly related AEs were injection site reactions (mainly pain and erythema), which appeared to be dose-dependent across the dose range tested (50 mg to 300 mg). All injection site reactions were transient and of mild intensity and apart from these reactions, no specific AEs were reported very frequently or showed a dose relationship. No differences were observed compared to the i.v. administration groups.

As expected from the mechanism of action, a mild transient decrease in fibrinogen, neutrophils and high sensitivity CRP levels was observed following administration of ALX-0061. One subject in the 300 mg i.v. group showed a clinically non-significant increase in ALT levels starting at 168 h post-dose up to a maximum of 150 U/L at 1080 h post dose. This was accompanied by a mild rise in AST and no rise in bilirubin. The ALT level had returned to baseline at follow-up.

The PK and PD results were used to determine the appropriate doses for the current Phase II study and are summarized in the Investigator's Brochure.

1.2.5. BENEFITS AND RISK ASSESSMENT

Although a number of treatment options are available for RA, there remains a clear need for novel therapeutics. Many patients do not benefit optimally from the available small molecule and biologic drugs, leaving opportunity for differentiated drugs with new modes of action and an improved safety profile.

Considering the importance of IL-6 in chronic inflammatory diseases, several companies are developing drugs that target this pathway, and multiple clinical

studies have demonstrated that treatment with IL-6 pathway inhibitors can improve manifestations of RA. ALX-0061, administered i.v. and in combination with MTX, has been shown to be effective in reducing signs and symptoms for the treatment of subjects with active RA.

The current study is designed to evaluate the efficacy and safety of ALX-0061, administered s.c. in subjects with moderate to severe active RA. Potential candidates for this study are required to have objective evidence of active disease, and have had an inadequate response to methotrexate.

The Sponsor is studying s.c. administration in an effort to develop a route of administration which will offer an alternative and more convenient option for administration, while maintaining its clinical efficacy and safety profile. Details on the design of, and rationale for, the current study are available in section 3.1.1 of the protocol.

An assessment of potential risks associated with inhibition of the IL-6 pathway, or inherent to the administration of therapeutic proteins, is described below. IL-6 is a pleiotropic cytokine with an important role in a broad spectrum of biological events, therefore, potential risks related to inhibition of the IL-6 pathway, as well as potential risks inherent to the administration of therapeutic proteins, are considered.

- Inhibition of the IL-6 pathway has immunomodulatory effects, and has been reported to increase the risk for infection [15, 16]. So far, serious infections have not been reported for ALX-0061.

- Suppression of IL-6 activity is known to reduce the levels of acute phase proteins such as CRP, SAA and fibrinogen [17, 18].
  - Rapid and long-lasting decreases in CRP, ESR, fibrinogen and SAA were observed across all ALX-0061 dose groups in study ALX-0061-1.1/10. In general, these pharmacological effects were reversible and associated with clinical response in signs and symptoms of RA.
  - In study ALX0061-C102, results indicate a trend towards a minor decrease in fibrinogen and (hs)CRP levels following administration of ALX-0061 in most subjects.

- Suppression of IL-6 signaling has been shown to lead to decreases in neutrophil and platelet counts [19].
  - In study ALX-0061-1.1/10, a rapid and reversible decrease in neutrophils and platelets was seen in the majority of subjects after administration of ALX-0061. No TEAEs related to the decreases in neutrophil and platelet count (or other hematology parameters) were reported, except for 1 subject with mild leukopenia (without neutropenia; MAD part of the study).
  - In study ALX0061-C102, the results show a tendency towards a transient and mild decrease neutrophil count.

- Increased transaminase levels (AST/ALT) in serum and increased cholesterol (HDL, LDL and triglycerides) levels have been reported following pharmacological inhibition of the IL-6 pathway [20]. With the exception of individual subjects showing increases beyond the normal range, there were no clinically relevant trends in mean liver (ALT/AST/GGT/LDH/bilirubin) parameters, mean lipid concentrations, or other safety-related biochemistry parameters across dose levels in study ALX-0061-1.1/10 or ALX0061-C102.

- Recent data indicate that RA subjects have a generally increased rate of gastrointestinal (GI) perforation [21]. At this time, it is not clear whether IL-6 inhibitors further increase the risk of this complication beyond that observed in the general RA population. To date, no cases of GI perforation have been observed following ALX-0061 administration.

- As with all therapeutic proteins used in humans, infusion reactions (e.g., either anaphylactic or anaphylactoid) cannot be excluded.
  - In study ALX-0061-1.1/10, two hypersensitivity reactions were reported (one serious and one moderate). For additional details, please refer to the Investigator's Brochure.
  - In study ALX0061-C102, no hypersensitivity reactions were reported.

- Administration of any protein therapeutic can lead to the development of ADA [22]. The currently available immunogenicity (ADA) results after i.v. and s.c. administration of ALX-0061 do not indicate meaningful risks related to pre-existing or treatment-emergent antibodies to ALX-0061.

In view of the early stage of development, it is not established whether the above mentioned effects would constitute clinically meaningful risks for administration of ALX-0061; additional clinical studies are needed for further evaluation. In general, the pharmacological effects reported during Study ALX-0061-1.1/10 were reversible and associated with clinical response in signs and symptoms of RA. For additional and more detailed information regarding ALX-0061, the investigator is referred to the current Investigator's Brochure.

2. OBJECTIVES

Primary objective:

- To assess the efficacy and safety of dose regimens of ALX-0061 administered s.c. in combination with MTX to subjects with active RA despite MTX therapy compared with placebo.

Secondary objective:

- To assess the effects of ALX-0061 on quality of life, PK, PD, and immunogenicity of ALX-0061, and to define the optimal dose regimen for ALX-0061, based on safety and efficacy, for further clinical development.

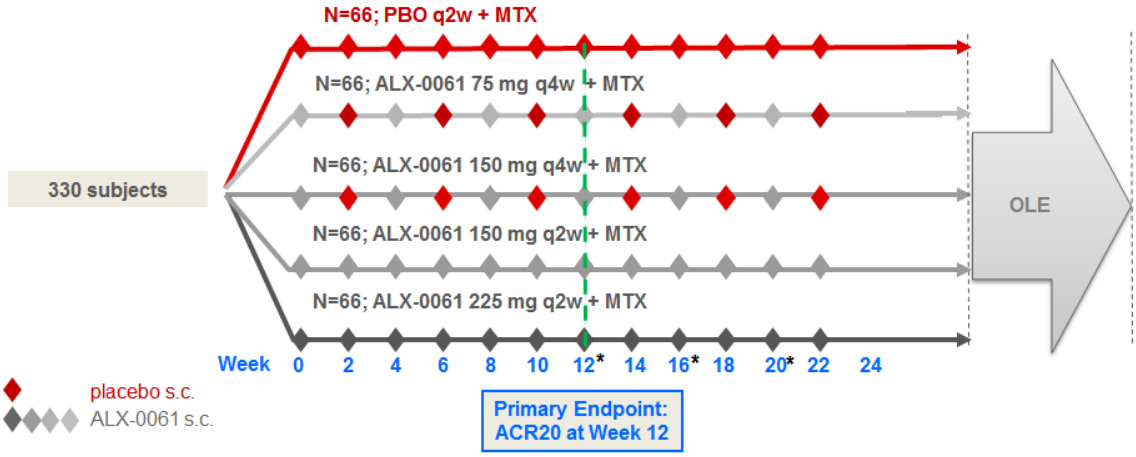
3. STUDY DESIGN

3.1. OVERALL STUDY DESIGN

3.1.1. STUDY OVERVIEW

This multicenter, randomized, double-blind, placebo-controlled dose-range finding Phase IIb study, is being conducted to evaluate the efficacy and safety of ALX-0061 administered s.c. in combination with MTX, in subjects with active RA despite MTX therapy. Approximately 330 subjects will be enrolled. An overview of the study design is included in Figure 1.

Figure 1: Overview of the design of Study ALX0061-C201



* At Weeks 12, 16 or 20 patients with < 20% improvement in both TJC and SJC from baseline will discontinue from the trial but remain blinded to study drug assignment.

MTX: methotrexate; OLE: open-label extension study ALX0061-C203 (in countries where study ALX0061-C203 is approved, eligible subjects who complete the 24-week assessment period of the current study will be invited to roll-over). q2w: every 2 weeks, q4w: every 4 weeks.

Subjects will be randomly assigned to receive ALX-0061 and/or placebo s.c. injections at Week 0 and every 2 weeks (q2w) thereafter, on top of their stable dose of MTX, up to and including Week 22.

The dosing regimens have been determined based on:

- Expected DAS28 response, ensuring characterization of the exposure-response curve (PK/PD modelling approach).
- Safety margins calculated by using the relevant observed exposure in nonclinical studies (cynomolgus monkey) versus the model-predicted human exposure of the selected dosing regimens for the clinical studies.
- Operational feasibility aspects for the study.

A PK-PD model, developed based on data pooled from Studies ALX-0061-1.1/10 and ALX0061-C102, was used to predict the response (in terms of DAS28) at different dose levels/regimens. The s.c. dose regimens 75 mg q4w, 150 mg q4w, 150 mg q2w and 225 mg q2w were selected as these are expected to be spread over the different levels of effect (low, medium, high), based on exposure-response modelling (PK-DAS28) of ALX-0061. Moreover, these regimens are covered by adequate safety margins when comparing the model predicted human exposure with the observed exposure in the toxicity studies.

In view of the availability of effective RA therapies and the current focus on early control of disease activity, prolonged treatment with placebo or ineffective therapies is considered unethical. Therefore, the proposed study includes provisions for study drug discontinuation for non-responding subjects at Week 12, 16, or 20. Subjects with < 20% improvement over baseline in both swollen joint count (SJC) and tender joint count (TJC) (66/68 counts) will discontinue from the trial but remain blinded to study drug assignment. Any future care will then be provided (outside of the study) at the discretion of the physician as part of usual clinical practice.

Subjects will have visits at the site q2w up to and including Week 24 (or early termination). A Follow-up Visit will be planned 12 weeks after last study drug administration. Note that for subjects who withdrew for reasons of lost to follow-up, informed consent withdrawal, or death will not have any follow-up assessments.

The ACR20 response was chosen as the primary endpoint since this is a broadly accepted clinical response measure to demonstrate reduction in RA signs and symptoms and sensitive enough to differentiate from placebo effects. For details on primary statistical analysis in this study, please refer to section 3.6.4.1.

Note that higher levels of response, as measured by ACR50 and ACR70 response rates, and measures of remission using the DAS28, CDAI, SDAI, as well as the Boolean remission definition, will be used as supportive evidence of efficacy. In addition, endpoints, including ACR responses and disease activity scores, will be documented over time, including earlier time points, before the therapeutic plateau is expected. This will allow evaluation of potential differences in early clinical efficacy between the doses. Other RA domains, such as improvement in physical function and health-related quality of life, will be evaluated using the HAQ-DI, FACIT-Fatigue scale and the SF-36 questionnaires.

Safety and tolerability assessments will include evaluation of AEs (including serious adverse events, infections, injection site and hypersensitivity reactions), laboratory assessment, urinalysis, vital signs, and physical examination.

Additional planned assessments include the determination of ALX-0061 levels in serum, and PD biomarkers (including sIL-6R) in blood. To assess immunogenicity, the presence of ADA will be measured in serum until the Follow-up Visit, with potentially further characterization by modified ADA assay (mADA) and neutralizing antibody assay (nAb).

Study Treatment Allocation

At the Screening Visit, informed consent will be obtained from all subjects who are deemed potentially eligible for the study, according to the protocol-specified inclusion and exclusion criteria. At randomization, subjects will be reassessed and, if they meet all specified entry criteria, randomized to receive either ALX-0061 or placebo, as described below (also see section 3.3.8 for additional information on randomization).

Eligible subjects will be randomly assigned in a 1:1:1:1:1 ratio to 1 of the treatment groups listed below. As the highest dose of ALX-0061 will be administered via 2 injections q2w, subjects in Groups 1-4 will also be administered 2 injections q2w with 1 or both syringes containing placebo depending on the assigned treatment group to maintain the blind (see section 3.1.2):

Group 1 (N=66) Placebo
Placebo s.c. injections (2 syringes [0.5 and 1.0 mL]) at Week 0 and q2w thereafter up to and including Week 22

Group 2 (N=66) 75 mg q4w
ALX-0061 75 mg s.c. injections (1 syringe [0.5 mL]) at Week 0 and q4w thereafter up to and including Week 20. To maintain the blind, subjects in this group will also receive placebo s.c. up to and including Week 22 (1 placebo syringe [1.0 mL] at Week 0 and q4w thereafter in combination with the ALX-0061 injection; 2 placebo syringes [0.5 and 1.0 mL] at Week 2 and q4w thereafter).

Group 3 (N=66) 150 mg q4w
ALX-0061 150 mg s.c. injections (1 syringe [1.0 mL]) at Week 0 and q4w thereafter up to and including Week 20. To maintain the blind, subjects in this group will also receive placebo s.c. up to and including Week 22 (1 placebo syringe [0.5 mL] at Week 0 and q4w thereafter in combination with the ALX-0061 injection; 2 placebo syringes [0.5 and 1.0 mL] at Week 2 and q4w thereafter).

Group 4 (N=66) 150 mg q2w
ALX-0061 150 mg s.c. injections (1 syringe [1.0 mL]) at Week 0 and q2w thereafter up to and including Week 22. To maintain the blind, subjects in this group will also receive placebo s.c. q2w up to and including Week 22 (1 placebo syringe [0.5 mL]).

Group 5 (N=66) 225 mg q2w
ALX-0061 225 mg s.c. injections (2 syringes [0.5 and 1.0 mL]) at Week 0 and q2w thereafter up to and including Week 22. These subjects will not receive placebo injections.

Efficacy Discontinuation Criteria at Week 12, 16, or 20

Any subject with < 20% improvement from baseline in both SJC and TJC (66/68 counts) at any of the visits at week 12, 16 or 20 will discontinue from the trial, but remain blinded to study drug assignment. The visit at which subjects will meet the efficacy discontinuation criteria, is defined as the Early Termination Visit for these patients. Following this Early Termination Visit, any future care will then be provided (outside of the study) at the discretion of the treating physician as part of usual clinical practice.

The blind will be maintained until the last enrolled subject completes the final evaluations and the database is locked.

At all visits, study drug is to be administered under supervision while the subject is at the study site.

In countries where open-label extension (OLE) study ALX0061-C203 is approved, subjects who complete the 24-week assessment period of the current study will be invited to roll-over. Details on the open-label extension (OLE) study are described in Clinical Study Protocol ALX0061-C203.

Each subject will stay in the study for approximately 37 weeks (up to 3 weeks of screening and 34 weeks after randomization). The end of the study is defined as the time of the last visit of the last subject participating in the study.

3.1.2. BLINDING

On the day of the Week 0 study drug injection, the IWRS will assign each subject by means of the randomization list to a treatment group in a blinded way. See IWRS Manual for further details.

All subjects are to receive 2 injections (Syringe A and Syringe B) in succession at each dosing day. Since the 225 mg dose of ALX-0061 exceeds the volume that can be administered in a single injection, the placebo and ALX-0061 groups will have 2 different combinations of dosing to ensure the double-blinded design. See Study Drug Manual for further details.

Therefore, there will be a total of 5 dosing combinations in the study, with 4 possible dose levels. These dosing combinations are shown below:

Syringes A and B contain 1 mL and 0.5 mL, respectively.

Placebo
Syringe A with placebo at Weeks 0, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, and 22.
Syringe B with placebo at Weeks 0, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, and 22.

75 mg q4w
Syringe A with placebo at Weeks 0, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, and 22.
Syringe B with ALX-0061 at Weeks 0, 4, 8, 12, 16, and 20, and syringe B with placebo at Weeks 2, 6, 10, 14, 18 and 22.

150 mg q4w
Syringe A with ALX-0061 at Weeks 0, 4, 8, 12, 16, and 20, and syringe A with placebo at Weeks 2, 6, 10, 14, 18, and 22.
Syringe B with placebo at Weeks 0, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, and 22.

150 mg q2w
Syringe A with ALX-0061 at Weeks 0, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, and 22.
Syringe B with placebo at Weeks 0, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, and 22.

225 mg q2w
Syringe A with ALX-0061 at Weeks 0, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, and 22.
Syringe B with ALX-0061 at Weeks 0, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, and 22.

In order to protect the integrity of the data, treatment assignment will be kept blinded for investigative sites, site monitors, subjects, Sponsor, and CRO until the final database lock (including the Follow-up Visit 12 weeks after the last dosing).

Identification of Sponsor and CRO personnel who will have access to the unblinded data of the Week 24 database lock will be documented prior to unblinding. The number of Sponsor personnel having access to the data will be limited.

All clinical laboratory samples will be analyzed by a central laboratory, except for ESR that will be measured via the local laboratory, by an independent laboratory representative who is not directly involved in the study.

Given the pronounced effect of an anti-IL-6 compound on the acute phase reactants, the results of CRP, ESR and fibrinogen tests will not be communicated to the investigational sites and CRO/sponsor (unless in case of an alert for CRP or fibrinogen), with the exception of the CRP and fibrinogen results at screening, which are needed for assessing the subject's eligibility for randomization.

Except for ESR, CRP, and fibrinogen, laboratory values outside the normal range will be flagged and clinical relevance will be assessed by the Investigator. If clinical signs and symptoms are present for which the Investigator needs to know the values of ESR, CRP or fibrinogen for medical care, he can request this information.

Emergency Unblinding Procedure
Code-breaking and unblinding in the event of medical emergencies can be done by the Investigator via the IWRS, which will be accessible 24 hours per day/7 days per week.

Unblinding by the Investigator should occur only in the event of AE for which it is necessary to know the study treatment to determine an appropriate course of therapy for the subject. If the Investigator must identify the treatment assignment of an individual subject, the Investigator or qualified designee is to contact the IWRS. Unblinding performed by the IWRS at the request of the Investigator is to be reported to the Sponsor. When possible the Investigator must first discuss options with the medical monitor prior to unblinding.

Subjects for whom the code has been broken by the Investigator will be withdrawn from the study.

3.2. SELECTION OF STUDY POPULATION

Up to approximately 330 subjects (i.e., 66 subjects per treatment arm) are planned to be included in the study.

3.2.1. INCLUSION CRITERIA

Each potential subject must satisfy all of the following criteria to be enrolled in the study:

1. Man or woman ≥ 18 years and < 75 years of age at the time of signing the informed consent form (ICF).
2. Diagnosis of RA (according to the 2010 EULAR/ACR classification criteria) for at least 6 months prior to screening, and ACR functional class I-III.
3. Treated with and tolerating MTX according to the following criteria:
   a. Minimum treatment duration of 4 months prior to screening.
   b. Stable dose of MTX of ≥ 12.5 mg/week to ≤ 25 mg/week for at least 6 consecutive weeks prior to screening.
   c. Expected to maintain that stable dose throughout the study as described in section "Concomitant Medication".
4. Active RA as defined, for the purpose of this study, by persistent disease activity with at least 6 swollen and 6 tender joints (66/68-joint count), at the time of screening and baseline, and CRP > 1.0 x upper limit of normal (ULN) at screening.
5. If using NSAIDs or other analgesics for RA, must be on a stable dose for at least 2 weeks prior to screening.
6. If using oral corticosteroids, must be on a stable dose equivalent to ≤ 10 mg of prednisone/day equivalent for at least 2 consecutive weeks prior to screening. If currently not using corticosteroids, must have not received oral corticosteroids for at least 2 weeks prior to first administration of study drug.
7. Chest radiograph must have been performed within 12 weeks prior to the Screening Visit or during the screening period documenting no evidence of malignancy, infection (including Histoplasmosis), or abnormalities suggestive of TB (report must be obtained and available in the subject's study file prior to baseline).
8. Subject is considered eligible according to the following TB screening criteria:
   a. Have no history of latent or active TB on or prior to screening. An exception is made for subjects with a history of latent TB and documentation of having completed appropriate treatment for latent TB prior to the first administration of study drug. It is the responsibility of the Investigator to

verify the adequacy of previous anti-TB treatment and provide appropriate documentation.

b. Have no signs or symptoms suggestive of active TB upon medical history and/or physical examination during screening.

c. Have had no recent close contact with a person with active TB or, if there has been such contact, will be referred to a physician specializing in TB to undergo additional evaluation and, if warranted, receive and complete appropriate treatment.

d. Subject should have a negative IGRA test result at screening. A subject whose initial IGRA test result is indeterminate and who has no other risk factors, radiologic findings, or physical evidence supporting latent or active TB, should have the test repeated. In case the test result is again indeterminate (or positive) the subject will be excluded from the study. An exception is made for subjects who have documentation of having completed appropriate treatment for latent TB prior to randomization and do not have other risk factors, radiologic findings, or physical evidence supporting latent or active TB.

e. Have a chest radiograph, read by a qualified radiologist, whose diagnostic assessment is consistent with no evidence of current active TB or old inactive TB, and taken within 12 weeks prior to screening.

   Note: If no chest radiograph has been performed within 12 weeks prior to screening, the assessment is to be performed during the screening period and the outcome is to be known by the time of the Baseline Visit.

9. Female subjects of childbearing potential (excluding postmenopausal women, sterilized, ovariectomized, and hysterectomized women) should have a negative pregnancy test at screening and baseline and must agree to use 2 generally accepted adequate contraceptive methods of which 1 is a barrier method (e.g., hormonal contraception stabilized for at least 1 month [oral, patch, depot, injectable, vaginal ring] in combination with condom by partner) or should agree upon continuous abstinence from heterosexual contact from screening until at least 6 months after last dosing.

   Male subjects must use condoms for the duration of the study and for at least 6 months after last administration of study drug.

10. Ability to comprehend and willingness to sign the informed consent form (ICF).

11. An understanding of and ability and willingness to adhere to the study visit schedule and other protocol requirements.

3.2.2. EXCLUSION CRITERIA

Subjects meeting any of the following criteria may not be enrolled in the study:

1. Have inflammatory diseases other than RA, including but not limited to psoriatic arthritis, ankylosing spondylitis, SLE, sarcoidosis, or Lyme disease.
2. Presence of active infection at screening, or history of serious infection (requiring parenteral antibiotic and/or hospitalization) within 4 weeks of Baseline Visit. Minor fungal infections (for example minor fungal nail infections) will be allowed.
3. Any recurrent viral infection that based on the Investigator´s clinical assessment make the subject unsuitable for the study, including recurrent/disseminated herpes zoster.
4. Have a history of, or current, congestive heart failure (CHF) class III or IV as defined by the New York Heart Association; history of unstable angina pectoris, myocardial infarction, cerebrovascular accident within 12 months before screening.
5. Have a history of demyelinating diseases such as multiple sclerosis or optic neuritis.
6. Have diverticulitis, complications of diverticulitis, a history of diverticulitis, or have symptoms potentially indicative of diverticulitis, such as gastro-intestinal hemorrhage and/or abdominal pain or unexplained change in bowel habits with fever. Diverticulosis without a history of diverticulitis or other complications is not an exclusion criterion.
7. Any history of malignancy or lymphoproliferative disease at any time, except curative treatment for non-melanoma skin cancer or resected carcinoma *in situ*.
8. Have a transplanted organ/tissue or stem cell transplantation.
9. Have a history of an infected joint prosthesis, or have received antibiotics for suspected infection of a joint prosthesis, if that prosthesis has not been removed or replaced.
10. Major surgery (including joint surgery) within 8 weeks prior to screening or planned major surgery during study or within 3 months after the subject's last visit. Hospitalization for a clinically relevant event within the 4 weeks prior to screening.
11. Have been treated with DMARDs/systemic immunosuppressives (e.g., oral or parenteral gold, sulfasalazine, azathioprine, cyclosporine, mycophenolate mofetil, hydroxychloroquine, chloroquine) other than MTX, during the 4 weeks or 12 weeks for leflunomide (except when an adequate wash-out procedure for leflunomide was completed), prior to first administration of study drug.
12. Have received intra-articular (i.a.), intramuscular (i.m.), or i.v. corticosteroids during the 4 weeks prior to screening.

13. Have received approved or investigational biological or targeted synthetic DMARD therapies for RA (including TNF α inhibitors, abatacept, rituximab, or Janus kinase [JAK]-inhibitors) less than 6 months prior to screening. For subjects who received prior rituximab, subjects with an inadequate recovery of B cells should be excluded regardless of when they received rituximab.
14. Have a history of toxicity, non-tolerance, primary non-response or inadequate response to a biological therapy, or targeted synthetic DMARDs (including JAK inhibitors), for RA.
15. Have received prior therapy blocking the IL-6 pathway, such as but not limited to ALX-0061, sirukumab, sarilumab, clazakizumab, olokizumab, tocilizumab (TCZ) at any time, will be excluded.
16. Have a known hypersensitivity to the active product or any excipient of the study drug.
17. Abnormality in screening laboratory test results:
    a. ALT and/or AST levels ≥ 1.5 times the ULN.
    b. Hemoglobin levels ≤ 85 g/L (8.5 g/dL).
    c. Platelet count ≤ 125 x 10^9/L (125,000 cells/mm³).
    d. White blood cell count ≤ 3.5 x 10^9/L (3,500 cells/ mm³); neutrophils: ≤ 2 x 10^9/L.
    e. Serum creatinine levels ≥ 1.5 mg/dL (133 µmol/L).
    f. Any other clinically significant abnormal screening laboratory results as evaluated by the Investigator.
18. Positive screening for hepatitis B, hepatitis C, or HIV.
19. At the discretion of the treating physician, subjects with impaired cellular or humoral immunodeficient (i.e., Ig deficiency, IgA, IgG etc.) disorders should be excluded.
20. History or presence of alcohol or drug abuse.
21. Blood donation (> 500 mL) or a blood loss of comparable volume within 3 months prior to first dosing.
22. Planned donation of germ cells, blood, organs, bone marrow during the course of the study or within 6 months thereafter.
23. Male with female partner who is planning to become pregnant within 6 months of last dosing.
24. Pregnant women or female subjects who are breastfeeding.
25. History of anaphylactic reaction.
26. Administration of a live, attenuated vaccine within 3 months before dosing with ALX-0061, or anticipation that such a live attenuated vaccine will be required during the study or within 6 months after last dosing.
27. Screening 12-lead ECG that demonstrates clinically relevant abnormalities.

28. Subject is considered by the Investigator, for any reason, to be an unsuitable candidate for the study.

3.2.3. REMOVAL OF SUBJECTS FROM THERAPY OR ASSESSMENT

3.2.3.1. CRITERIA FOR WITHDRAWAL OF SUBJECTS FROM STUDY

Participation in the study is strictly voluntary. A subject has the right to withdraw from the study at any time, for any reason.

Subjects who terminate study participation for reasons of lost to follow-up, informed consent withdrawal, or death will not have any follow-up assessments.

In the event a subject is discontinued from the study, the study monitor and the Sponsor will be informed immediately.

3.2.3.2. SUBJECT DISCONTINUATION CRITERIA

The subject discontinuation criteria are described below:

Efficacy discontinuation criteria at a Week 12, 16 or 20:

Any subject with < 20% improvement from baseline in both swollen and tender joint count (SJC and TJC; 66/68 counts) at any of the visits at week 12, 16 or 20 will discontinue from the trial, but remain blinded to study drug assignment. The visit at which subjects will meet the efficacy discontinuation criteria, is defined as the Early Termination Visit for these patients. Subjects who have to discontinue study drug but are not withdrawing consent for post-treatment follow-up, should return for the Follow-up Visit, planned 12 weeks after the last study drug administration, according to section 3.4.1.3.

Study drug must also be permanently discontinued if any of the following occurs:

- Serious hypersensitivity reaction.
- Following abnormalities in laboratory test results: ALT and/or AST elevations between > 3 and ≤5 x ULN (confirmed by repeat testing on 2 consecutive visits),

ALT or AST elevations > 5 x ULN, absolute neutrophil count < 1 x 10^9/L, or a platelet count < 50 x 10^3/µL.

- Diagnosis of or suspicion of a serious infection (requiring parenteral antibiotic and/or hospitalization) or TB.
- Malignancy.
- Pregnancy or pregnancy planned within the study period.
- Demyelinating disease.
- The initiation of protocol-prohibited medications (see section 3.3.6).
- Congestive heart failure (CHF) class III or IV as defined by the New York Heart Association, unstable angina pectoris, myocardial infarction, cerebrovascular accident.
- In case of interruption of study drug administration for 2 consecutive doses.
- The randomization code is broken prematurely by the Investigator or his/her staff.
- The Investigator or the Sponsor's medical monitor deems it is in the subject's best interest.

Discontinuation of study drug must be considered for subjects who develop a severe study drug injection-site reaction or a severe hypersensitivity reaction.

Subjects who have to discontinue according to these criteria but are not withdrawing consent for post-treatment follow-up should return for the Early Termination Visit planned 2 weeks after the last study drug administration (unless they discontinue during a study visit, in which case that becomes their Early Termination Visit). Subjects should also have a Follow-up Visit planned 12 weeks after the last study drug administration, according to section 3.4.1.3.

A description of assessments to be performed for subjects who discontinue from the study is provided in section 3.4.1.3 (also see Early Termination Visit in the Schedule of Assessments).

For all subjects, every effort should be made to contact the medical monitor prior to discontinuing study drug, where medically feasible. If there is a medical reason for discontinuation, the subject will remain under the supervision of the Investigator until satisfactory health has returned unless the subject withdraws his consent and is no longer willing to come to the visits. Subjects who discontinue will not be replaced.

3.2.3.3. STUDY TERMINATION

If the Sponsor abandons the study prior to commencement of any protocol activities, and after IEC/IRB and Competent Authority (CA) approvals have been

received, the Investigator or Sponsor must notify the IEC/IRB and CA by letter outlining the reasons for abandonment of the study.

At any time during the study, the Sponsor may suspend or terminate the study or part of the study for any reason. If the Investigator suspends or terminates participation in the study, the Investigator will promptly inform the Sponsor and the IEC/IRB and provide them with a detailed written explanation. The Investigator will also return all study drug, study drug containers, and other study materials to the sponsor.

Upon study completion, the Sponsor will provide the Investigator, IEC/IRB, and CA with final reports and summaries as required by regulations.

In case of suspension or halt due to safety reasons, the CA and IEC/IRB will be notified immediately and at the latest within 15 days after the study is halted, clearly explaining the reasons, and describe follow-up measures if any, taken for safety reasons.

3.3. TREATMENT OF SUBJECTS

For an overview of the treatments to be administered, please refer to section 3.1.

3.3.1. IDENTITY OF STUDY DRUG

- Study drug:
  - Active substance: ALX-0061 Nanobody.
  - Activity: ALX-0061 Nanobody binds to the IL-6R and inhibits the interaction between the IL-6 ligand and the receptor subunit, thereby preventing receptor signaling.
  - Pharmaceutical formulation: [redacted] ALX-0061 will be supplied as a sterile liquid for s.c. injection at a volume of 0.5 mL or 1.0 mL in pre-filled single-use syringes. No preservatives are present.
  - Route and volume of administration: s.c. injections at a volume of 0.5 mL and/or 1.0 mL.

- Placebo:
  - Substance: placebo.
  - Activity: none.
  - Pharmaceutical formulation: [redacted] Placebo will be supplied as a sterile liquid for s.c. injection at a volume of 0.5 mL or 1.0 mL in pre-filled single-use syringes. No preservatives are present.
  - Route and volume of administration: s.c. injections at a volume of 0.5 mL and/or 1.0 mL.

The sponsor will be providing adequate supplies of ALX-0061 and placebo for this study.

Details on study drug allocation and dosing are provided in section 3.1.1.

3.3.2. OTHER MEDICATION ADMINISTERED IN THE STUDY

Stable dose and route of MTX (12.5-25 mg weekly) maintained during the 6 consecutive weeks prior to screening and for the duration of the study. The concomitant medication dose may be reduced or temporarily discontinued because of abnormal laboratory values, side effects, concurrent illness, or the performance of a surgical procedure, but the change and reason for the medication should be clearly documented in the subject's medical record and in the electronic case report form ([e]CRF).

Commercially available MTX will be used in this study and will not be provided by the Sponsor.

It is mandatory that all subjects should receive at least 5 mg oral folic acid or oral folinic acid weekly.

Subjects who will meet the efficacy discontinuation criteria (see section 3.2.3.2) will discontinue from the trial and any future care will then be provided (outside of the study) at the discretion of the treating physician as part of usual clinical practice.

3.3.3. DRUG ACCOUNTABILITY

The Pharmacist or his/her designee is responsible for acknowledge receipt of each shipment of study drug and will verify the condition and quantity of the study drug.

The study drug will be kept in a locked and secured storage facility accessible only to those authorized by the Investigator to dispense the study drug.

The responsible person will keep an inventory. This will include a description of the formulation and the quantity of study drug received for the study and a record of the materials that are dispensed, to whom and when.

On termination of the study, the pharmacist, the Investigator and/or designated personnel will conduct a final inventory of the study drug supply and will record the results of this inventory in the Drug Accountability Form. All study drug supplies will be returned to and destroyed by a vendor upon Sponsor approval, or will be locally destroyed according to site procedure upon Sponsor approval.

Instructions for drug accountability are available in the Study Drug Manual and the IWRS Instruction Manual.

3.3.4. STUDY DRUG HANDLING

Instructions for study drug administration, handling, and storage, are available in the Study Drug Manual and the IWRS Instruction Manual.

Packaging and Labeling
The study drug will be labeled in accordance with local regulations. Each label will contain but will not be limited to, study number, storage conditions, dosing instructions, sponsor's name, address, and telephone number.

One kit will contain 2 syringes. A randomization system will assign each of the treatment kits to a subject. The content of each treatment kit will be determined according to the randomization schedule.

Storage
Study drug will be provided under refrigerated conditions and must be stored in a secure, limited-access location under the storage conditions specified by the Sponsor.

Active ALX-0061 and placebo must be refrigerated at 2°C to 8°C (35.6 °F to 46.4 °F), and should be stored in the secondary packaging until administration. It should not be frozen or shaken.

Site storage conditions should be monitored by the site personnel and reviewed by the monitor during site visits. Deviations from the storage requirements must be documented and reported to the Sponsor, according to the instructions provided in the Study Drug Manual.

Dispensing
The Investigator or qualified designee(s) will dispense study drug to subjects who have met the entry criteria. Clinical supplies may not be used for any purpose other than that which is stated in this protocol.

Product Quality Complaint
Any malfunctioning pre-filled syringe has to be communicated (written or electronically) and returned to the Sponsor or its designee.

3.3.5. STUDY DRUG INJECTIONS

ALX-0061 s.c. or placebo s.c. injections, as applicable, will be administered using the single-use pre-filled syringe at the site under the supervision of an appropriate licensed and authorized health professional at all visits.

All subjects are to receive 2 injections in the abdominal region in succession at each dosing day. Each injection should be given at a different quadrant in the abdominal region. As injections are to be performed q2w, all injections can be performed in an abdominal quadrant of choice. However, note that the area of administration needs to be evaluable for local skin reaction (normal skin without skin burns, scars, or large tattoos in the area of administration). The abdominal regions used for the administrations will be recorded in the (e)CRF. All subjects will remain at the site for 60 minutes after the injection in order to assess potential adverse reactions.

Detailed instructions for study drug administration are available in the Study Drug Manual.

No constraints with regard to timing of study drug administration during the day of dosing are to be taken into account. The exact times of study drug dosing at the clinical site will be recorded in the (e)CRF.

3.3.6. PRIOR AND CONCOMITANT THERAPY

Prior and concomitant medication are documented throughout the study.

Prior medications as per in- and exclusion criteria are detailed in section 3.2.

During the screening and 24-week treatment and assessment period of the study, subjects are not allowed to initiate DMARDs other than MTX for RA (see permitted and prohibited medication below).

Permitted Medication
Stable dose and route of MTX (12.5-25 mg weekly) maintained during the 6 consecutive weeks prior to screening and for the duration of the study. The concomitant medication dose may be reduced or temporarily discontinued because of abnormal laboratory values, side effects, concurrent illness, or the performance of a surgical procedure, but the change and reason for the medication should be clearly documented in the subject's medical record and in the (e)CRF.

Subjects treated with NSAIDs (including aspirin and selective cyclooxygenase 2 inhibitors) and other analgesics (except high-potency opioid analgesics, such as World Health Organization [WHO] class IV drugs [e.g., morphine; see prohibited

medication]) should receive the usual marketed doses approved in the country in which the study is being conducted and should be on a stable dose from at least 2 weeks prior to screening until the Week 24 Visit, or until the Early Termination Visit. Changes in the dose may be done at the discretion of the Investigator if the subject develops unacceptable side effects. Whenever possible, short-acting NSAIDs and other analgesics should not be administered within 6 hours before study assessments. Long-acting ones can be maintained at their usual dosing intervals before study assessments.

Subjects treated with oral corticosteroids should receive a stable dose equivalent to ≤ 10 mg of prednisone/day, for at least 2 consecutive weeks prior to screening, and continue this dose up to and including Week 24, or until the Early Termination Visit. The dose of oral corticosteroid may be decreased at the discretion of the Investigator only if the subject develops unacceptable side effects.

The number of intra-articular corticosteroid injections is limited to 2 injections over a 24-week period. Intra-articular injections may not be given from Week 8 until Week 12. The joint(s) affected by the procedure(s) will be considered as swollen and tender for 28 days/4 weeks in the data analyses from the date of the procedure onward.

The expression of hepatic CYP450 enzymes is suppressed by IL-6. IL-6 blocking might therefore influence (normalize) CYP450 expression and products that are substrates for CYP450 enzymes (e.g., statins, warfarin, theophylline, oral contraceptives, calcium antagonists, phenytoin, cyclosporine, benzodiazepines) could be metabolized faster. Subjects taking medicinal products which are metabolized via CYP450 3A4, should be closely monitored and their treatment might have to be adapted if necessary in order to maintain therapeutic efficacy. Subjects on warfarin will be monitored by assessment of INR (See Schedule of Assessments); the lipid levels will be evaluated which will be of help to monitor the subjects on statins (See Schedule of Assessments). If needed, the Investigator or the relevant treating physician should adapt the treatment of the concerned subject (unscheduled visits can be planned upon the discretion of the treating physician). Given the long half-life of ALX-0061, the influence on the hepatic enzymes can persist for several weeks.

Other medication (e.g., to treat AEs) may only be prescribed after consultation with the Investigator, unless in case of an emergency situation that does not allow discussion.

Prohibited Medication

The following medications are prohibited during the study (up to and including Week 24 or Early Termination Visit):

- DMARDs other than a stable background dose of MTX.
- i.m or i.v. administration of corticosteroids for the treatment of RA. Any increase in oral corticosteroids above the baseline. For intra-articular dosing see "permitted medication".
- High-potency opioid analgesics, including but not limited to hydrocodone, metopon, oxycodone, clonitazene, hydromorphone, oxymorphone, morphine, fentanyl, levorphanol, buprenorphine, methadone, meperdine.
- Use of any biologic DMARD, targeted synthetic DMARD (such as tofacitinib), or investigational drugs.
- Use of any live attenuated vaccine.

Contraceptives
Female subjects of childbearing potential (excluding postmenopausal women, sterilized, ovariectomized, and hysterectomized women) must agree to use 2 generally accepted adequate contraceptive methods of which 1 is a barrier method (e.g., hormonal contraception stabilized for at least 1 month [oral, patch, depot, injectable, vaginal ring] in combination with condom by partner) or should agree upon continuous abstinence from heterosexual contact from screening until at least 6 months after last dosing.

No additional contraceptive method is needed in case of surgical sterilization (at least 3 months prior to screening), hysterectomy, or a partner who has been vasectomized (at least 3 months prior to screening).

Male subjects should use condoms for the duration of the study and for at least 6 months after last administration of study drug.

Other
During the study, no alcohol abuse or drug abuse is allowed.

3.3.7. TREATMENT COMPLIANCE

To ensure treatment compliance, medication dosing will be supervised by the Investigator or his/her designee at all visits.

The exact times of study drug dosing at the clinical site will be recorded in the (e)CRF. Compliance will be further confirmed by bioanalytical assessment of ALX-0061 in serum samples. Treatments that are administered outside of the scheduled windows, as well as missed visits, will be recorded on the (e)CRF.

All subjects' (e)CRFs will be monitored by a site monitor (also see section 5.2.4).

3.3.8. RANDOMIZATION

After obtaining oral and written informed consent, subjects will be screened according to the inclusion and exclusion criteria and will receive a unique subject identification (ID) number, assigned by IWRS. The site will contact IWRS, provide details of the site and the subject, and receive a subject ID number for the subject.

At randomization, subjects will be reassessed and, if they meet the specified entry criteria, subjects will be randomly assigned to 1 of 5 treatment groups in a 1:1:1:1:1 ratio, and will receive a randomization number just prior to dosing according to the randomization scheme.

3.4. ASSESSMENTS

3.4.1. TIMING OF ASSESSMENTS

Written informed consent will be obtained before the first study-related procedure.

After informed consent has been obtained, each subject will be assigned a unique subject ID number.

AEs and previous/concomitant medications will be recorded from the study inclusion date (ICF signed) to the subject's last visit.

3.4.1.1. ELIGIBILITY PROCEDURES

At screening, which will take place within 21 to 1 day before the first administration of study drug, subjects will be asked to attend the clinical site to be screened according to the inclusion and exclusion criteria (section 3.2) and to have other assessments performed as specified in the Schedule of Assessments.

Subjects who signed an informed consent form, but do not meet the eligibility criteria and are not randomized, will be designated a screen failure. Subjects who meet all eligibility criteria but discontinue from the study for other reasons (eg, subject request) will not be considered screen failures.

Data of all subjects screened will be collected in the (e)CRF in order to assess the numbers and characteristics of the excluded subjects, and the reasons for their exclusion.

The results from the screening procedures needed to evaluate eligibility must be available prior to the first administration of the study drug. Sites will use the central laboratory selected for the study to analyze screening samples and to use these reported values to determine eligibility.

Unscheduled visits may be planned to assess, confirm, and follow up on clinically relevant AEs or laboratory abnormalities. Findings made during these unscheduled visits should be reported in the designated sections of the (e)CRF.

3.4.1.2. TREATMENT AND ASSESSMENT PERIOD

Week 0 (Baseline)
For details with regard to randomization, please refer to section 3.3.8.

On Week 0/Day 0, assessments and procedures should be performed as outlined in the Schedule of Assessments.

Post-Randomization Assessments

Eligible subjects will receive treatment from Week 0 up to and including Week 22. Subjects will return for 13 ambulatory visits planned at Weeks 0, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, and Week 24.

An End of Treatment Visit will be performed at Week 24.

For subjects who discontinue due to fulfilling the **efficacy** discontinuation criteria (see section 3.2.3.2) at weeks 12, 16, or 20, the visit at which they meet these discontinuation criteria is defined as the Early Termination Visit.

Subjects who discontinue early for reasons other than the efficacy discontinuation criteria should have an Early Termination Visit 2 weeks after the last study drug administration (unless they discontinue during a study visit in which case that visit becomes their Early Termination Visit).

All assessments will be performed at the visits as indicated in the Schedule of Assessments.

All post-baseline visits may occur at the indicated week ± 3 days throughout the study versus the date of the Baseline Visit.

At Week 12, 16, or 20, any subject with < 20% improvement in both SJC and TJC (66/68 counts) will have to discontinue from the trial but remain blinded to study drug assignment. The IWRS will be used to qualify subjects for study drug discontinuation based on non-response defined as < 20% improvement in both SJC and TJC.

Missed visits:

- If a subject misses a visit but a new visit can be performed within 1 week of the originally planned missed visit (i.e., within 3 weeks of the previous visit), then all assessments per missed visit should be performed at this new visit and the study staff should administer the study drug to the subject and maintain the subject's original injection schedule. In case of rescheduling of missed visits, total duration of the assessment period should remain 24 weeks.
  - For example, if a subject receives the first dose of study drug on January 1st, that is considered "Day 0 (Week 0) of the study"; the next target day of administration will be January 15th.
  - If the subject misses this second visit and comes in on January 19th (i.e. within 3 weeks of the previous visit), then the study staff should administer the study drug on that day. The next visit should be scheduled for January 29th (i.e. 4 weeks after January 1st).
- If a subject misses a visit and the visit can only be performed later than 3 weeks of the previous visit, the site should contact the CRO.
- If a subject misses a dose of MTX on their regularly scheduled dosing date, they should take the forgotten dose as soon as they remember; however, if more than 72 hours have elapsed since the missed dose, the subject should contact the Investigator for further dosing instructions.

For all subjects, injections should not occur less than 1 week apart. The CRO/Sponsor should be contacted if this cannot be respected. In case of interruption of 2 consecutive drug administrations, the subject should be discontinued from the study.

3.4.1.3. END OF TREATMENT VISIT AND FOLLOW-UP

Subjects who are eligible to participate in the OLE study, will have the End of Treatment Visit at Week 24, and no further Follow-up Visit.

Subjects who are not eligible to participate in the OLE study and who received all study drug up to and including Week 22, should return for the Week 24 End of Treatment Visit, and for the Follow-up Visit approximately 12 weeks after the last study drug administration.

Discontinuation of Study Drug Administration

For subjects who discontinue study participation for fulfilling the **efficacy** discontinuation criteria (see section 3.2.3.2) at weeks 12, 16, or 20, the visit at which subjects will meet these discontinuation criteria, is defined as the Early Termination Visit for these patients. These subjects and those who are not

withdrawing consent for post-treatment follow-up should return for a Follow-up Visit 12 weeks after last study drug administration to undergo the assessments as specified in the Schedule of Assessments.

Subjects who discontinue early for reasons other than the efficacy discontinuation criteria but are not withdrawing consent for post-treatment follow-up should return for an Early Termination Visit 2 weeks after the last study drug administration, unless they discontinue during a study visit in which case that visit becomes their Early Termination Visit. Subjects should also return for a Follow-up Visit 12 weeks after last study drug administration to undergo the assessments as specified in the Schedule of Assessments.

Termination of Study Participation

Subjects who terminate study participation for reasons of lost to follow-up, informed consent withdrawal, or death should not return for the Early Termination Visit or for the Follow-up Visit.

3.4.2. ASSESSMENTS OF EFFICACY

3.4.2.1. PHYSICIAN'S ASSESSMENT OF TENDER/PAINFUL AND SWOLLEN JOINT COUNT

To be performed as part of efficacy measurements (for more detail see sections 3.4.2.11 to 3.4.2.18) at visits as indicated in the Schedule of Assessments.

All joints listed are used in the determination of the ACR response, where 68 joints are assessed for tenderness and 66 joints are assessed for swelling (see Appendix 9). The 28 joints indicated in the grey-shaded fields are used to determine the DAS28, EULAR response, CDAI, SDAI, and Boolean score.

If tenderness or swelling is noted, enter a "1" for that joint in the appropriate field. If tenderness or swelling is absent, enter a "0" for that joint in the appropriate field.

Joints that undergo intra-articular corticosteroid injection will be considered as swollen and tender for 28 days/4 weeks in the data analyses from the date of the procedure onward.

An independent joint assessor (and backup independent joint assessor) will be designated at each study center to perform all joint assessments during the 24-weeks assessment period of the study. This individual should have at least 1 year of experience in performing joint assessments. The proposed assessors having less than 1 year of experience will need to be approved by the Sponsor. The independent joint assessor will perform only the joint assessment; this individual will not perform or assist in any other assessments in this study.

The CRO will provide training to an independent assessor from each site prior to the start of subject enrollment. In case the independent assessor cannot attend, the CRO will provide training to the Investigator who will then train the assessor. If possible, the independent assessor for the study should not be changed during the study. However, the independent assessors from each site may train additional assessors at the site for coverage during their absences. If more than 1 blinded assessor at a site performs joint assessments during the study, the names of the joint assessor performing the joint evaluation must be listed in the "Investigator Site File" and be documented in the source document at each visit.

It is recommended that the independent joint assessor who performed the baseline joint assessments for a subject should also perform the joint assessments for that subject for all subsequent visits during the 24-week assessment period of the study.

3.4.2.2. DURATION OF MORNING STIFFNESS

The average duration of morning stiffness during the previous week in minutes will be assessed at visits as indicated in the Schedule of Assessments. If a subject has stiffness that lasts the entire day, this should be recorded as 1440 minutes of morning stiffness.

3.4.2.3. PATIENT'S ASSESSMENT OF PAIN (100 MM-VAS)

To be performed as part of ACR response and prior to the joint count assessments at visits as indicated in the Schedule of Assessments.

The subject will be asked "How much pain have you had because of your illness in the past week?" and then instructed to place a mark between 0 ("no pain") and 100 mm ("severe pain") on the VAS.

3.4.2.4. PATIENT'S GLOBAL ASSESSMENT OF DISEASE ACTIVITY (VASPA) (100 MM-VAS)

To be performed as part of ACR response, DAS28 score, EULAR response, SDAI, CDAI, and Boolean remission at visits as indicated in the Schedule of Assessments.

The subject must complete the patient's global assessment independently of the physician when completing the physician global assessment (see section 3.4.2.5).

The subject will be instructed "Considering all the ways that your arthritis affects you, rate how you are doing on the following scale" and will be asked to place a mark between 0 ("very well") and 100 mm ("very poor") on the VAS.

3.4.2.5. PHYSICIAN'S GLOBAL ASSESSMENT OF DISEASE ACTIVITY (VASPHA) (100 MM-VAS)

To be performed as part of ACR response, SDAI, and CDAI at visits as indicated in the Schedule of Assessments.

The physician must complete the physician's global assessment independently of the subject when completing the patient's global assessment (see section 3.4.2.4).

The same physician should preferably be performing the assessment at each visit for each subject. The physician performing the assessment of the disease activity cannot be the independent joint assessor as described in section 3.4.2.1. The results of the joint assessment will be available to the physician performing the assessment of the disease.

The physician will make a mark between 0 ("no disease") and 100 mm ("severe disease") on the VAS to indicate the patient's current disease activity (independent of the subject's self-assessment).

3.4.2.6. C-REACTIVE PROTEIN

To be measured as part of ACR response, DAS28 score, SDAI, Boolean remission, and EULAR Response at visits as indicated in the Schedule of Assessments.

The CRP concentration is to be provided in mg/dL.

3.4.2.7. ERYTHROCYTE SEDIMENTATION RATE

To be measured as part of DAS28 score and EULAR Response at visits as indicated in the Schedule of Assessments. This will be measured via the local laboratory, by an independent laboratory-representative, or at the site by a designated independent unblinded ESR person, to maintain blinding.

The ESR result is to be provided in mm/h.

ESR results are to be maintained in a secure fashion, to prevent unblinding of blinded study personnel. ESR results will be transmitted by the site's designated unblinded person (at site or at local laboratory) to the central laboratory.

The designated unblinded ESR person at the site may only perform ESR assessments; this individual will not perform or assist in any other assessments in the study aside from collection of blood for other laboratory samples, if needed.

3.4.2.8. HEALTH ASSESSMENT QUESTIONNAIRE-DISABILITY INDEX

To be performed as part of ACR response and on its own at visits as indicated in the Schedule of Assessments.

The HAQ-DI is a 20-question instrument which assesses the degree of difficulty the subject had in accomplishing tasks in 8 functional areas over the previous week [23].

The HAQ-DI will be provided to the subject during a visit and the subject will be asked to complete the questionnaire while at the study site.

The HAQ-DI is composed of 20 items in 8 categories:

- Dressing and grooming.
- Hygiene.
- Arising.
- Reach.
- Eating.
- Grip.
- Walking.
- Common daily activities.

Each category has at least 2 sub-category questions. Within each category, subjects report the amount of difficulty they have in performing the specific sub-category items. There are 4 response options ranging from:

- 0 = No Difficulty.
- 1 = With Some Difficulty.
- 2 = With Much Difficulty.
- 3 = Unable to Do.

3.4.2.9. SF-36

The SF-36 will be completed at visits as indicated in the Schedule of Assessments.

The SF-36 consists of 36 items that can be summarized into 8 domains: physical functioning, role limitations due to physical health problems (role-physical), bodily pain, general health, vitality, social functioning, role limitations due to emotional problems (role-emotional), and mental health. Two summary measures, the physical component summary and the mental component summary, can be derived based on these domain scores.

The concepts measured by the SF-36 are not specific to any disease, allowing comparison of relative burden of different diseases, in addition to the relative benefit of different treatments.

3.4.2.10. FACIT-FATIGUE

The FACIT-fatigue scale will be completed at visits as indicated in the Schedule of Assessments.

The FACIT Measurement System is a collection of health-related quality of life questionnaires that assess multidimensional health status in people with various chronic illnesses, including RA.

3.4.2.11. ACR RESPONSE

ACR responses are presented as the numerical measurement of improvement in multiple disease assessment criteria.

ACR20/50/70 responses are defined as below:

- ≥ 20/50/70% improvement in tender/painful joint count (68 joints) relative to baseline AND
- ≥ 20/50/70% improvement in swollen joint count (66 joints) relative to baseline AND
- ≥ 20/50/70% improvement in 3 of the following 5 areas relative to baseline:
  - Patient's Assessment of Pain (100 mm-VAS).
  - Patient's Global Assessment of Disease Activity (100 mm-VASPA).
  - Physician's Global Assessment of Disease Activity (100 mm-VASPHA).
  - Patient's assessment of physical function as measured by HAQ-DI.
  - CRP.

The ACR-N Index of Improvement [24, 25] is defined as the minimum of the following 3 criteria:

- The percent improvement from baseline in TJCs.
- The percent improvement from baseline in SJCs.
- The median percent improvement from baseline for the following 5 assessments:
  - Patient's assessment of pain (VAS).
  - Patient's global assessment of disease activity (VASPA).
  - Physician's global assessment of disease activity (VASPHA).
  - Patient's assessment of physical function as measured by the HAQ-DI.
  - CRP.

3.4.2.12. DAS28 SCORE USING ESR

The DAS28 based on ESR is a statistically derived index combining TJC (28 joints), SJC (28 joints), ESR, and VASPA [26]. It is a continuous parameter and is defined as specified in Figure 2 [27]:

Figure 2: Calculation of DAS28 (ESR) score

$$\text{DAS28 (ESR)} = \left(0.56 \times \sqrt{TJC28}\right) + \left(0.28 \times \sqrt{SJC28}\right) + (0.70 \times \text{Ln[ESR]}) + (0.014 \times \text{VASPA})$$

VASPA = GH

As the results of ESR will be blinded to the investigative sites, the DAS28 will not be calculated on site but during the statistical analysis by the Biometrics-CRO.

3.4.2.13. DAS28 SCORE USING CRP

CRP will be used in addition to ESR in the calculation of DAS28, using the formula below. CRP is a more direct measure of inflammation than ESR, and it is more sensitive to short-term changes [28]. CRP is considered at least as valid as ESR to measure RA disease activity [29].

The DAS28 using CRP is a statistically derived index combining TJC (28 joints), SJC (28 joints), CRP (mg/L), and VASPA. The DAS28 is a continuous parameter and is defined as specified in Figure 3 [27]:

Figure 3: Calculation of DAS28 (CRP) score

$$\text{DAS28 (CRP)} = \left(0.56 \times \sqrt{TJC28}\right) + \left(0.28 \times \sqrt{SJC28}\right) + (0.36 \times \text{Ln[CRP} + 1]) + (0.014 \times \text{VASPA}) + 0.96$$

VASPA = GH

As the results of CRP will be blinded to the investigative sites, the DAS28 will not be calculated on site but during the statistical analysis by the Biometrics-CRO.

3.4.2.14. EULAR RESPONSE

By comparing a subject's DAS28 score (using CRP and ESR) relative to baseline, you can substantiate his/her improvement or response. The EULAR response criteria are defined in Table 1 [27].

As the results of ESR and CRP will be blinded to the investigative sites, the EULAR response will not be calculated on site but during the statistical analysis by the Biometrics-CRO.

Table 1: EULAR Response

Present DAS28	Improvement in DAS28 Relative to Baseline		
	> 1.2	> 0.6 and ≤ 1.2	≤ 0.6
≤ 3.2	good response	moderate response	no response
>3.2 and ≤ 5.1	moderate response	moderate response	no response
> 5.1	moderate response	no response	no response

3.4.2.15. CUT-OFF POINTS TO DEFINE DISEASE ACTIVITY

Cut-off points for DAS28 to define if a subject is in clinical remission or in a state of high, moderate, or low disease activity have been defined [27]:

High disease activity	DAS28 > 5.1
Moderate disease activity	3.2 < DAS28 ≤ 5.1
Low disease activity	2.6 ≤ DAS28 ≤ 3.2
Remission	DAS28 (ESR) < 2.6

As the results of ESR and CRP will be blinded to the investigative sites, the cut-off points will not be calculated on site but during the statistical analysis by the Biometrics-CRO.

3.4.2.16. BOOLEAN REMISSION

Boolean remission will be determined according to the criteria shown in Figure 4 [30].

As the results of CRP will be blinded to the investigative sites, the Boolean remission will not be calculated on site but during the statistical analysis by the Biometrics-CRO.

Figure 4: Calculation of Boolean Remission

If TJC28 ≤ 1 and SJC28 ≤ 1 and VASPA (cm) ≤ 1 and CRP (mg/dL) ≤ 1
Then remission = "yes"
Else remission = "no"

3.4.2.17. CDAI SCORE

The CDAI clinical score is determined as specified in Figure 5 and Figure 6 [30, 31].

Figure 5: Calculation of CDAI Score

CDAI = TJC28 + SJC28 + VASPA + VASPHA

Figure 6: Classification of CDAI Score

CDAI Score	CDAI ≤ 2.8	2.8 < CDAI ≤ 10	10 < CDAI ≤ 22	22 < CDAI
Disease Activity	remission	low disease activity	moderate disease activity	high disease activity

3.4.2.18. SDAI SCORE

The SDAI clinical score is determined as specified in Figure 7 and Figure 8 [31].

As the results of CRP will be blinded to the investigative sites, the SDAI will not be calculated on site but during the statistical analysis by the Biometrics-CRO.

Figure 7: Calculation of SDAI Score

SDAI = TJC28 + SJC28 + VASPA + VASPHA + CRP (mg/dL)

Figure 8: Classification of SDAI Score

SDAI Score	SDAI ≤ 3.3	3.3 < SDAI ≤ 11.0	11.0 < SDAI ≤ 26.0	SDAI > 26.0
Disease Activity	remission	low disease activity	moderate disease activity	high disease activity

3.4.3. PHARMACOKINETIC ASSESSMENTS

3.4.3.1. SAMPLE COLLECTION AND HANDLING

Throughout the study, blood samples of approximately 3.5 mL will be taken for analysis of ALX-0061 in serum, according to the time points defined in the Schedule of Assessments.

The exact times of blood sampling will be recorded. Of note, the day and approximate time of administration of the last dose of study drug will be available in the (e)CRF.

The blood samples will be collected via an indwelling i.v. catheter or by direct venipuncture. For further details on sample collection, shipment, storage and processing, please refer to a separate Lab Manual.

Samples that remain after protocol-specific assessments have been performed may be used by the Sponsor for further exploratory work on PK, PD, immunogenicity, metabolites, plasma protein binding, protein analysis, potency, and biochemistry. No human DNA or RNA analysis will be performed.

3.4.3.2. BIOANALYSIS

Concentrations of ALX-0061 in serum will be determined by a validated ligand-binding assay method according to bioanalytical methodology and procedures described in a separate Bioanalytical Analysis Plan. Results will be presented in the Bioanalytical Analysis Report and will be included in the Clinical Study Report.

3.4.4. PHARMACODYNAMIC ASSESSMENTS

3.4.4.1. SAMPLE COLLECTION AND HANDLING

Throughout the study, blood samples will be taken for analysis of soluble IL-6R, MMP-3, and CXCL13, according to the time points defined in the Schedule of Assessments.

- For determination of serum MMP-3 and CXCL13, blood samples of approximately 6 mL will be collected and aliquoted.
- For determination of plasma sIL-6R, blood samples of approximately 1.8 mL will be collected and aliquoted.

For more details on PD parameters CRP, ESR and fibrinogen, please refer to section 3.4.5.2.

The exact times of blood sampling will be recorded.

All PD blood samples will be taken via an indwelling i.v. catheter or by direct venipuncture. For further details on sample collection, shipment, storage and processing, please refer to a separate Lab Manual.

Samples that remain after protocol-specific assessments have been performed may be used by the Sponsor for further exploratory work on PK, PD, immunogenicity, metabolites, plasma protein binding, protein analysis, potency, and biochemistry. No human DNA or RNA analysis will be performed.

3.4.4.2. BIOANALYSIS

Concentrations of sIL-6R in plasma will be determined by a validated enzyme-linked immunosorbent assay (ELISA) method and concentrations of MMP-3 and CXCL13 in serum will be determined by qualified ELISA methods. All biomarkers will be measured according to bioanalytical methodology and procedures described in a separate Bioanalytical Analysis Plan. Results will be presented in the Bioanalytical Analysis Report and will be included in the Clinical Study Report.

Information on CRP, ESR and fibrinogen is specified in section 3.4.5.2.

3.4.5. ASSESSMENTS OF SAFETY

Safety and tolerability assessments consist of AEs (including injection site reactions), as well as laboratory assessments, urinalysis, vital signs, 12-lead ECG (at screening only), and physical examinations. The time points are defined in the Schedule of Assessments.

In case of acute or delayed severe/serious hypersensitivity reactions, an additional serum sample should be collected as soon as possible after the start of the event (blood volume: 5 mL) to characterize the cause of hypersensitivity by immunogenicity testing and/or protein analysis. No human DNA or RNA analysis will be performed.

Independent Data and Safety Monitoring Board (DSMB)
The DSMB will be an independent committee. None of the members will be participating in the study. The major function of this committee will be to monitor the safety of the subjects participating in the ALX-0061 clinical program.

Prior to any DSMB review, the DSMB charter will define and document the content of the safety summaries, the DSMB's role and responsibilities, and the general procedures (including communications).

3.4.5.1. ADVERSE EVENTS

General information on evaluation and reporting of AEs is provided in section 3.5.

All AEs occurring during the clinical investigation must be documented in the source documents and the (e)CRF.

Criteria for determining whether an abnormal objective test finding (e.g., laboratory, vital signs), a complication of a protocol mandated procedure (e.g., blood draw, injection of study drug) or a change in physical examination findings should be reported as an AE are as follows, but not limited to:

1. Result/finding is associated with accompanying clinical signs and symptoms, and/or
2. Result/finding requires extra diagnostic testing (other than diagnostic exclusion tests) or medical/surgical intervention, and/or
3. Result/finding would require a change in study drug dosing or discontinuation from the study, significant additional concomitant drug treatment or other therapy, and/or
4. Result/finding leads to any of the outcomes included in the definition of an SAE, and/or
5. Result/finding is considered to be an AE by the Investigator.

Any abnormal test result that is determined to be an error and merely repeating an abnormal test does not require reporting as an AE.

The Investigator will also need to indicate whether the AE is a serious infection.

A "serious infection" is any infection that meets the criteria for an SAE:
- requires hospitalization and/or
- requires i.v. antibiotics and/or
- results in death.

All serious infections should be reported as SAE.

3.4.5.2. LABORATORY ASSESSMENTS

Blood samples for routine and extended (including fasting serum lipids) clinical laboratory analyses will be collected at time points as indicated in the Schedule of Assessments.

In general, blood samples will be collected via an indwelling i.v. catheter or by direct venipuncture. Details on method, sampling and processing procedures will be provided in a separate Lab Manual.

The following tests will be included in the routine clinical laboratory analysis:
- Biochemistry: total bilirubin, alkaline phosphatase, gamma-glutamyltransferase, AST, ALT, lactate dehydrogenase, creatinine, urea, total protein, albumin, glucose, inorganic phosphate, sodium, potassium, calcium, and chloride.
- Hematology: leukocytes, erythrocytes, hemoglobin, hematocrit, thrombocytes, partial automated differentiation (lymphocytes, monocytes, eosinophils, basophils, neutrophils), mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration.
- Acute phase proteins: fibrinogen, CRP, and ESR.
- Urinalysis: erythrocytes/blood, urobilinogen, ketones, glucose, protein, pH, and leukocytes.
- Coagulation: activated partial prothrombin time, prothrombin time, and INR (the latter for subjects on warfarin only).

The following additional tests will be included in the extended clinical laboratory analysis:
- Biochemistry: total cholesterol, HDL-cholesterol, LDL-cholesterol, and triglycerides (i.e., fasting serum lipids).

Note that at visits when extended clinical laboratory analysis samples are planned to be taken, samples should be taken predose after the subject has been fasting for at least 10 h.

In females of childbearing potential, a blood pregnancy test will be performed at time points as indicated in the Schedule of Assessments. Of note, additional pregnancy testing is allowed according to local guidelines; however, this additional pregnancy testing is not part of and cannot replace the protocol specific procedures.

At screening, seropositivity for hepatitis B, hepatitis C, anti-HIV1 and anti-HIV2 will be tested and the levels of Rheumatoid Factor and anti-CCP antibodies will be determined.

In addition, an IGRA test to detect latent or active TB and a chest radiograph (performed within 12 weeks prior to the screening visit or performed during the screening period) to detect evidence of malignancy, infection, or abnormalities suggestive of TB will be performed at screening and at any time during the study if TB is suspected.

All samples will be analyzed by a central laboratory, except for ESR that will be measured via the local laboratory, by an independent laboratory representative.

Except for ESR, CRP, and fibrinogen, laboratory values outside the normal range will be flagged and clinical relevance will be assessed by the Investigator. The results of CRP, ESR and fibrinogen tests will not be communicated to the investigational sites and CRO/Sponsor (unless in case of an alert for CRP or fibrinogen), with the exception of the CRP and fibrinogen results at screening which are needed for assessing the subject's eligibility for randomization.
If clinical signs and symptoms are present for which the Investigator needs to know values of ESR, CRP, or fibrinogen for medical care, he can request this information.

All clinically significant abnormal laboratory findings will be recorded as AEs in the (e)CRF (also see section 3.4.5.1).

In the event of unexplained or unexpected clinical laboratory test values, the test(s) will be repeated and followed up until the results have returned to the normal range and/or an adequate explanation for the abnormality is found.

During the screening period, subjects with an abnormal clinical laboratory value (i.e., biochemistry, hematology, urinalysis, fibrinogen, or coagulation) may have one laboratory analysis repeated if the Investigator considers the result to be inconsistent with prior determination and/or not representative of the subject's clinical condition at screening. Only the clinical laboratory test not meeting entry criterion should be repeated (not the entire panel).

To this note, the site is allowed to repeat the CRP test once during the screening period if the result would be considered as an occasional finding and/or inconsistent with prior determinations and/or the patient's clinical status in the opinion of the Investigator.

In case any test is repeated, it should be performed as an unscheduled lab test and the last laboratory result should be used as the final screening value.

Repeat testing of the serology (hepatitis B, hepatitis C, HIV) is not allowed. Repeat testing of the Quantiferon is only allowed if the result is indeterminate (see inclusion criterion 8).

Samples that remain after protocol-specific assessments have been performed may be used by the Sponsor for further exploratory work on PK, PD, immunogenicity, metabolites, plasma protein binding, protein analysis, potency, and biochemistry. No human DNA or RNA analysis will be performed.

3.4.5.3. VITAL SIGNS

Vital signs parameters (assessed after 5 min in supine position) will be measured at the time points indicated in the Schedule of Assessments. These observations will be made using an automated device. All parameters will be recorded in the (e)CRF.

The following vital signs parameters will be assessed: height, weight, blood pressure, pulse, and temperature (such as oral, axillar, or tympanic).

To obtain the actual body weight, subjects must be weighed lightly clothed. The height should be measured barefoot at the Screening Visit.

Clinically relevant abnormalities occurring during the study should be recorded as AE in the (e)CRF.

3.4.5.4. ELECTROCARDIOGRAM

12-lead ECGs assessed after 5 min in supine position will be recorded at the screening visit only.

The following ECG parameters will be recorded: heart rate, RR interval, PR interval, QRS-duration, QT interval, QT interval corrected for heart rate (QTc) (corrected according to Bazzet's and Fridericia's formula [QTcB and QTcF]) and Investigator's conclusion on the ECG profile.

3.4.5.5. PHYSICAL EXAMINATION

A complete physical examination will be performed at the time points indicated in the Schedule of Assessments. Of note, additional physical examinations may be performed upon the discretion of the Investigator (e.g., in case of AEs).

Physical examination will be recorded as "normal", "abnormal, not clinically significant" or "abnormal, clinically significant" at every assessment. A new finding or a change of a finding that is judged as an undesirable medical event (including all findings recorded as "abnormal, clinically significant") shall be reported as an AE.

The physical examination will include at least:

- Head, eyes, ears, nose, throat.
- Respiratory system.
- Cardiovascular system.
- Gastrointestinal system.
- Musculoskeletal system.
- Central and peripheral nervous system.
- Skin.
- Lymph node palpation.
- Urogenital system (kidneys).
- General appearance.

Any clinically relevant changes occurring during the study must be recorded in the (e)CRF and any clinically significant abnormalities persisting at the end of the study will be followed by the Investigator until resolution or until reaching a clinically stable endpoint.

3.4.6. OTHER ASSESSMENTS

3.4.6.1. IMMUNOGENICITY

To assess systemic immunogenicity of ALX-0061, blood samples of approximately 7 mL will be collected at the time points defined in the Schedule of Assessments.

Blood samples will be taken via an indwelling i.v. catheter or by direct venipuncture. The exact times of blood sampling will be recorded. For further details on sample collection, shipment, storage and processing, please refer to a separate Lab Manual.

Anti-ALX-0061 antibodies (ADA) will be determined, potentially with further characterization by mADA and nAb assay. The immunogenicity data will be

processed according to a separate analytical plan, and the results from this analysis will be included in the Clinical Study Report.

As described previously, in case of acute or delayed severe/serious hypersensitivity reactions, an additional serum sample should be collected as soon as possible after the start of the event (blood volume: 5 mL) to characterize the cause of hypersensitivity by immunogenicity testing and/or protein analysis. No human DNA or RNA analysis will be performed.

Samples that remain after protocol-specific assessments have been performed may be used by the Sponsor for further exploratory work on PK, PD, immunogenicity, metabolites, plasma protein binding, protein analysis, potency, and biochemistry. No human DNA or RNA analysis will be performed.

3.4.7. TOTAL BLOOD VOLUME

The estimated number and volume of blood samples and the total volume of blood that will be collected per subject throughout the study are provided in Table 2.

If necessary, in order to obtain additional information to ensure safety to the subject, additional blood (and urine) samples may be taken at the discretion of the Investigator. Due to this possibility, the blood volumes presented in the following table are provided as best estimations.

The total volume of blood taken during the study will be approximately 233.7 mL.

Table 2: Estimated Number and Volume of Blood Samples to be Obtained During the Study

Assessments	# samples	Volume (mL) /sample	Volume (mL)
Pharmacokinetics	10	3.5	35
Pharmacodynamics: sIL-6R	9	1.8	16.2
Pharmacodynamics: MMP-3, CXCL13	6	6	36
Routine clinical laboratory	5	6.5	32.5
Extended clinical laboratory, including fasting lipids	8	6.5	52
Serology (at screening only)	1	5	5
Rheumatoid factor and anti-CCP antibodies	1	5	5
Immunogenicity	7	7	49
Quantiferon test	1	3	3
Total			**233.7** [a]

[a] In case of acute or delayed severe/serious hypersensitivity reactions, an additional serum sample should be collected as soon as possible after the start of the event (blood volume: 5 mL)

3.4.8. APPROPRIATENESS AND TIMING OF MEASUREMENTS

The assessments which will be made in this study are standard and generally recognized as reliable, accurate, and relevant.

The timing of all assessments is detailed in the Schedule of Assessments.

All visits should occur in the specified week (± allowed time window) without further specification of the timing (visit may be planned at the time most appropriate for the subject). Of note, at baseline and at Weeks 4, 8, 12, 16, 20, 22 and 24, or at the Early Termination Visit, blood samples should be taken after at least 10 hours of fasting.

For PK, PD, immunogenicity and safety, predose samples will be obtained between waking up and dosing.

If assessments are planned at the same time, the order of the assessments should be arranged according to the following principles:

1. Vital signs should be assessed prior to blood sampling,
2. Patient reported outcomes should occur prior to the physician's joint evaluation, and
3. Study drug should be dosed after all other assessments have been performed.

3.5. ADVERSE EVENT EVALUATION AND REPORTING

3.5.1. ADVERSE EVENTS

AE definitions will be followed as stated in the "Note for Guidance on clinical safety data management: definitions and standards for expedited reporting" (International Conference on Harmonization [ICH] topic E2A).

An AE is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. An AE does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not considered related to that medicinal (investigational or non-investigational) product.

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

In the differentiating between medical history and AEs, the following points will be considered.

- Conditions that started before signing of informed consent and for which no symptoms or treatment are present up to the timing of signing of the informed consent are recorded as medical history (e.g., seasonal allergy without acute complaints).
- Conditions that started before signing of informed consent and for which symptoms or treatment are present after signing of informed consent, but with unchanged severity, are recorded as medical history (e.g., allergic pollinosis).
- Conditions that started or deteriorated after signing of informed consent will be documented as AEs.

All AEs will be reported from the time a signed and dated ICF is obtained until completion of the subject's last visit.

A TEAE is any AE temporally associated with the use of study drug, whether considered related to the study drug or not. TEAEs are recorded from the start of study drug administration, until completion of the subject's last visit.

It is the responsibility of the Investigator to collect all AEs (both serious and non-serious) derived by spontaneous, unsolicited reports of subjects, by

observation, and by routine open questioning (e.g., "How have you felt since I saw you last?"; "Is there anything new that you wish to discuss?").

All AEs will be assessed by the Investigator and recorded on the AE (e)CRF page. AE entry should indicate time of onset and end time and rating of the seriousness (see section 3.5.2), severity (see section 3.5.1.1), and outcome (see section 3.5.1.2) of the AEs, and relationship to study drug and study procedures (see section 3.5.1.3), action taken regarding study drug (see section 3.5.1.4), and concomitant therapy taken for the AE.

The Investigator will judge upon the severity of the AEs and relation to study drug and study procedures.

3.5.1.1. AE SEVERITY

The severity of AEs will be rated on a 3-point scale according to the Common Terminology Criteria for AEs (CTCAE v4.0):

- Mild: discomfort noticed but no disruption of normal daily activity (signified by grade 1 of CTCAE v4.0).
- Moderate: discomfort sufficient to reduce or affect normal daily activity (signified by grade 2 of CTCAE v4.0).
- Severe: incapacitating with inability to work or perform normal daily activity, (signified by grade 3 or 4 or 5 of CTCAE v4.0).

It is emphasized that the term severe is a measure of intensity: a severe AE is not necessarily serious.

Please refer to the Common Terminology Criteria for Adverse Events (CTCAE v4.0) for assessment of severity of AEs related to laboratory abnormalities.

3.5.1.2. OUTCOME

The outcome of the AE is to be documented as follows:

- Recovered / resolved.
- Recovering / resolving.
- Recovered / resolved with sequelae.
- Not recovered / not resolved.
- Fatal.
- Unknown.

3.5.1.3. RELATION TO STUDY DRUG OR STUDY PROCEDURES

The assessment of the causal relationship between an AE and the administration of treatment is a clinical decision based on all available information at the time of the completion of the (e)CRF.

The assessment is based on the question whether there was a "reasonable causal relationship" to the study treatment in question. Possible answers are:

- Unlikely/Not related.
- Possibly related.
- Related.
- Not applicable.

If the causal relationship to the study drug is unknown, the answer is defined as "related".

Note that only AEs starting after administration of study drug can be assigned a causal relationship between the AE and study drug administration. For AEs starting prior to study drug administration, causal relationship between the AE and study drug should be not applicable.

Assessment of causal relationship of any AE to protocol-required procedures can be completed with:

- Yes (specify).
- No.

3.5.1.4. ACTION TAKEN REGARDING STUDY DRUG

Any action taken regarding study drug due to an AE is to be documented using following categories:

- Dose not changed.
- Drug interrupted.
- Drug withdrawn.
- Not applicable.
- Unknown.

3.5.2. SERIOUS ADVERSE EVENTS

An SAE is any untoward medical occurrence that at any dose meets any of the following conditions:

- Results in death.
- Is life-threatening: the subject is at risk of death at the time of the event. It does not refer to an event that hypothetically might cause death if it were more severe.
- Requires in-subject hospitalization or prolongation of existing hospitalization; an AE associated with a hospitalization or prolongation of hospitalization will not be regarded as an SAE if at least one of the following exceptions is met:
  - The admission results in a hospital stay of less than 12 hours.
  - The admission is pre-planned (i.e., elective or scheduled surgery arranged prior to the start of the study).
  - The admission is not associated with an AE (e.g., social hospitalization for purposes of respite care).

  However, it should be noted that invasive treatment during any hospitalization may fulfill the criterion of "medically important" and as such may be reportable as an SAE dependent on clinical judgment. In addition, where local regulatory authorities specifically require a more stringent definition, the local regulation takes precedence.
- Results in persistent or significant disability/incapacity. Disability means a substantial disruption of a person's ability to conduct normal life's functions.
- Results in a congenital anomaly/birth defect.
- Is another medically important serious event as judged by the Investigator, or is defined as requiring intervention to prevent one of the outcomes listed in the definition above (including suspected transmission of an infectious agent by a medicinal product should be reported as an SAE). Other examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse. Any AE is considered an SAE if it is associated with clinical signs or symptoms judged by the Investigator to have a significant clinical impact.

All serious infections should be reported as SAE.

A treatment-emergent SAE is any SAE temporally associated with the use of study drug, whether considered related to the study drug or not.

The Investigator or clinical site personnel should notify the CRO of all SAEs, regardless of relationship to the study drug, within 24 hours of clinical site personnel becoming aware of the event (see Investigator Site File).

The Investigator will provide the initial notification by faxing a completed "SAE Notification Form", which must include the Investigator's assessment of the relationship of the event to study drug, and must be signed by the Investigator.

The first report of an SAE may also be made by telephone. The Reporter must provide the minimal information: i.e., reporter identification, study number, year of birth, medication code number, period of intake, nature of the AE, and relation to study drug.

This report of an SAE by telephone must always be confirmed by a written, more detailed report (the SAE Form) to be completed and signed by the Investigator.

Follow-up information, or new information regarding an ongoing SAE, must be provided promptly to the contacts provided in the Investigator Site File.

The SAE should also be recorded in the (e)CRF. Any medications necessary for the treatment of the SAE must be recorded on the concomitant medication section of the (e)CRF.

SAEs that begin after the subject's participation in the study is complete, but that the Investigator considers to be related to study drug, should be reported to the CRO/Sponsor at any time.

3.5.3. SUSPECTED UNEXPECTED SERIOUS ADVERSE REACTIONS (SUSAR)

Unexpected adverse reactions are adverse reactions of which the nature or severity is not consistent with the applicable product information (as described in the Reference Safety Information, provided in the Investigator's Brochure).

The CRO will report expedited the following SUSARs to the IEC/IRB on behalf of the Sponsor:

- SUSARs that have arisen in the current clinical study that was assessed by the IEC/IRB.
- SUSARs that have arisen in other clinical studies of the same Sponsor and with the same study drug and that could have consequences for the safety of the subjects involved in the current clinical study that was assessed by the IEC/IRB.

The CRO will report expedited all SUSARs to the relevant CA on behalf of the Sponsor.

The Sponsor (or CRO on behalf of the Sponsor) will also report to all concerned Investigators all SAEs that are unlisted (unexpected) and associated with the use of the drug.

SUSARs that are already present in the European Medicines Agency Eudravigilance database do not have to be once again reported to the CA because they have direct access to the Eudravigilance database.

The expedited reporting will occur no later than 15 calendar days after the Sponsor (or the CRO on behalf of the Sponsor) has first knowledge of the adverse reactions.

For fatal or life-threatening cases the term will be maximal 7 calendar days for a preliminary report with another 8 days for completion of the report.

3.5.4. REPORTING OF ADVERSE EVENTS

AE reporting, including SUSARs, will be carried out in accordance with applicable local regulations. For reported deaths, the Investigator should supply the Sponsor and the IEC/IRB with any additional requested information (e.g., autopsy reports and terminal medical reports).

After termination of the clinical study (last subject last visit in the study), any unexpected safety issue that changes the risks benefit analysis and is likely to have an impact on the subjects who have participated in it, will be reported by the Sponsor as soon as possible to the competent authority(ies) concerned together with proposed actions.

3.5.5. FOLLOW-UP OF ADVERSE EVENTS

AEs will be handled according to common clinical practice. If necessary, in order to obtain additional information to ensure safety to the subject, additional blood and urine samples may be taken at the discretion of the Investigator. Information relative to other means of investigational diagnostics used in relation to the AE will also be communicated.

AEs are recorded from signing the ICF until completion of the subject's last visit. TEAEs are recorded from the start of study drug administration, until the subject's last visit.

All AEs occurring at any time during the study (including the follow-up period) will be followed until satisfactory outcome.

For subjects that are considered lost to follow-up, reasonable attempts must be made to obtain information on the final status of the subject.

3.5.6. OTHER REPORTABLE INFORMATION

3.5.6.1. PREGNANCY

The Investigator must report to the Sponsor any pregnancy occurring in a study subject, or in his partner, during the subject's participation in this study and until 6 months after last study drug dose. The report should be submitted within the same timelines as an SAE, although a pregnancy per se is not considered an SAE.

For a study subject, the outcome of the pregnancy should be followed up carefully, and any abnormal outcome of the mother or the child should be reported.

For the pregnancy of a study subject's partner, all efforts should be made to obtain similar information on course and outcome.

All pregnancies including study subjects and female partners should be reported using the pregnancy form.

Note that as indicated in section 3.2.3.2, subjects who get pregnant during the study should be withdrawn from the study.

3.5.6.2. MEDICATION ERROR

Medication errors include, but are not limited to, the following:

- Administration of the wrong dosage (including overdose) to the subject.
- Administration of the study drug that has not been assigned to the subject.
- Administration of expired study drug.
- Administration by a route (e.g., i.m.) other than s.c.
- Deviations to the study drug storage conditions only when administered to the subject.

Medication errors with signs and symptoms need to be reported as an AE/SAE.

Medication errors that occur during the study should be documented and reported to the Sponsor or designee whether or not it results in an AE/SAE.

3.6. STATISTICS

3.6.1. STUDY POPULATIONS

The following populations will be considered for analysis:

- **Intent-to-treat (ITT) Population**: All randomized subjects.
- **Safety Population**: All subjects who received at least 1 administration of study drug, as treated.
- **PK Population**: consists of a subset of the Safety Population, for whom the primary PK data are considered to be sufficient and interpretable.
- **Per Protocol (PP) Population**: consists of a subset of the ITT population, and excludes those subjects who have had a major protocol violation or deviation. All violations and deviations will be reviewed prior to database lock and classified as major or minor.

Unless otherwise specified, the ITT Population will be used for the analysis of efficacy, the Safety Population for analysis of safety, PD, and immunogenicity data, while the PK Population will be used for analysis of the PK variables.

3.6.2. STATISTICAL AND ANALYTICAL PLAN

The statistical analysis plan (SAP), will be generated under responsibility of the Sponsor. The SAP will be finalized prior to the Week 24 database lock. Any deviation from the reporting and analysis plan will be reported in the section "Changes in the planned analysis" in the Clinical Study Report.

Data analysis will start after all subjects completed the Week 24 Visit. Efficacy will be analyzed at the time of this Week 24 database lock only.

Analysis of safety, PD, Modelling and Simulations, and immunogenicity will be initiated or repeated at the time of final database lock, i.e., after the last subject completed the Follow-up Visit (i.e., 12 weeks after the last dosing). Details of the data analyses will be specified in the SAP.

3.6.3. INITIAL CHARACTERISTICS OF SUBJECT SAMPLE

The statistical evaluation will be descriptive and by treatment (including mean, standard deviation, median, maximum, and minimum) for continuous variables and counts and percentages for categorical variables.

3.6.4. EVALUATION OF EFFICACY PARAMETERS

The primary endpoint is the reduction of signs and symptoms of RA evaluated by calculating the proportion of subjects achieving an ACR20 response at Week 12.

The following efficacy analyses will be performed in addition to the primary analysis:

- The proportion of subjects achieving an ACR response of 20, 50, and 70 over time will be summarized by treatment group.
- ACR-N index of improvement over time will be summarized by treatment group.
- The DAS28 (using CRP and ESR) score over time will be summarized by treatment group.
- The proportion of subjects with EULAR response over time will be summarized by treatment group.
- The change from baseline (absolute change) in disease activity over time will be summarized by treatment group. The following disease activity scores will be used:
  - DAS28 (CRP and ESR)
  - SDAI
  - CDAI
- The proportion of subjects in remission over time will be summarized by treatment group and compared between the groups. The proportion of subjects who maintained in remission at consecutive time points; i.e., at Weeks 12, 16, 20, 24 will be summarized by treatment group.

  The following disease remission definitions will be used:
  - DAS28 (ESR) < 2.6
  - SDAI ≤ 3.3
  - CDAI ≤ 2.8
  - Boolean: TJC ≤1, SJC ≤ 1, CRP ≤1 mg/dL, VASPA ≤1 (on a 0-10 scale)
- The change from baseline (absolute change) in HAQ-DI over time will be summarized by treatment group.
- The proportion of HAQ-DI responders (i.e., those who have a clinically meaningful improvement from baseline of ≥ 0.25 [absolute change] in HAQ-DI) over time will be summarized by treatment group.
- The proportion of subjects with HAQ-DI ≤ 0.5, defining normal physical function, over time will be summarized by treatment group.
- The proportion of subjects with HAQ-DI ≤ 0.5 (normal physical function) with or without remission (DAS28, SDAI, CDAI, and Boolean) at Week 24 will be summarized by treatment group.

- The changes from baseline (absolute change) in the physical and mental component scores of the SF-36 at Week 12 and at Week 24 will be summarized by treatment group.
- The change from baseline (absolute change) in SF-36 scales at Week 12 and at Week 24 will be summarized by treatment group.
- The change from baseline (absolute change) in FACIT-Fatigue at Week 12 and at Week 24 will be summarized by treatment group.
- The duration of morning stiffness at Week 24 will be summarized by treatment group.

Primary and secondary efficacy endpoints will be analyzed according to the ITT principle. Summary statistics for continuous efficacy endpoints include mean (and associated 95% confidence interval), standard deviation, median, minimum and maximum. For categorical efficacy endpoints frequency and proportion or percentage (together with 95% confidence interval) will be calculated. Analysis on the primary endpoint will be repeated for the PP population, as a sensitivity analysis.

Subgroup analyses will be performed to evaluate consistency of the primary and secondary efficacy endpoints over covariates including demographics (including weight and region), baseline disease characteristics (including disease duration, RF category and anti-CCP category), baseline and prior medications, and site.

Unless specified otherwise, non-responder imputation for missing binary efficacy endpoints will be applied, whereas missing continuous efficacy endpoints will be imputed by last observation carried forward.

3.6.4.1. PRIMARY EFFICACY ENDPOINT

Under the assumption of monotonicity, a trend test will be performed as primary efficacy analysis. For small deviations from monotonicity (comprised in standard variation on ACR20 response rate), the power of the trend test remains sufficiently high. For the descriptive statistics (frequency, percentage) and trend test on the primary efficacy endpoint, data will be analyzed according to the ITT principle; thus, subjects will be analyzed according to the treatment to which they were assigned. Subjects with missing ACR20 response at Week 12 will be treated as non-responders (non-responder imputation approach).

Additionally, each dose group will be tested separately against placebo using a Chi^2 or Fisher exact test (or other test if deemed more relevant). The study is only powered for testing the trend of the primary endpoint. All other p-values are exploratory and no correction for multiple testing is foreseen.
If ACR20 cannot be calculated at Week 12, such subjects will be considered to not have achieved an ACR20 response.

Subjects who meet any of the following treatment failure criteria will be considered nonresponder for the primary endpoint analysis:

- Initiate treatment with DMARDs (other than MTX), systemic immunosuppressives, and/or biologics for RA prior to Week 12.
- Increase dose of MTX above the baseline dose for RA prior to Week 12.
- Initiate treatment with oral corticosteroids for RA, increase the dose of oral corticosteroids for RA above the baseline dose, or receive i.v. or i.m. administration of corticosteroids for RA prior to Week 12.
- Treatment with intra-articular corticosteroids between Week 8 and Week 12.

3.6.4.2. SECONDARY EFFICACY ENDPOINTS

For secondary efficacy endpoint evaluation summary statistics will be calculated as appropriate over time and by treatment group.

3.6.5. EVALUATION OF PHARMACOKINETIC PARAMETERS

The procedures for obtaining ALX-0061 serum concentrations are found in section 3.4.3.

Evaluation of Pharmacokinetics
PK analysis will be performed on the PK population.

Individual study drug concentrations will be listed. In addition a listing of the actual sampling times relative to the study drug administration times will be presented.

Drug concentrations will be summarized by treatment group and scheduled sampling time.

The descriptive statistics on drug concentrations will be performed under the responsibility of Ablynx NV.

Pharmacokinetic Model
ALX-0061 serum concentrations obtained from all subjects in the study will be pooled together with available data collected so far in previous studies. A population PK analysis will be conducted to describe the population mean and variability of ALX-0061 exposure in the study population based on pharmaco-statistical nonlinear mixed effect models.

PK Modelling will be performed under the responsibility of Ablynx NV. Results will be provided in a separate Modelling and Simulation report.

3.6.6. EVALUATION OF PHARMACODYNAMIC PARAMETERS

All PD data will be summarized using descriptive statistics and will be listed and summarized in tabular and/or graphical form. Additional exploratory modelling (e.g., predictive analysis of specific biomarkers) may be performed.

Exposure-response Model(s)
An Exposure-Response analysis will be performed to determine the relationship between ALX-0061 serum exposure and PD and efficacy endpoints i.e., DAS28 and ACR20 using nonlinear mixed effects modelling.

Details on the exposure-response modelling will be included in a separate Data Analysis Plan, and will be performed under the responsibility of Ablynx NV. Results of this analysis will be provided in a separate Modelling and Simulation report.

3.6.7. EVALUATION OF SAFETY PARAMETERS

The DSMB will evaluate the safety data periodically (see section 3.4.5).

The following analyses will be performed to assess the safety of subjects in this study.

- The incidence and type of AEs.
- The incidence and type of SAEs.
- The incidence and type of related AEs (including study drug injection-site reactions and hypersensitivity reactions).
- The laboratory parameters and change from baseline in these laboratory parameters.
- The incidence of antibodies to ALX-0061.

All safety, PD and immunogenicity analyses will be performed using the Safety Population of all subjects who received at least 1 dose of study drug. Analyses will be performed using the treatment that the subject actually received.

In addition, subgroup analyses will be performed to evaluate consistency of safety over covariates including demographics (including weight), and concomitant medication (including immunosuppressants and corticosteroids).

AEs will be fully described and coded according to the Medical Dictionary for regulatory Activities. A treatment-emergent analysis of AEs will be done. Frequency of subjects presenting AEs, AEs leading to withdrawal, adverse drug reactions, and

SAEs will be tabulated for each treatment group by system organ class and preferred term.

For laboratory parameters, descriptive statistics (mean, median, standard deviation, minimum, and maximum) will be computed on the actual values and the change from baseline (absolute) for each parameter. All laboratory values will be categorized according to their normal ranges as below, within or above normal. A shift table versus baseline (including final value versus baseline and worst value versus baseline) will be created.

Vital signs variables will be fully depicted using descriptive statistics (for actual values and changes from baseline) and shift tables according to their normal ranges. Screening ECG values will be assessed through listing of individual results by subject and summary tables.

Abnormal findings in physical examinations will be listed.

Immunogenicity will be assessed through listing of individual results by subject and summary tables.

3.6.8. DETERMINATION OF SAMPLE SIZE

Simulations were performed to evaluate the power for detecting a significant trend effect in the different ALX-0061 doses versus placebo. Assuming ACR20 response rates of 25%, 30%, 45%, 55%, and 55% for placebo, ALX-0061 75 mg q4w, ALX-0061 150 mg q4w, ALX-0061 150 mg q2w, and ALX-0061 225 mg q2w respectively, a sample size of 66 subjects per arm will provide more than 90% power using the Cochran Armitage test for trend at significance level of 0.05 (2-sided).

Drop-out rate is assumed to be low (i.e., between 5 and 15%) and considered equally distributed between subjects receiving placebo and ALX-0061. Subjects who drop-out are considered as non-responders (non-responder imputation approach).

3.7. DATA QUALITY ASSURANCE AND DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

An audit may be conducted to evaluate systems, processes, and expertise for the subcontracted activities and to assess compliance with the contractual agreements, the protocol, applicable Standard Operating Procedures, and regulatory requirements. During or after the conduct of the study, process-related audits may be performed as well. When performed, an audit certificate will be provided in appendix of the final study report, outlining the audit performed.

The clinical research facility will be monitored by the study monitor, to ensure correct performance of the study procedures and to assure that the study is conducted according to the relevant regulatory requirements.

Regulatory authorities, the IEC/IRB, and/or the Sponsor representative may request access to all source documents, (e)CRFs and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the Investigator, who must provide support at all times for these activities.

Quality control principles will be applied throughout the performance of this study i.e., to collect full date of birth and subject initials is NOT allowed.

3.8. DATA PROTECTION

During this clinical study, all clinical data will be identified only through an ID number in order to protect the rights of the subjects to privacy and to the protection of their personal data in accordance with the European Data Protection Directive 95/46/EC. Global principles and standards for Processing Personal Data and for meeting Data Transfer Obligations will be applied. If local requirements are more specific or expansive, Ablynx NV and subcontractors will abide to the strongest requirements.

4. ETHICS

4.1. ETHICS COMMITTEES AND COMPETENT AUTHORITIES

The Clinical Study Protocol(s) and the ICF(s) will be submitted for review and approval by the IEC/IRB prior to the eligibility screening. The composition of the IEC/IRB is in accordance with the recommendations of the WHO, the ICH E6 Guideline for GCP, and the European Union Clinical Trial Directive (CTD) (Directive 2001/20/EC).

The Investigator will keep the IEC/IRB informed about the progress of the study. All changes in research activities and all unanticipated problems involving risks to human subjects will be immediately reported to the responsible persons. The study may be suspended pending further review by the IEC/IRB, unless suspension would jeopardize the subject's health. The Investigator will take care that all subjects are kept informed.

No substantial amendments will be made to the study without prior IEC/IRB approval and CA approval (if applicable according to local regulations), except when required to eliminate apparent immediate hazards to human subjects.

Notification of the end of the study will be sent to the CA and to the IEC/IRB, within 90 days after completion of follow-up for the last subject. In case the study has ended prematurely, the IEC/IRB and the CA will be notified within 15 days, including the reasons for the premature termination. A summary of the results of the study will be sent to the CA and the IEC/IRB within 1 year after the end of the study.

4.2. ETHICAL CONDUCT OF THE STUDY

This study will be conducted in compliance with the ICH Guidance for Industry E6 GCP (including archiving of essential study documents), the Declaration of Helsinki, the applicable regulations of the country(ies) in which the study is conducted, and with the European Commission Directives 2001/20/EC and 2005/28/EC.

ICH-adopted guidelines and other relevant international guidelines, recommendations, and requirements will be taken into account as comprehensively as possible, as long as they do not violate Local laws.

The Investigator will be responsible for the care of the subjects throughout the study. If the Investigator is not present at the study site, he/she will leave instructions for the staff and a telephone number where he/she can be reached.

In the event a subject refuses to follow the instructions of the Investigator, the latter is released from any legal responsibility.

4.3. SUBJECT INFORMATION AND CONSENT

Each subject must give written consent according to local requirements after the nature of the study has been fully explained. The consent form must be signed before performance of any study-related activity. The consent form that is used must be approved by both the Sponsor or designee and by the reviewing IEC/IRB. The informed consent should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and Sponsor policy.

Before undertaking any study-related procedure in the study, the Investigator or an authorized member of the investigational staff must explain to potential subjects the aims, methods, objectives, no intended clinical benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Subjects will be informed that their participation is voluntary and that the subject may refuse to participate or withdraw from the study, at any time, without penalty or loss of benefits to which the subject is otherwise entitled and that all data collected up to the point of withdrawal will be used and reported in an anonymous way. Finally, they will be told that the Investigator will maintain a subject identification register for the purposes of long-term follow-up if needed and that their records may be accessed by health authorities, authorized Sponsor staff, and Sponsor representative without violating the confidentiality of the subject, to the extent permitted by the applicable law(s) or regulations. By signing the ICF the subject is authorizing such access, and agrees to allow his study physician to recontact the subject for the purpose of obtaining consent for additional safety evaluations, if needed.

The language used in the oral and written information about the study, including the ICF, should be as nontechnical as practical and should be understandable to the subject (i.e., lay terminology). The subject will be given sufficient time to read the ICF and given the opportunity to ask questions. After this explanation and before entry into the study, consent should be appropriately recorded by means of the subject's personally dated signature and by the Investigator (or an authorized person) who conducted the ICF discussion. After having obtained the consent, a copy of the signed ICF must be given to the subject. The original of the ICF will be retained by the Investigator in the "Investigator Site File".

In addition, insurance coverage provided during the study is explained.

4.4. PRIVACY

The collection and processing of personal data from subjects enrolled in this study will be limited to those data that are necessary to investigate the safety, quality, and utility of the study drug(s) used in this study.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of study subjects confidential. Subjects will be identified by his/her assigned unique subject number or subject ID number and his/her date of birth (when allowed by local regulations). Personal data will only be collected and processed using these unique identification items.

The informed consent obtained from the subject includes explicit consent for the processing of personal data and for the Investigator to allow direct access to his original medical records for study-related monitoring, audit, IEC/IRB review, and regulatory inspection. This consent also addresses the transfer of the data to other entities and to other countries.

5. DATA HANDLING AND RECORD KEEPING

5.1. DISTRIBUTION OF ACTIVITIES

Contact details of the Sponsor and third parties are available in the "Investigator Site File".

5.2. DOCUMENTATION

Study documentation required for study start (as specified in the ICH E6 Guideline for GCP (CPMP/ICH/135/95) shall be exchanged between Ablynx NV and CRO prior to the administration of study drug.

5.2.1. CASE REPORT FORM COMPLETION

Case report forms are provided for each subject (including screen failures).

The Investigator will ensure that data are recorded on the (e)CRF as specified in the Clinical Study Protocol and in accordance with the instructions in the (e)CRF. The Investigator will ensure the accuracy, completeness, legibility, and timeliness of the data recorded in the (e)CRF, and of the provision of answers to data queries according to the Clinical Study Agreement. All (e)CRF entries, corrections, and alterations must be made by the Investigator or other authorized study-site personnel. The Investigator will sign the completed (e)CRF. A copy of the completed (e)CRF will be archived at the study site.

5.2.2. SOURCE DOCUMENTATION

At a minimum, source documentation must be available for the following: medical history, subject identification, eligibility, and study identification; date of informed consent; dates of visits; results of all efficacy evaluations; results of safety parameters as required by the protocol; record of all AEs; and follow-up of AEs; prior and concomitant medication; study drug receipt records; study drug administration information; any medical notes (original documents, data and records, e.g., laboratory data, ECG printouts); date of study completion, and reason for early discontinuation of study procedures or withdrawal from the study, if applicable.

In addition, the author of an entry in the source documents should be identifiable.

At a minimum, the type and level of detail of source data available for a study subject should be consistent with that commonly recorded at the site as a basis for standard medical care (Patient's Medical File).

Following the ICH-GCP guidelines, direct access to source documentation (medical records) must be allowed.

5.2.3. RECORD RETENTION

In compliance with the ICH/GCP guidelines, the Investigator/Institution will maintain all (e)CRFs and all source documents that support the data collected from each subject, as well as all study documents as specified in ICH/GCP section 8, Essential Documents for the Conduct of a Clinical Study, and all study documents as specified by the applicable regulatory requirement(s). The Investigator/Institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained until at least 10 years after completion of the study, 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 until at least 2 years have elapsed since the formal discontinuation of clinical development of the study drug. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the Investigator/Institution as to when these documents no longer need to be retained. The Sponsor will receive the original (e)CRFs and study-related documents.

If the responsible Investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The Sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the Investigator relocate or dispose of any study documents before having obtained written approval from the Sponsor.

The Investigator should take measures to prevent accidental or premature destruction of study documents.

If it becomes necessary for the Sponsor or the appropriate regulatory authority to review any documentation relating to this study, the Investigator must permit access to such reports.

The CRO is responsible for organizing and maintaining a clear documentation of the course of the study.

The Trial Master File maintained during the study by the responsible persons of CRO will be sent back to the Sponsor upon Sponsor approval.

Patients medical files, consent forms, and identification codes if relevant, will be kept by the Investigator in his/her personal files during the timeframe specified in local regulations or until the Sponsor decides that these documents no longer need to be retained (CPMP/ICH/135/95 § 4.95).

5.2.4. MONITORING

The monitor will perform on-site monitoring visits as specified in a monitoring plan to ensure that all aspects of the protocol, contractual agreements, and regulatory requirements are followed and that subject's human rights, safety, and well-being are protected. The monitor will record dates of monitoring in a study center visit log that will be kept at the site. At these visits, the monitor will perform source data verification and check the data entered into the (e)CRF for completeness and accuracy. The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the (e)CRF are known to the Sponsor and investigational staff and are accessible for verification by the Sponsor site contact. If electronic records are maintained at the investigational site, the method of verification must be discussed with the investigational staff.

Direct access to source documentation ([electronic] medical records) must be allowed at any time. Findings from this review of captured data will be discussed with the investigational staff. The Sponsor expects that, during on-site monitoring visits, the relevant investigational staff will be available, the source documentation will be accessible, and a suitable environment will be provided for review of study-related documents. The monitor will meet with the Investigator on a regular basis during the study to provide feedback on the study conduct. The Investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits will be resolved.

6. FINANCING AND INSURANCE

Ablynx NV holds and will maintain an adequate insurance policy covering damages arising out of Ablynx-sponsored clinical research studies.

Ablynx NV will indemnify the Investigator and hold him/her harmless for claims for damages arising out of the investigation in excess of those covered by his/her own professional liability insurance providing that the drug was administered under his/her or deputy's supervision and in strict accordance with accepted medical practice and the study protocol.

The Investigator must notify Ablynx NV immediately upon notice of any claims or lawsuits.

Participants in this study are covered by an Insurance Policy. This insurance covers any damage as a result of death or injury caused by participation in the study. The damage is considered having become apparent after notice has been given to the insurance company.

Any identified Investigator or subinvestigator directly involved in the treatment or evaluation of research subjects will disclose for the time period during which the Investigator is participating in the study and for 1 year following completion of the study that he/she entered a financial arrangement between the Sponsor and the Investigator. The Investigator should promptly update this information if any relevant changes occur during this period.

The subjects will be compensated for reasonable expenses made related to the study such as travel costs to visit the study center for assessments related to the study.

7. USE OF INFORMATION AND PUBLICATION

By signing this protocol, the Investigator reaffirms to the Sponsor that he or she will maintain in confidence all information furnished to him, or resulting from this study. He or she will only divulge such information as may be necessary to the IEC and the members of the staff and the subjects who are involved in this study.

All data and records provided by the Sponsor or generated during the study (other than subject's medical records) and all data and inventions covered in the course of conducting the study, whether patentable or not, are the sole and exclusive property of the Sponsor.

The Investigator and all other study team members at any service provider involved will keep strictly confidential all information provided by the Sponsor related to this study and all data and records generated in the course of the study. They will not use the information, data, or records for any other purpose than conducting the study without prior written approval of the Sponsor.

Publication of any results from this study will be according to the principles of the Declaration of Helsinki, in particular point 30, and will require prior review and written agreement of the Sponsor.

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9. APPENDIX: TENDER AND SWOLLEN JOINT COUNT

Tender and swollen joint count (TJC 68/ SJC 66)

	Joint	**Patient Right**		**Patient Left**	
		Tender	**Swollen**	**Tender**	**Swollen**
1	TMJ				
2	SC				
3	AC				
4	Shoulder				
5	Elbow				
6	Wrist				
7	MCP I				
8	MCP II				
9	MCP III				
10	MCP IV				
11	MCP V				
12	Thumb Interphalangeal				
13	PIP II				
14	PIP III				
15	PIP IV				
16	PIP V				
17	DIP II				
18	DIP III				
19	DIP IV				
20	DIP V				
21	Hip		N.A.		N.A.
22	Knee				
23	Ankle				
24	Subtalar / tarsus				
25	MTP I				
26	MTP II				
27	MTP III				
28	MTP IV				
29	MTP V				
30	IP I				
31	IP II				
32	IP III				
33	IP IV				
34	IP V				
	TOTAL (ACR)				
	ACR TOTAL Tender Joint Count (for 68 joints):				
	ACR TOTAL Swollen Joint Count (for 66 joints):				
	TOTAL (for DAS28 score – shaded joints only)				
	DAS28 TOTAL Tender Joint Count (for 28 joints):				
	DAS28 TOTAL Swollen Joint Count (for 28 joints):				

AC=acriomioclavicular; ACR=American College of Rheumatology; DAS28=Disease Activity Score using 28 joint counts; DIP=distal intraphalangeal; IP=interphalangeal; MCP=metacarpophalangeal; MTP=metatarsophalangeal; PIP=proximal interphalangeal; TMJ=temporal mandibular joint; SC=sternoclavicular; SJC=swollen joint count; TJC=tender joint count

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