

Janssen Research & Development***Clinical Protocol**

A Multicenter, Parallel-group Study of Long-term Safety and Efficacy of CNTO 136 (sirukumab) for Rheumatoid Arthritis in Subjects Completing Treatment in Studies CNTO136ARA3002 (SIRROUND-D) and CNTO136ARA3003 (SIRROUND-T)

**Protocol CNTO136ARA3004; Phase 3
AMENDMENT 3****CNTO 136 (sirukumab)**

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This study will be conducted under US Food & Drug Administration IND regulations (21 CFR Part 312).

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Compliance: This study will be conducted in compliance with this protocol, Good Clinical Practice, and applicable regulatory requirements.

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SYNOPSIS

A Multicenter, Parallel-group Study of Long-term Safety and Efficacy of CNTO 136 (sirukumab) for Rheumatoid Arthritis in Subjects Completing Treatment in Studies CNTO136ARA3002 (SIRROUND-D) and CNTO136ARA3003 (SIRROUND-T)

CNTO 136 (sirukumab) is a human anti-interleukin-6 (IL-6) mAb currently under development by the Sponsor in collaboration with GlaxoSmithKline, plc. It binds to human IL-6 with high affinity and specificity, and has been shown to inhibit IL-6-mediated signal transducer and activator of transcription-3 (STAT3) phosphorylation, resulting in the inhibition of the biological effect of IL-6. The target indications for sirukumab are rheumatoid arthritis (RA) and lupus nephritis, both of which are diseases that involve IL-6.

OBJECTIVES AND HYPOTHESIS

Primary Objective

To evaluate the long-term safety of sirukumab in subjects with RA who are refractory to DMARDs or anti-TNF α agents.

Secondary Objectives

The secondary objectives are to observe the following long-term effects of sirukumab in subjects with RA who are refractory to DMARDs or anti-TNF α agents on:

- Efficacy
- Pharmacokinetics
- Immunogenicity
- Pharmacodynamics
- Pharmacogenetics
- PFS-AI Usability (as defined in separate substudy protocol)

Hypothesis

No hypothesis is being tested.

OVERVIEW OF STUDY DESIGN

Subjects will become eligible to participate in this LTE study when they have completed participation in studies CNTO136ARA3002 (104 weeks) or CNTO136ARA3003 (52 weeks). The purpose of this LTE study is to evaluate the safety, efficacy, and pharmacologic effects of sirukumab for a minimum duration of 1 additional year and a maximum total duration of approximately 5 years across the combined protocols (CNTO136ARA3002 (2 years) or CNTO136ARA3003 (1 year) + CNTO136ARA3004 (1 to 4 years) = maximum of 5 years treatment).

The SmartJect™ Autoinjector (PFS-AI) is expected to be used by the majority of subjects in study CNTO136ARA3004. In the event PFS-AIs are unavailable at the time of a subject's enrollment in this protocol, sirukumab PFS-Ultrsafe (PFS-U), the same device used in the CNTO136ARA3002 and CNTO136ARA3003 studies, will be provided until such time as the PFS-AIs become available. Upon availability of PFS-AI trial supplies, subjects who are newly entering the CNTO136ARA3004 protocol will be trained on the operation of PFS-AI and perform self-administration of study agent using PFS-AI at the Week 2 study visit and return to the study site at Week 4 for self-administration with PFS-AI. In the event PFS-AIs are unavailable at the time of a subject's enrollment in this protocol, training on the use of a PFS-AI will be provided at the next study visit when the PFS-AI is available.

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During the Week 104 visit in CNTO136ARA3002 or the Week 52 visit in CNTO136ARA3003, subjects will sign the informed consent form (ICF) to enter study CNTO136ARA3004. As a result, the Week 104 visit in study CNTO136ARA3002 and the Week 52 visit in study CNTO136ARA3003 will correspond to the Week 0 visit in the CNTO136ARA3004 study.

After a minimum of 1 year treatment in CNTO136ARA3004 for subjects from study CNTO136ARA3002, or a minimum of 2 years of treatment in CNTO136ARA3004 for subjects from CNTO136ARA3003, and after sirukumab is approved for the treatment of RA in the subject's country of residence, the Sponsor may no longer offer study treatment in CNTO136ARA3004 for those specific subjects. At that point the subject will have the opportunity to discuss treatment options with their treating physician.

The maximum duration of participation in this study is 208 weeks, followed by approximately 16 weeks of safety and efficacy follow-up after the administration of the final study agent injection of sirukumab. The study will end with the last visit for the last subject participating in the study.

Study treatment will remain blinded in CNTO136ARA3004 until the following 3 conditions have been met: the Week 52 DBL occurs in study CNTO136ARA3002, the Week 24 DBL occurs in study CNTO136ARA3003, and the last AI usability substudy subject completes the Week 16 visit or terminates from the study. Thereafter treatment in study CNTO136ARA3004 becomes open-label, and placebo injections are discontinued in the SC sirukumab 50 mg treatment group.

Subject safety will be monitored and assessments will be done through the end of the study as delineated in the Time and Events Schedule ([Table 1](#) and [Table 2](#)).

Only 1 DBL (at the end of the study) is planned. Additional data releases or locks may occur as needed.

An Independent Data Monitoring Committee (DMC) and Clinical Events Committee (CEC) will be commissioned for this study.

SUBJECT SELECTION

To be eligible to enroll in this long-term extension study, subjects will have to have fulfilled the following conditions:

- For subjects in study CNTO136ARA3002, have completed the Week 104 visit and study agent administration
- For subjects in study CNTO136ARA3003, have completed the Week 52 visit and study agent administration.

Subjects who withdraw consent and/or have permanently discontinued study agent administration prior to the final visit in study CNTO136ARA3002 or CNTO136ARA3003 will be excluded from enrollment in the CNTO136ARA3004 study.

DOSAGE AND ADMINISTRATION

Dosing Regimen

Subjects will continue to receive the sirukumab dosing regimen they received at the end of the primary studies (CNTO136ARA3002, CNTO136ARA3003).

Group 1: Sirukumab 100 mg SC at Weeks 0 (administered as the last dose in CNTO136ARA3002 or CNTO136ARA3003), 2 and q2 weeks through Week 156 for subjects who enrolled after completing participation in CNTO136ARA3002 and through Week 208 for subjects who enrolled after completing participation in CNTO136ARA3003.

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Group 2: Sirukumab 50 mg SC at Weeks 0 (administered as the last dose in CNTO136ARA3002 or CNTO136ARA3003), 4 and q4 weeks through Week 156 for subjects who enrolled after completing participation in CNTO136ARA3002 and through Week 208 for subjects who enrolled after completing participation in CNTO136ARA3003. Between sirukumab injections, placebo SC injections will be administered at Weeks 2, 6, and q4 weeks until the study becomes open-label and placebo injections will be discontinued.

After the study becomes open-label, subjects treated with SC sirukumab 100 mg q2 weeks will be offered the option to reduce the dose to 50 mg q4 weeks at the investigator's discretion. This decision can be made at the subject's first or second major resupply visit (up until approximately 7 months) after implementation of Amendment 3 at the study site. Once a subject's dose is reduced to 50 mg q4 weeks, the subject will receive that dose for the remainder of the trial (ie, a return to 100 mg q2 weeks will not be allowed). If a subject opts to remain on the sirukumab 100 mg q2 weeks dose, he or she will remain on that dose for the duration of their participation in the study (ie, the subject will not have the option to reduce the dose at a subsequent timepoint).

If an injection is missed, every effort should be made to have the missed injection administered within 7 days after the scheduled date for that injection. In case it is not possible to administer the missed injection in time, site personnel should discuss the issue with the medical monitor.

If sirukumab becomes approved in the subject's country of residence, study agent administrations in CNTO136ARA3004 may be discontinued after 52 weeks of treatment for subjects who enrolled after completing participation in study CNTO136ARA3002, and after 104 weeks of treatment for subjects who enrolled after completing participation in CNTO136ARA3003. Therefore, all subjects in study CNTO136ARA3004 are expected to receive a minimum of 3 years of treatment with study agent (primary study + LTE study).

Blinding

To maintain the blind, all subjects will receive study agent as 1 SC injection as follows:

Group 1 (sirukumab 100 mg): 1.0 mL sirukumab 100 mg injection q2 weeks.

Group 2 (sirukumab 50 mg): 1.0 mL sirukumab 50 mg injection q4 weeks. Between sirukumab injections, placebo SC injections will be administered at Weeks 2, 6, and q4 weeks until the study becomes open-label, and placebo injections will be discontinued.

Timing and Study Agent Administration

Through the end of the study, it is recommended that both the visit and the SC study agent administration occur within 7 days of the scheduled visit day. The SC study agent administrations must always be at least 7 days apart.

Self-Administration

The SmartJect™ Autoinjector (PFS-AI) is expected to be used by the majority of subjects in study CNTO136ARA3004. In the event PFS-AIs are unavailable at the time of a subject's enrollment in this protocol, sirukumab PFS-Ultrasafe (PFS-U), the same device used in the CNTO136ARA3002 and CNTO136ARA3003 studies will be provided until such time as the PFS-AIs become available. Upon availability of PFS-AI trial supplies, subjects who are newly entering the CNTO136ARA3004 protocol will be trained on the operation of PFS-AI and perform self-administration of study agent using PFS-AI at the Week 2 study visit and return to the study site at Week 4 for self-administration with PFS-AI. In the event PFS-AIs are unavailable at the time of a subject's enrollment in this protocol, training on the use of a PFS-AI will be provided at the next study visit when the PFS-AI is available.

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The self-injection training consists of a face-to-face, “hands-on” training, with an explanation of each task in the Instructions For Use (IFU), a demonstration performed by the study site staff with the PFS-AI trainer device, followed by practice injections performed by the subject using the trainer device, until the study site staff and subject are satisfied that the injections can be performed as stated in the IFU. This mimics the typical training by a physician’s office staff that is likely to be received by a patient for the prescribed marketed product, per the final product’s labeling. The step-by-step Training Guide for investigators or site staff to follow when providing training of subjects will be provided in the Site IP Procedures Manual. If subjects are competent in using PFS-AI, they will subsequently be provided with study agent for self-administration at home, and instructed how to transport and store medication for at-home use as indicated for this protocol. Subjects will be instructed to contact the investigator promptly in the event of any signs of an allergic reaction, infection, or bleeding. Subjects may continue to administer the study agent at home for the duration of the study. Although additional face-to-face training sessions after the first training session are not scheduled, the site staff will be available to provide additional training if needed. If subjects or health care providers are uncertain about how to administer the study agent, the Sponsor recommends a review of the IFU and performing practice injections with the PFS-AI trainer device, and if necessary, to ask for retraining at the study site.

Subjects unable or unwilling to self-administer will continue to have study agent injections performed by a health care professional at the study site. A caregiver may also be trained to administer study agent at home.

Once the study becomes open-label, the Week 2 visit for training may be skipped by subjects who are to receive open label sirukumab 50 mg q4 weeks and training in the use of an PFS-AI will be provided at Week 4.

EFFICACY EVALUATIONS

The efficacy evaluations chosen for this study are as follows:

RA response evaluations include:

- American College of Rheumatology (ACR) responses
- Disease Activity Index Score 28 (DAS28)
- Health Assessment Questionnaire-Disability Index (HAQ-DI)
- ACR/The European League Against Rheumatism (EULAR) remission

Patient Reported Outcome (PRO) evaluations include:

- 36-Item Short Form (SF-36)
- Work Limitations Questionnaire (WLQ)
- Health Economics Questionnaire (HECONQ)

PHARMACOKINETIC AND IMMUNOGENICITY EVALUATIONS

Blood samples for the measurement of serum sirukumab concentrations and the detection of antibodies to sirukumab will be collected according to the Time and Events Schedule ([Table 1](#)).

PHARMACODYNAMIC EVALUATIONS

Samples for the analysis of pharmacodynamic markers will be collected. The samples will be used to better understand the biology of RA, to provide a biological assessment of the loss of response of subjects to treatment with sirukumab, and to determine if the markers can be used to classify patients as potential

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responders to treatment. The samples to be collected include whole blood for RNA and serum for the evaluation of inflammation-associated proteins and other analytes such as but not limited to microRNAs.

PHARMACOGENETIC (DNA) EVALUATIONS

Pharmacogenetic testing will be undertaken in this study for only those subjects who have provided voluntary consent. Assessment of genetic factors such as DNA methylation testing will be performed to better understand the response of subjects to treatment with sirukumab. A whole blood sample will be collected for DNA methylation testing. Only DNA research related to sirukumab or to the diseases for which this drug is developed will be performed.

SAFETY EVALUATIONS

Subject safety evaluations including the reporting of adverse events, clinical laboratory tests (hematology, serum chemistry including liver function tests, and lipid panels), pregnancy tests, and vital signs (blood pressure and body weight) etc. will be monitored through the end of the study as delineated in the Time and Events Schedules ([Table 1](#) and [Table 2](#)).

In addition, an independent DMC will review unblinded data periodically for the blinded portion of the study and whenever deemed necessary to monitor subject safety.

The CEC is an independent committee composed of external specialists, blinded to treatment assignment, which will be commissioned to review case information on serious cardiovascular (CV) events (myocardial infarction, stroke, death, hospitalization for angina, hospitalization for transient ischemic attack [TIA]). The operations, processes, and definitions to be employed by the committee will be defined in the CEC charter.

SMARTJECT™ AUTOINJECTOR USABILITY SUBSTUDY

In this substudy, a select number of subjects at selected sites in English-speaking countries who are enrolled in CNTO136ARA3004 will be consented and enrolled in a SmartJect™ AI Usability substudy. Site personnel in this substudy will observe and document 2 scheduled self-administrations of study agent by subjects using the PFS-AI. All substudy subjects will also complete an e-diary regarding their experiences with at-home use of PFS-AI.

STATISTICAL METHODS

Statistical analysis will be done by the Sponsor or under the authority of the Sponsor.

Subjects will continue to receive the same treatment regimen administered in studies CNTO136ARA3002 and CNTO136ARA3003 at Weeks 104 and 52, respectively:

- Group 1: Sirukumab 100 mg SC q2 weeks
- Group 2: Sirukumab 50 mg SC q4 weeks

After the study becomes open-label, subjects in Group 1 will be offered the option (at the discretion of the investigator) to reduce the sirukumab dose to 50 mg q4 weeks for the remainder of the trial.

Since the treatment groups are not randomly assigned in this study, no formal hypothesis testing is planned. The efficacy, safety, and PK/PD/immunogenicity analyses will be performed separately for subjects who complete studies CNTO136ARA3002 and CNTO136ARA3003. The analyses will include all subjects enrolled by study and by treatment group above.

Only 1 DBL (at the end of the study) is planned. Safety, efficacy, and PK/PD/immunogenicity assessments will be analyzed for subjects enrolled in the CNTO136ARA3004 by previous study and by treatment group.

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Additional data releases or locks may occur as needed. The analyses based on these data releases or locks intend to integrate data from CNTO136ARA3002 and CNTO136ARA3003 with this study for the long-term PK, immunogenicity, safety and efficacy data of all subjects enrolled in these studies. A separate SAP for integration will be developed to specify the analyses and data handling rules.

- **Sample Size Determination**

All eligible subjects will be included in this LTE study. No power calculations were performed as there is no statistical hypothesis testing planned.

- **Interim Analysis**

No formal interim analyses are planned, though analyses based on interim releases and locks may be carried out for integrated PK, immunogenicity, safety and efficacy data.

- **Primary Analyses**

The number of subjects with each of the following long-term safety events: cardiovascular SAEs, malignancies, serious infections, and gastrointestinal perforations will be summarized. Serious cardiovascular events adjudicated by the CEC will be summarized by treatment group. No hypothesis testing will be performed.

- **Secondary Analyses**

The laboratory parameters of interest (neutrophils, platelets, hepatobiliary parameters, and lipid parameters) will be summarized by the treatment group over time. Baseline value is defined as the baseline value of study CNTO136ARA3002 or CNTO136ARA3003, respectively.

- **Other Planned Analyses**

- **Safety Analyses**

Additional analyses will be performed for the number of patients with cardiovascular SAEs by cardiovascular type and the number of patients with malignancies by malignancy type (eg, lymphoma, nonmelanoma skin cancers, other malignancies).

Other safety data will be assessed by summarizing the proportion of subjects with AEs, the types of AEs, infections, SAEs, AEs leading to discontinuation, and changes in laboratory parameters.

- **Efficacy Analysis**

The following efficacy endpoints will be summarized by treatment group over time:

- ACR responses
- DAS28
- HAQ-DI
- SF-36

Baseline value in efficacy is defined as the baseline value of study CNTO136ARA3002 or CNTO136ARA3003. No missing data imputation will be used.

- **Medical Resource Usage and Health Economics**

WLQ and HECONQ data will be summarized over time.

- **Pharmacokinetic and Immunogenicity Analyses**

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Serum sirukumab concentration data including C_{trough} will be summarized. PK data may be displayed graphically. If sufficient samples are collected, steady-state trough serum sirukumab concentrations before and after switching from PFS-U to PFS-AI will be evaluated.

The incidence of antibodies to sirukumab will be summarized for subjects with appropriate samples for detection of antibodies to sirukumab (ie, at least 1 sample obtained after sirukumab administration).

- **Pharmacodynamic Analyses**

Changes in the concentration of individual pharmacodynamic markers from baseline to the selected post treatment time points will be summarized. Association between baseline levels and changes from baseline in select biomarkers and clinical response will be explored. The pharmacodynamic analysis will characterize the response of subjects to sirukumab, to determine if loss of response to sirukumab can be predicted, and to better understand RA. Data will be summarized in a separate technical report.

- **Pharmacogenetic Analyses**

Pharmacogenetic tests will be summarized by treatment group. Genetic factors and changes in expression of DNA methylation markers from baseline (CNTO136ARA3002 and CNTO136ARA3003 studies) to the collection time point in study CNTO136ARA3004 will also be summarized. The pharmacogenetic analyses will be summarized in a separate technical report.

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TIME AND EVENTS SCHEDULE

Table 1: Times and Events in Long-term Extension																				
	Wk 0	Wk 2 ^b	Wk 4	Wk 16	Wk 28	Wk 40	Wk 52	Wk 64	Wk 76	Wk 88	Wk 104	Wk 116	Wk 128	Wk 140	Wk 156 ^c	Wk 168	Wk 180	Wk 192	Wk 208 ^d	
Study Procedures^a																				
Administrative																				
Informed consent	X																			
Pharmacogenetic (DNA) consent	X																			
Training session ^{b,c}		X																		
Study Agent Administration																				
SC administration of study agent		X	← administrations q2 or q4 weeks depending upon dosing regimen →																	
Post-administration injection-site evaluation		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Safety Assessments																				
Urine pregnancy test (local) ^f			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination						X				X				X					X	
Body weight measurement						X				X				X					X	
Blood pressure			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
TB evaluation			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Efficacy Assessments																				
Joint assessment				X		X		X		X		X		X		X		X		X
RA assessments ^g				X		X		X		X		X		X		X		X		X
SF-36				X		X		X		X		X		X		X		X		X
WLQ				X		X		X		X		X		X		X		X		X
Health Economics				X		X		X		X		X		X		X		X		X

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Table 1: Times and Events in Long-term Extension																			
	Wk 0	Wk 2 ^b	Wk 4	Wk 16	Wk 28	Wk 40	Wk 52	Wk 64	Wk 76	Wk 88	Wk 104	Wk 116	Wk 128	Wk 140	Wk 156 ^c	Wk 168	Wk 180	Wk 192	Wk 208 ^d
Exploration of Placebell[®]™ technology for RA																			
Placebell Multidimensional Personality Questionnaire ^h				← optional at selected sites for consenting subjects at a single visit after implementation of Amendment 3 →															
Clinical Laboratory Assessments																			
Hematology panel				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Chemistry panel				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Lipid panel (fasting)					X		X		X		X		X		X		X		X
CRP					X		X		X		X		X		X				X
Pharmacokinetics / Immunogenicity																			
Sirukumab concentration (pharm serum sample) ^{ij}		X	X	X	X		X				X				X				X ^k
Antibodies to sirukumab (pharm serum sample) ^{ij}				X	X		X				X				X				X ^k
Pharmacodynamics																			
Pharmacodynamics serum sample							X				X				X				X
Whole blood sample for RNA							X				X				X				X
Pharmacogenetics(DNA)																			
Pharmacogenetics sample ^l			X																
Ongoing Subject Review																			
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

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Table 1: Times and Events in Long-term Extension

- a. All assessments are to be completed prior to study agent administration, unless otherwise specified. For subjects who discontinue study agent injections, see [Table 2](#) for required follow-up assessments. Administration of study agent and visit windows should be within 7 days for all visits. Administration of study agent must occur no less than 7 days apart throughout the study.
- b. Once the study becomes open-label, the Week 2 visit will not be conducted for subjects in treatment Group 2. The training session for these subjects will occur at Week 4 or at a subsequent visit following the availability of the PFS-AI.
- c. Last study agent administration for subjects who enrolled after participating in CNTO136ARA3002. These subjects will then have follow-up assessments as described in [Table 2](#).
- d. Last study agent administration for subjects who enrolled after participating in CNTO136ARA3003. These subjects will then have follow-up assessments as described in [Table 2](#).
- e. Training in the use of a PFS-AI will be provided at the first scheduled visit that the subject receives the PFS-AI for the self-administration of study agent.
- f. Urine pregnancy testing during the study for women of childbearing potential only. Additional pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the subject's participation in the study.
- g. RA assessments include the following: patient pain assessment; patient global assessment of disease activity, physician global assessment of disease activity, Health Assessment Questionnaire-Disability Index, and duration of morning stiffness.
- h. At selected sites, the MPSQ will be administered as an optional paper questionnaire to subjects who consent to participate after implementation of Amendment 3 at the study site.
- i. Pharm serum samples (sirukumab concentration and antibodies to sirukumab) will be collected from subjects who had pharm serum samples collected at earlier time points in study CNTO136ARA3002 (approximately 750 subjects randomized in CNTO136ARA3002 before 18 November 2013) and from all subjects enrolled after participating in study CNTO136ARA3003.
- j. On days of study agent administration, Pharm serum samples (sirukumab concentration and antibodies to sirukumab) must be collected prior to administration. Blood collected from one venipuncture will be divided into 3 serum aliquots (1 each sirukumab concentration, antibodies to sirukumab and a backup sample). Refer to the Central Laboratory Manual for more detailed instructions.
- k. Pharm serum samples (sirukumab concentration and antibodies to sirukumab) will be collected only from those subjects who enrolled after participating in study CNTO136ARA3003.
- l. An optional pharmacogenetics blood sample will be collected from those subjects who sign a separate consent form (where local regulations permit).

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Table 2: Times and Events in Safety and Efficacy Follow-up After Last Study Agent Injection or after Discontinuation of Study Agent				
	Week 4	Week 8	Week 12	Week 16/Final Safety and Efficacy Follow-up Visit
Study Procedure ^{a,b}				
Safety Assessments				
Blood pressure	X	X	X	X
Efficacy Assessments				
Patient pain assessment		X		X
Patient global assessment of disease		X		X
Physician global assessment of disease		X		X
Clinical Laboratory Assessments				
Hematology panel		X		X
Chemistry panel		X		X
Lipid panel (fasting)		X		X
CRP		X		X
Pharmacokinetics/ Immunogenicity				
Sirukumab concentration (pharm serum sample) ^{c,d}				X
Antibodies to sirukumab (pharm serum sample) ^{c,d}				X
Ongoing Subject Review				
Injection-site evaluations	X			
Adverse events	X	X	X	X
Concomitant medications	X	X	X	X
<p>a. Subjects who discontinue study agent injections and who are not terminating study participation should return for all scheduled follow-up assessments through approximately 16 weeks after the last study agent injection as specified in this table.</p> <p>b. The first safety and efficacy follow-up visit should occur 4 weeks \pm 14 days after their last study agent injection. The visit window for follow-up assessments is \pm 14 days.</p> <p>c. Pharm serum samples (sirukumab concentration and antibodies to sirukumab) will be collected at the final safety and efficacy follow up visit only from those subjects who had pharm serum samples collected at earlier time points in study CNTO136ARA3002 (approximately 750 subjects randomized in CNTO136ARA3002 before 18 November 2013) and from all subjects enrolled after participating in study CNTO136ARA3003.</p> <p>d. Blood collected from one venipuncture will be divided into 3 serum aliquots (1 each for sirukumab concentration, antibodies to sirukumab and a backup sample). Refer to the Central Laboratory Manual for more detailed instructions.</p>				

ABBREVIATIONS

ACR	American College of Rheumatology
AE	adverse event
AI	Autoinjector
ALT	alanine aminotransferase
anti-HBc total	hepatitis B core antibody
anti-HBs	hepatitis B surface antibody
AST	aspartate aminotransferase
BD	Becton-Dickinson
BUN	blood urea nitrogen
CDAI	Clinical Disease Activity Index
CEC	Clinical Events Committee
CQ	chloroquine
CRF	case report form
CRP	C-reactive protein
CSR	Clinical Study Report
C _{trough}	Observed serum concentration immediately prior to the next administration
CV	cardiovascular
CYP	cytochrome P450
DAS28	Disease Activity Index Score 28
DBL	database lock
DMARD	disease modifying antirheumatic drugs
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DSUR	Development Safety Update Report
ECG	electrocardiogram
eCRF	electronic case report form
eDC	Electronic Data Capture
EULAR	The European League Against Rheumatism
Fc	fragment crystallizable
FDA	Food and Drug Administration
G	gauge
GCP	Good Clinical Practice
GH	Patient's Global Assessment of Disease Activity
GMS	Global Medical Safety
HAQ-DI	Health Assessment Questionnaire-Disability Index
HBsAg	hepatitis B surface antigen
HCQ	hydroxychloroquine
HDL	high-density lipoprotein
HECONQ	Health Economics Questionnaire
HIV	human immunodeficiency virus
IA	intra-articular
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IgG1	immunoglobulin G1
IL	interleukin
IL-6R	interleukin 6 receptor
sIL-6R	soluble interleukin 6 receptor
IM	intramuscular
INR	international normalized ratio
IRB	Institutional Review Board
IV	intravenous
IVRS	interactive voice response system
IWRS	interactive web response system
JAK/STAT	janus kinase/signal transducer and activator of transcription
LDL	low-density lipoprotein
LE	lupus erythematosus

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LN	Lupus Nephritis
LSLV	last subject's last visit
LTE	long-term extension
mAb	monoclonal antibody
MACE	Major Adverse Cardiovascular Events
MCS	Mental Component Score
MedDRA	Medical Dictionary for Regulatory Activities
MPSQ	Multidimensional Personality Questionnaire
MTX	methotrexate
NCEP	National Cholesterol Education Program
NK	natural killer
NSAID	nonsteroidal anti-inflammatory drug
PCS	Physical Component Score
PD	pharmacodynamics
PFS	Pre-filled Syringe
PFS-AI	Pre-filled Syringe Autoinjector
PFS-U	Pre-filled Syringe Ultrasafe Device
PGH	Physician's Global Assessments of Disease Activity
PI	principal investigator
PK	pharmacokinetics
PO	by mouth
PQC	product quality complaint
PRO	Patient Reported Outcome
q2	every 2
q4	every 4
QT	the time between the beginning of the QRS complex and the end of the T-wave
QTc	the time between the beginning of the QRS complex and the end of the T-wave, adjusted for heart rate (normal 350-440 milliseconds)
RA	rheumatoid arthritis
RAS	rat sarcoma viral oncogene homolog
RBC	red blood cell (count)
RNA	ribonucleic acid
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	subcutaneous
SDAI	Simplified Disease Activity Index
SF-36	36-item short form health survey
SI	International System of Units
SSZ	sulfasalazine
STAT3	signal transducer and activator of transcription-3
SUSAR	suspected unexpected serious adverse reaction
TB	tuberculosis
TIA	transient ischemic attack
TNF α	tumor necrosis factor alpha
ULN	upper limit of normal
US	United States
VAS	Visual Analogue Scale (Score)
WBC	white blood cell
WLQ	Work Limitations Questionnaire

1 INTRODUCTION

CNTO 136 (sirukumab) is a human anti-IL-6 mAb currently under development by the Sponsor in collaboration with GlaxoSmithKline, plc. It binds to human IL-6 with high affinity and specificity, and has been shown to inhibit IL-6-mediated signal transducer and activator of transcription-3 (STAT3) phosphorylation, resulting in the inhibition of the biological effect of IL-6. The target indications for sirukumab are rheumatoid arthritis (RA) and lupus nephritis (LN), both of which are diseases that involve IL-6.

IL-6 is a pleiotropic cytokine known for proinflammatory functions.¹⁹ The physiological and pathological role of IL-6 has been illustrated in many in vitro and in vivo studies which collectively suggest that IL-6 induces the differentiation of B cells into antibody-producing cells; promotes the development of cytotoxic T cells³⁴; supports differentiation of Th17 cells; affects macrophage differentiation³²; is an independent regulator of granulopoiesis²⁴; increases hepatic acute-phase reactants, and promotes mesangial cell proliferation, keratinocyte growth, megakaryocytic differentiation, and thrombosis.¹⁶ IL-6 levels are increased in obesity, as IL-6 is produced from adipose tissue.⁴⁶ Increased levels of IL-6 also correlate with insulin resistance.³⁷ IL-6 blockade has been shown to have a potent effect on neutrophil recruitment.³⁰

IL-6 knockout mice have a normal phenotype. The animals are viable and fertile, but have a slightly decreased number of T-cells and a decreased acute phase protein response to tissue injury.²⁰ IL-6 deficient mice have been noted to be susceptible to infections with *Listeria monocytogenes*, *Toxoplasma gondii*, and *Candida albicans*.^{6,38,44} In contrast, transgenic mice that over-express IL-6 in lymphoid cells have massive plasmacytosis, increased megakaryocytes, and mesangial cell proliferation in the kidney.⁴³ Over-expression of IL-6 in the brain results in neurologic disease such as neurodegeneration, astrocytosis, and proliferative angiopathy.⁵

Published studies have demonstrated the involvement of IL-6 in various disease processes including lupus erythematosus (LE), RA, anemia of chronic inflammation, insulin resistance, and cancer.

1.1 IL-6 as a Target in Rheumatoid Arthritis

Patients with RA often have increased levels of proinflammatory cytokines such as IL-6, IL-1, and tumor necrosis factor alpha (TNF α)³ in the synovial fluid and serum. TNF α and IL-1 both can stimulate IL-6 production by multiple cell types in the RA synovium.¹³ Local concentrations of IL-6 may in turn stimulate leukocyte recruitment to the joint, promote osteoclast maturation and activation, suppress chondrocytes, and stimulate synovial proliferation, contributing to joint damage.^{11,23} Systemically, elevated IL-6 in patients with RA may induce hepatic production of acute phase proteins, increase platelet production, and the development of anemia of chronic inflammation via induction of hepcidin.³¹ It also may be chiefly responsible for autoimmune features in RA such as autoreactive T cell activation and hypergammaglobulinemia.¹⁷

Early studies focused on IL-6 signaling identified 2 mechanisms for signal transduction. The first occurs when IL-6 binds specifically to the membrane-bound IL-6 receptor (IL-6R, or CD126). This IL-6/IL-6R complex then binds 2 gp130 co-receptor molecules (CD130) on the cell membrane and triggers gp130-dependent intracellular signaling cascades via the janus

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kinase/signal transducer and activator of transcription (JAK/STAT) and rat sarcoma viral oncogene homolog (RAS) pathways. While gp130 is expressed on many cell types, the expression of membrane IL-6R is restricted to hepatocytes, neutrophils, monocytes, and other leukocyte populations and hence this classical or “cis” signaling mechanism is limited to these cell types. However, a second mechanism was discovered when it was reported that soluble IL-6R (sIL-6R) can be secreted as a truncated form of the IL-6R in cells, or released from the cell surface due to proteolytic cleavage of membrane-bound IL-6R.^{25,29} IL-6 can form complexes with sIL-6R, and then initiate signaling on cells that express only the gp130 co-receptor.²⁶ This “trans” signaling therefore extends the effects of IL-6 to many other cell types that do not express endogenous IL-6R.³⁹

Sirukumab binds to IL-6 and prevents its binding to both the membrane and soluble forms of IL-6R and therefore will provide similar inhibition of both “cis” and “trans” signaling due to IL-6. In contrast, tocilizumab binds to the membrane and soluble forms of IL-6R in order to prevent IL-6 signaling.²⁸ Tocilizumab inhibits signal transduction mediated by both mIL-6R and sIL-6R, but not by the receptors of other members of IL-6 cytokine family.²⁸ As a result, tocilizumab may not be as potent for the neutralization of “cis” signaling due to lower affinity for membrane IL-6R, or the cells expressing membrane IL-6R may be less accessible. In addition, tocilizumab is a human IgG1 antibody that, when bound to membrane IL-6R, potentially can trigger cell lysis via complement or fragment crystallizable (Fc) receptor-expressing natural killer (NK) cells.^{4,14,40}

IL-6 inhibition results in improvement in patients with active arthritis.^{21,33,51} The effectiveness of the anti-IL-6 receptor mAb, tocilizumab, in reducing joint swelling and tenderness, improving physical function, and reducing the rate of radiographic progression was firmly established in pivotal registration studies.^{7,18,21,33,41} Additionally, in smaller RA studies biologic agents targeting the IL-6 cytokine ligand have also been shown to be efficacious.^{27,49}

Safety issues related to the inhibition of IL-6 inhibition by tocilizumab include increased risk of serious infections and abnormalities in hematology, hepatobiliary, and lipid parameters. In addition, upper and lower gastrointestinal tract perforations occurred in the anti-IL-6 receptor (tocilizumab) Phase 3 program. The potential differences in safety or efficacy between agents that bind to the IL-6 receptor versus ones that bind to the IL-6 ligand (sirukumab) remain unclear, but warrant further study.

In summary, IL-6 plays a major role in the pathophysiology of RA, and this is confirmed by the efficacy of IL-6 and IL-6 receptor inhibitors in clinical studies of patients with inflammatory arthritis.

For the most comprehensive nonclinical and clinical information regarding the efficacy and safety of sirukumab, refer to the latest version of the Investigator's Brochure for sirukumab.

The term "Sponsor" used throughout this document refers to the entities listed in the Contact Information page(s), which will be provided as a separate document.

1.2 Overall Rationale for the Study

This is a parallel-group long-term extension (LTE) trial of studies CNTO136ARA3002 and CNTO136ARA3003 to assess the long-term safety and efficacy of sirukumab in subjects with moderately to severely active RA. Subjects who have completed participation in studies CNTO136ARA3002 or CNTO136ARA3003 will be eligible to enroll in this study. Subjects are to continue to receive the identical sirukumab SC dose regimen of 100 mg every 2 (q2) weeks or 50 mg every 4 (q4) weeks that they were receiving upon completion of participation in studies CNTO136ARA3002 and CNTO136ARA3003.

Following the database lock for the primary endpoint, analysis of CNTO136ARA3002 and CNTO136ARA3003 PK and efficacy data showed that there was no clear dose response between the sirukumab SC 50 mg q4 weeks and sirukumab SC 100 mg q2 weeks dose groups across efficacy endpoints. Furthermore, there were a greater proportion of subjects with hypersensitivity reactions and injection site reactions in the sirukumab 100 mg q2 weeks dose group compared with the sirukumab 50 mg q4 weeks dose group. Therefore, to allow for minimization of the exposure to this immunosuppressant biologic agent, subjects treated with SC sirukumab 100 mg q2 weeks will be offered the option to reduce the sirukumab dose to 50 mg q4 weeks at the investigator's discretion after the study becomes open-label. This decision can be made at the subject's first or second major resupply visit (up until approximately 7 months) after implementation of Amendment 3 at the study site. Once a subject's dose is reduced to 50 mg q4 weeks, the subject will receive that dose for the remainder of the trial (ie, a return to 100 mg q2 weeks will not be allowed). If a subject opts to remain on the sirukumab 100 mg q2 weeks dose, he or she will remain on that dose for the duration of their participation in the study (ie, the subject will not have the option to reduce the dose at a subsequent timepoint).

Additionally, a substudy of enrolled subjects in CNTO136ARA3004 will further assess the usability of the SmartJect™ Autoinjector (PFS-AI).

2 OBJECTIVES AND HYPOTHESES

2.1 Objectives

Primary Objective

To evaluate the long-term safety of sirukumab in subjects with RA, who are refractory to disease modifying antirheumatic drugs (DMARD) or anti-TNF α agents.

Secondary Objectives

The secondary objectives are to observe the following long-term effects of sirukumab in subjects with RA who are refractory to DMARDs or anti-TNF α agents on:

- Efficacy
- Pharmacokinetics
- Immunogenicity
- Pharmacodynamics

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- Pharmacogenetics
- PFS-AI usability (as defined in a separate substudy protocol)

2.2 Hypothesis

No formal hypothesis is being tested.

3 STUDY DESIGN AND RATIONALE

3.1 Overview of Study Design

Subjects will become eligible to participate in this LTE study when they have completed participation in studies CNTO136ARA3002 (104 weeks) or CNTO136ARA3003 (52 weeks). The purpose of this LTE study is to evaluate the safety, efficacy, and pharmacologic effects of sirukumab for a minimum duration of 1 to 4 additional years and a maximum total duration of approximately 5 years across the combined protocols (CNTO136ARA3002 (2 years) or CNTO136ARA3003 (1 year) + CNTO136ARA3004 (1 to 4 years) = maximum of 5 years treatment).

The SmartJect™ Autoinjector (PFS-AI) is expected to be used by the majority of subjects in study CNTO136ARA3004. In the event PFS-AIs are unavailable at the time of a subject's enrollment in this protocol, sirukumab PFS-UltrSAFE (PFS-U), the same device used in the CNTO136ARA3002 and CNTO136ARA3003 studies, will be provided until such time as the PFS-AIs become available. Upon availability of PFS-AI trial supplies, subjects who are newly entering the CNTO136ARA3004 protocol will be trained on the operation of PFS-AI and perform self-administration of study agent using PFS-AI at the Week 2 study visit and return to the study site at Week 4 for self-administration with PFS-AI. In the event PFS-AIs are unavailable at the time of a subject's enrollment in this protocol, training on the use of a PFS-AI will be provided at the next study visit when the PFS-AI is available.

During the Week 104 visit in CNTO136ARA3002 or the Week 52 visit in CNTO136ARA3003, subjects will sign the informed consent form (ICF) to enter study CNTO136ARA3004. As a result, the Week 104 visit in study CNTO136ARA3002 and the Week 52 visit in study CNTO136ARA3003 will correspond to the Week 0 visit in the CNTO136ARA3004 study.

After a minimum of 1 year treatment in CNTO136ARA3004 for subjects from study CNTO136ARA3002, or a minimum of 2 years of treatment in CNTO136ARA3004 for subjects from CNTO136ARA3003, and after sirukumab is approved for the treatment of RA in the subject's country of residence, the Sponsor may no longer offer study treatment in CNTO136ARA3004 for those specific subjects. At that point the subject will have the opportunity to discuss treatment options with their treating physician.

The maximum duration of participation in this study is 208 weeks, followed by approximately 16 weeks of safety and efficacy follow-up after the administration of the final study agent injection of sirukumab. Only 1 database lock (DBL; at the end of the study) is planned. Additional data releases or locks may occur as needed. The study will end with the last visit for the last subject participating in the study.

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Study treatment will remain blinded in CNTO136ARA3004 until the following 3 conditions have been met: the Week 52 DBL occurs in study CNTO136ARA3002, the Week 24 DBL occurs in study CNTO136ARA3003, and the last AI usability substudy subject completes the Week 16 visit or terminates from the study. Thereafter study CNTO136ARA3004 will become open-label and placebo injections will be discontinued in the SC sirukumab 50 mg treatment group. Once study CNTO136ARA3004 becomes open-label, study subjects will receive open-label study agent through IVRS/IWRS. However, when this study becomes open-label, any subjects who still remain in studies CNTO136ARA3002 and CNTO136ARA3003 due to staggered enrollment will continue to receive blinded treatment until they complete participation in those studies.

Protocol waivers or exemptions are not allowed with the exception of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the Time and Events Schedules are essential and required for study conduct.

Subject safety will be monitored through the end of the study as delineated in the Time and Events Schedules.

The primary endpoint is the number of subjects with each of the following long-term safety events through the end of the study: cardiovascular (CV) SAEs, malignancies, serious infections, and gastrointestinal perforations.

The major secondary endpoint is laboratory parameters of interest (neutrophils, platelets, hepatobiliary parameters, and lipid parameters).

Serum samples will be collected for the evaluation of sirukumab PK and antibodies to sirukumab. Other samples to be collected include serum and whole blood RNA for the evaluation of inflammation-associated proteins and other analytes. These samples will be used to better understand the biology of RA, to analyze differences between responders and non-responders, and to assess loss of response.

A pharmacogenetics blood sample to assess genetic factors such as DNA methylation patterns will be collected from subjects who consent separately to the pharmacogenetics component of the study where local regulations permit. Participation in the pharmacogenetics research component of this study is optional.

Health economics data including subject employability, daily work productivity, and reduced time lost from work will be collected.

Safety and tolerability will be assessed by monitoring AEs, clinical laboratory tests, vital signs, physical examinations, and concomitant medication review.

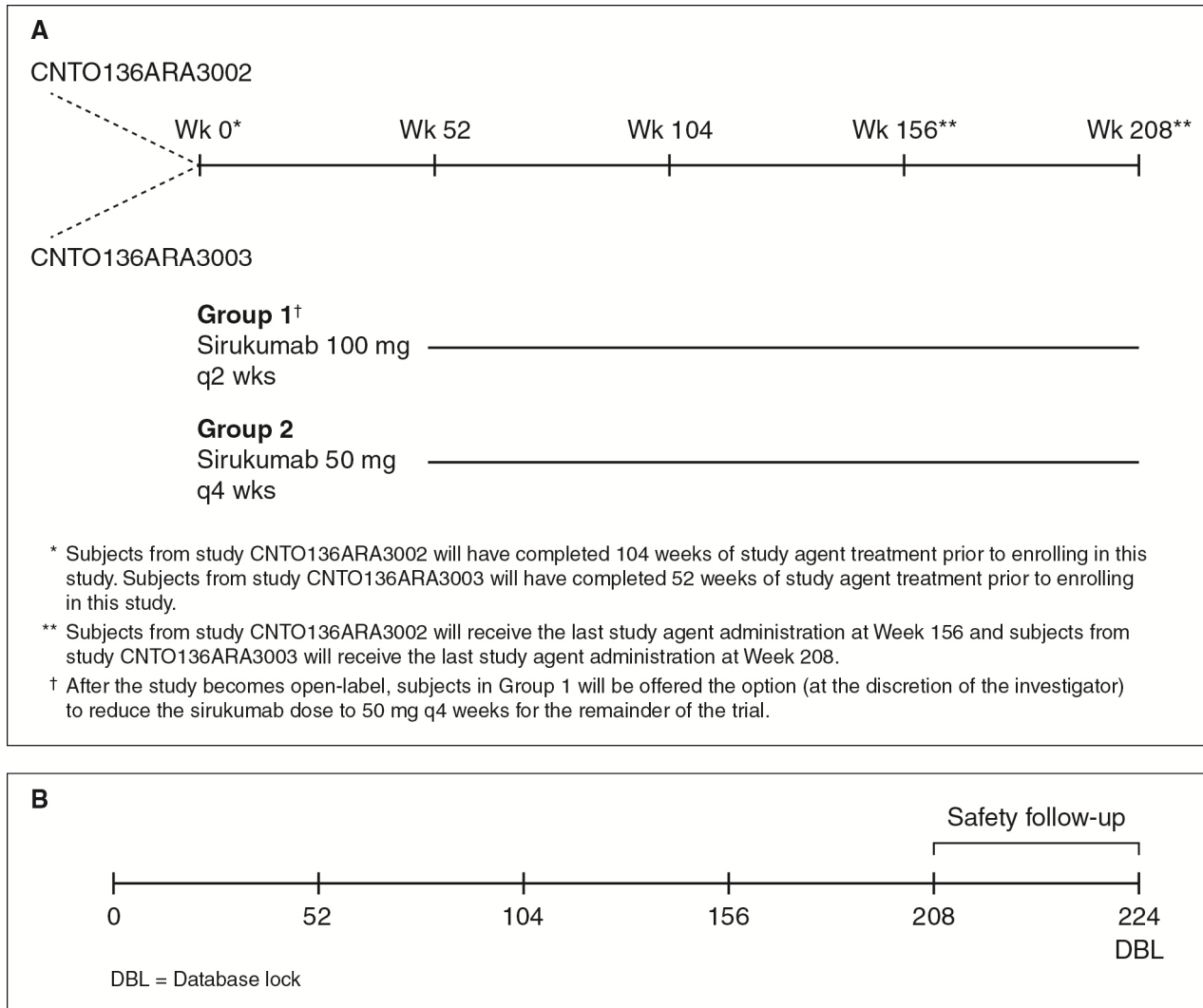
An independent Clinical Events Committee (CEC) will be established for this study to review case information on serious cardiovascular (CV) events (myocardial infarction, stroke, death, hospitalization for angina, hospitalization for transient ischemic attack (TIA); see Section 11.11).

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An independent Data Monitoring Committee (DMC) will be commissioned for this study to review unblinded data periodically for the blinded portion of the study and whenever deemed necessary to monitor subject safety (see Section 11.10).

All assessments will be performed according to the Time and Events Schedules. A diagram of the study design is provided below (Figure 1).

Figure 1: CNTO136ARA3004 Study Design and Study Timeline



3.2 Study Design Rationale

This study is designed to examine the long-term safety and efficacy of sirukumab, the effects of sirukumab on physical function, pharmacokinetics, and immunogenicity of sirukumab in subjects with moderately to severely active RA who are refractory or intolerant to DMARDs or anti-TNF α therapy.

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Additionally, this study is designed to obtain experience in the use of the SmartJect™ Autoinjector (PFS-AI) in all subjects enrolled in CNTO136ARA3004. More data regarding the usability of the autoinjector will be evaluated in the PFS-AI substudy. Additional details are provided in Section 9.6.

3.2.1 Study Population

Subjects who complete the Week 104 (CNTO136ARA3002) visit and study agent administration or the Week 52 (CNTO136ARA3003) visit and study agent administration will be deemed to have completed participation in those studies and will be eligible to enroll in this long-term extension study.

3.2.2 Treatment Groups, Dosage, and Dose Administration Interval

Subjects will continue to receive the same dosing regimen they received at the Week 104 (CNTO136ARA3002) and at Week 52 visit (CNTO136ARA3003) in blinded fashion until the following 3 conditions have been met: the Week 52 DBL occurs in study CNTO136ARA3002, the Week 24 DBL occurs in study CNTO136ARA3003, and the last AI usability substudy subject completes the Week 16 visit or terminates from the study. Thereafter the same treatment assignment will be continued, but the study will no longer be blinded and will become open-label.

The 2 sirukumab doses to be administered in this study are as follows:

- 100 mg q2 weeks
- 50 mg q4 weeks

Following the database lock for the primary endpoint, analysis of CNTO136ARA3002 and CNTO136ARA3003 PK and efficacy data showed that there was no clear dose response between the sirukumab SC 50 mg q4 weeks and sirukumab SC 100 mg q2 weeks dose groups across efficacy endpoints. Furthermore, there were a greater proportion of subjects with hypersensitivity reactions and injection site reactions in the sirukumab 100 mg q2 weeks dose group compared with the sirukumab 50 mg q4 weeks dose group. Therefore, to allow for minimization of the exposure to this immunosuppressant biologic agent, subjects treated with SC sirukumab 100 mg q2 weeks will be offered the option to reduce the sirukumab dose to 50 mg q4 weeks at the investigator's discretion after the study becomes open-label. This decision can be made at the subject's first or second major resupply visit (up until approximately 7 months) after implementation of Amendment 3 at the study site.

3.2.3 Study Phases and Duration of Treatment

There will be 3 phases of this LTE study: Blinded active treatment, open-label treatment, and safety and efficacy follow-up.

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As described in Section 3.2.2, the blinded active treatment phase will continue until following 3 conditions have been met: the Week 52 DBL occurs in study CNTO136ARA3002, the Week 24 DBL occurs in study CNTO136ARA3003, and the last AI usability substudy subject completes the Week 16 visit or terminates from the study.

The open-label treatment phase of the study will begin after those 3 conditions have been met, and will continue through the last scheduled dose for all subjects. The safety and efficacy follow-up will include approximately 16 weeks of study evaluations following the last administration of study agent, including follow-up for patients who discontinued study treatment prior to their last scheduled dose. The safety and efficacy follow-up allows for monitoring of the subject for a period of equivalent to at least 5 times the half-life of sirukumab.

The maximum duration of the study is expected to be 156 weeks for subjects enrolling after participation in study CNTO136ARA3002 and 208 weeks for subjects enrolling after participation in study CNTO136ARA3003, followed by approximately 16 weeks of safety and efficacy follow-up after the administration of the final study agent injection of sirukumab.

After a minimum of 1 year treatment in CNTO136ARA3004 for subjects from study CNTO136ARA3002, or a minimum of 2 years of treatment in CNTO136ARA3004 for subjects from CNTO136ARA3003, and after sirukumab is approved for the treatment of RA in the subject's country of residence, the Sponsor may no longer offer study treatment in CNTO136ARA3004 for those specific subjects. At that point the subject will have the opportunity to discuss treatment options with their treating physician.

3.2.4 Study Control, Randomization, and Blinding

Blinded matching placebo injections will be used to reduce potential bias during data collection and evaluation of clinical endpoints and will be maintained until the following 3 conditions have been met: the Week 52 DBL occurs in study CNTO136ARA3002, the Week 24 DBL occurs in study CNTO136ARA3003, and the last AI usability substudy subject completes the Week 16 visit or terminates from the study. Thereafter the CNTO136ARA3004 study will become open-label.

3.2.5 Efficacy Evaluations

The efficacy evaluations chosen for this study are consistent with those in primary studies CNTO136ARA3002 and CNTO136ARA3003.

RA response evaluations include:

- American College of Rheumatology (ACR) responses
- Disease Activity Index Score 28 (DAS28)
- Health Assessment Questionnaire-Disability Index (HAQ-DI)
- ACR/The European League Against Rheumatism (EULAR) remission

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Patient Reported Outcome (PRO) evaluations include:

- 36-Item Short Form (SF-36)
- Work Limitations Questionnaire (WLQ)
- Health Economics Questionnaire (HECONQ)

The medical resource usage and health economics evaluations chosen for this study have also been used in studies CNTO136ARA3002 and CNTO136ARA3003.

3.2.6 Safety Evaluations

Based upon the emerging safety profile of other anti-IL-6 agents, as well as the sirukumab safety data to date, several AE of interest have been identified and will be monitored and assessed in this study. These are: hematologic laboratory abnormalities (decreases in neutrophils and platelets), hepatobiliary laboratory abnormalities, lipid parameter abnormalities, serious CV events, infections, malignancies, and gastrointestinal perforations.¹

Subject safety evaluations including the reporting of AEs, clinical laboratory tests (hematology, serum chemistry, and lipid panels), pregnancy tests, and vital signs (blood pressure and body weight) etc. will be monitored through the end of the study as delineated in the Time and Events Schedules. In addition, an independent DMC will review unblinded data periodically for the blinded portion of the study and whenever deemed necessary to monitor subject safety.

Laboratory parameter abnormalities:

IL-6 is a pleiotropic cytokine necessary for hematopoiesis and IL-6 inhibition has been shown to cause a reduction in both neutrophils and platelets. In addition, IL-6 inhibition has been associated with reversible elevation in liver enzymes. Mechanisms by which this might occur include inhibition of the hepatoprotective effect of IL-6, leaving hepatocytes susceptible to effects of toxins and other stresses. Lipid abnormalities have also been observed, both in the sirukumab Phase 2 study C1377T04, as well as with other anti-IL-6 agents. The mechanism by which this occurs is not fully understood.

Cardiovascular events:

Patients with RA are known to have an increased risk of serious CV events compared with the general population. In addition, in the sirukumab clinical programs, significant changes in lipid laboratory parameters have been observed, as with other agents that block IL-6. The clinical significance of these changes is not known. Nonetheless, serious CV events are considered AEs of interest and will be closely monitored in the sirukumab program. In order to fully understand CV events in this study, Major Adverse Cardiovascular Events (MACE), defined as myocardial infarction, stroke, death, hospitalization for unstable angina, and hospitalization for TIA, will be collected and prospectively adjudicated by an external CEC. The CEC is an independent committee composed of external specialists, blinded to treatment assignment, who will be commissioned to review case information on serious CV events (myocardial infarction, stroke,

death, hospitalization for angina, hospitalization for TIA). The operations, processes, and definitions to be employed by the committee will be defined in the CEC charter. This will allow external review of cases and determination of diagnosis prior to analysis. See Section 11.11 for a complete discussion of the CEC.

Other events of interest:

Sirukumab, by its mechanism of action as an IL-6 inhibitor, would be expected to have some properties of immunosuppression. As such, increased susceptibility to certain infections is a potential risk. IL-6 deficient mice have been found to be susceptible to infections with *Listeria monocytogenes*, *Toxoplasma gondii*, and *Candida albicans*.^{6,38,44} In addition, as an IL-6 inhibitor, sirukumab may have some effect on the risk of malignancy by affecting immune surveillance, particularly in a subject population (RA) already at increased risk for the development of lymphoma and leukemia. Further, gastrointestinal perforations have been reported with another anti-IL-6 agent at rates higher than the rate found in RA subjects.¹

3.2.7 Pharmacokinetic Evaluations

To evaluate the PK of sirukumab in subjects with RA following long-term treatment, serum samples for the measurement of sirukumab concentrations will be collected according to the Time and Events Schedules.

3.2.8 Immunogenicity Evaluations

To evaluate the immunogenicity of sirukumab in subjects with RA following long-term treatment, serum samples for the detection of antibodies to sirukumab will be collected according to the Time and Events Schedules.

3.2.9 Pharmacodynamic Evaluations

Whole blood and serum samples for the analysis of pharmacodynamic markers will be collected and analyzed for proteins, RNA, and other analytes such as but not limited to microRNAs. The samples will be used to better understand the biology of RA, to provide a biological assessment of the response of subjects to treatment with sirukumab, to analyze responders, to assess loss of response, and to determine if the markers can be used to classify patients as potential responders to treatment.

3.2.10 Pharmacogenetic (DNA) Evaluations

Genetic variation and methylation status of DNA can be an important contributory factor to interindividual differences in drug disposition and response and may also serve as a marker for disease susceptibility and prognosis. Pharmacogenetics research may help to explain interindividual variability in clinical outcomes and identify population subgroups that respond differently to a drug. The goal of the pharmacogenetics component is to collect DNA to allow the identification of genetic factors or methylation patterns that may influence the pharmacokinetics, pharmacodynamics, efficacy, or tolerability of sirukumab and to identify genetic factors associated with RA. DNA samples may be used to help address emerging issues and to enable the development of safer, more effective, and ultimately individualized therapies. For details, see Section 9.5.

3.2.11 Self-Administration

Self-administration of SC products in subjects with RA is common practice and subjects with RA are familiar and comfortable with self-injection. In addition, other biologic agents for the treatment of RA are approved for self-administration at home. For additional details, see Section 6.5.

The SmartJect™ AI platform technology device, referred to as PFS-AI, is a prefilled, spring-powered, single use, disposable device for the SC administration of a single dose of a liquid biologic drug product. The PFS-AI was designed as a platform device for several liquid biologic drug products and has a simple, universal design that is suitable for use by clinicians, caregivers, and patients, including those with hand impairment and pain in the hands and wrists resulting from diseases such as rheumatoid arthritis (RA), and psoriatic arthritis (PsA). The PFS-AI is designed to operate effectively in a number of hand orientations. Since the needle is shielded from sight at all times, the PFS-AI also accommodates those patients with a needle phobia who cannot tolerate seeing injections administered.

3.2.12 Health Economics Data Collection

RA is a chronic, progressive, and disabling condition that significantly diminishes physical functioning and health related quality of life. Loss of physical function in RA patients can significantly affect their ability to work and perform other activities of daily living. Indirect costs, primarily associated with loss of income among persons who have left work or reduced work, contribute substantially to the economic impact on patients, families and society. Approximately half of all newly diagnosed RA patients had to stop working within the ensuing 10 years.^{42,50} Hence, maintaining long-term function with resulting maintenance of productivity and employability is an important therapeutic goal in RA.

Treatment of subjects with RA with sirukumab may have a positive impact on subjects' employability, daily work productivity, and reduced time lost from work, compared among treatment groups. For additional details, see Section 9.7.

4 SUBJECT SELECTION

The inclusion and exclusion criteria for enrolling subjects in this study are described in the following 2 subsections. If there is a question about the inclusion or exclusion criteria below, the investigator should consult with the appropriate Sponsor representative before enrolling a subject in the study.

Deviations from the inclusion and exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

4.1 Inclusion Criteria

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

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1. Have completed the final study agent administrations in the primary study (Week 104 injection in CNTO136ARA3002 or Week 52 injection in CNTO136ARA3003) including all other assessments required for these visits. The subject will then be deemed to have completed participation in those studies and will be eligible to enroll in this long-term extension study.
2. Sign an informed consent form (ICF) indicating that they understand the purpose of and procedures required for the study and are willing to participate in the study.
3. Sign an informed consent form (ICF) for pharmacogenetics research in order to participate in the optional pharmacogenetics component of this study, where local regulations permit. Refusal to give consent for this component does not exclude a subject from participation in this clinical study.

4.2 Exclusion Criteria

Any potential subject who meets any of the following criteria will be excluded from participating in the study. The subject will be excluded if he or she:

1. Withdraws consent and/or discontinues participation in study CNTO136ARA3002 or CNTO136ARA3003.
2. Is pregnant
3. Has active diverticulitis.
4. Has any condition that, in the opinion of the investigator, would make participation not be in the best interest (eg, compromise the well-being) of the subject or that could prevent, limit, or confound the protocol-specified assessments.

4.3 Prohibitions and Restrictions

Potential subjects must be willing and able to adhere to the following prohibitions and restrictions during the course of the study to be eligible for participation:

1. If a woman of childbearing potential, she must remain on a highly effective method of birth control during the study and for 4 months after receiving the last study agent. If she is using hormonal contraceptives, she must use an additional non-hormonal birth control method. The exception to this restriction is if the subject or her male partner is sterilized; this situation does not require birth control. A woman must not donate eggs (ova, oocytes) for the purposes of assisted reproduction during the study and for 4 months after receiving the last dose of study agent.

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2. Men must use an effective method of birth control during the study and for 4 months after receiving the last dose of study agent. The exception to this is if the subject or his female partner is sterilized. Also, men must not donate sperm during the study and for 4 months after receiving the last dose of study agent.
3. See Section 8.2 for prohibited medications.
4. Must agree not to receive a live virus or live bacterial vaccination during the study. Subjects must also agree not to receive a live vaccine for 4 months after receiving the last administration of study agent.
5. Must agree not to receive an investigational medical device or other investigational drugs.

5 TREATMENT ALLOCATION AND BLINDING

5.1 Treatment Allocation

There will be 2 treatment groups for the duration of this study:

Group 1: Sirukumab 100 mg q2 weeks through Week 156 for subjects who enrolled after completing participation in CNTO136ARA3002 and through Week 208 for subjects who enrolled after completing participation in CNTO136ARA3003.

Group 2: Sirukumab 50 mg q4 weeks through Week 156 for subjects who enrolled after completing participation in CNTO136ARA3002 and through Week 208 for subjects who enrolled after completing participation in CNTO136ARA3003.

After the study becomes open-label, subjects treated with SC sirukumab 100 mg q2 weeks will be offered the option to reduce the sirukumab dose to 50 mg q4 weeks at the investigator's discretion. This decision can be made at the subject's first or second major resupply visit (up until approximately 7 months) after implementation of Amendment 3 at the study site.

5.2 Blinding

To maintain the study blind, the study agent container will have a multipart label with directions for use and other information, but not the identity of the study agent, on each part. One part of the label is designed to be torn off, separated from the study agent container, and attached to the subject's source documents. The rest of the label will remain affixed to the study agent container. Thus, the study agent assigned to a subject will be linked between the container and the subject without breaking the study blind. The study agent kit number will be entered in the electronic case report form (eCRF) or other equivalent data capture method when the drug is administered.

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The investigator will not be provided with treatment codes, but the codes will be maintained within the IVRS/IWRS, which has the functionality to allow the investigator to break the blind for an individual subject when there is a need based on medical judgment.

The study will remain blinded until the following 3 conditions have been met: the Week 52 DBL occurs in study CNTO136ARA3002, the Week 24 DBL occurs in study CNTO136ARA3003, and the last AI usability substudy subject completes the Week 16 visit or terminates from the study.

The blind should be broken only if specific emergency treatment/course of action would be dictated by knowing the treatment status of the subject. In such cases, the investigator may determine the identity of the treatment from the IVRS/IWRS provider. It is strongly recommended that the investigator contact the Sponsor or its designee if possible to discuss the particular situation prior to unblinding in IVRS/IWRS. Telephone contact with the Sponsor or its designee will be available 24 hours per day, 7 days per week. In the event the blind is broken, the Sponsor must be informed as soon as possible. The date and reason for the unblinding must be documented in the appropriate section of the eCRF, and in the source document. The documentation received from the IVRS/IWRS indicating the code break must be retained with the subject's source documents in a secure manner (eg, sealed envelope) so as not to unblind the treatment assignment to the subject, the study site, or Sponsor personnel. The investigator is also advised not to reveal the study treatment assignment to the subject, the study site, or Sponsor personnel.

Subjects who have had their treatment assignment unblinded are expected to continue to return for scheduled evaluations. Further study agent administrations should be discussed with the study responsible physician.

Additionally, a given subject's treatment assignment may be unblinded to the Sponsor, Institutional Review Board/Independent Ethics Committee (IRB/IEC), and site personnel to fulfill regulatory reporting requirements for SUSARs.

A separate code break procedure will be available for use by Janssen Global Medical Safety (GMS) to allow for unblinding of individual subjects to comply with specific requests from regulatory or health authorities.

6 DOSAGE AND ADMINISTRATION

6.1 Dosing Regimen

Subjects will continue to receive the sirukumab dosing regimen they received at the end of the primary studies (CNTO136ARA3002, CNTO136ARA3003).

Group 1: Sirukumab 100 mg SC at Weeks 0 (administered as the last dose in CNTO136ARA3002 or CNTO136ARA3003), 2, and q2 weeks through Week 156 for subjects who enrolled after completing participation in CNTO136ARA3002 and through Week 208 for subjects who enrolled after completing participation in CNTO136ARA3003.

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Group 2: Sirukumab 50 mg SC at Weeks 0 (administered as the last dose in CNTO136ARA3002 or CNTO136ARA3003), 4, and q4 weeks through Week 156 for subjects who enrolled after completing participation in CNTO136ARA3002 and through Week 208 for subjects who enrolled after completing participation in CNTO136ARA3003. Between sirukumab injections, placebo SC injections will be administered at Weeks 2, 6, and q4 weeks until the study becomes open-label and placebo injections will be discontinued.

After the study becomes open-label, subjects treated with SC sirukumab 100 mg q2 weeks will be offered the option to reduce the sirukumab dose to 50 mg q4 weeks at the investigator's discretion. This decision can be made at the subject's first or second major resupply visit (up until approximately 7 months) after implementation of Amendment 3 at the study site. Once a subject's dose is reduced to 50 mg q4 weeks, the subject will receive that dose for the remainder of the trial (ie, a return to 100 mg q2 weeks will not be allowed). If a subject opts to remain on the sirukumab 100 mg q2 weeks dose, he or she will remain on that dose for the duration of their participation in the study (ie, the subject will not have the option to reduce the dose at a subsequent timepoint).

If an injection is missed, every effort should be made to have the missed injection administered within 7 days after the scheduled date for that injection. In case it is not possible to administer the missed injection in time, site personnel should discuss the issue with the medical monitor.

After a minimum of 1 year treatment in CNTO136ARA3004 for subjects from study CNTO136ARA3002, or a minimum of 2 years of treatment in CNTO136ARA3004 for subjects from CNTO136ARA3003, and after sirukumab is approved for the treatment of RA in the subject's country of residence, the Sponsor may no longer offer study treatment in CNTO136ARA3004 for those specific subjects. At that point the subject will have the opportunity to discuss treatment options with their treating physician.

For details on self-administration of study agent see Section 6.5.

6.2 Blinding

To maintain the blind, all subjects will receive study agent as 1 SC injection as follows:

Group 1 (sirukumab 100 mg): 1.0 mL sirukumab 100 mg injection q2 weeks.

Group 2 (sirukumab 50 mg): 1.0 mL sirukumab 50 mg injection q4 weeks. Between sirukumab injections, placebo SC injections will be administered at Weeks 2, 6, and q4 weeks until the study becomes open-label and placebo injections will be discontinued.

After the study becomes open-label, subjects treated with SC sirukumab 100 mg q2 weeks will be offered the option to reduce the sirukumab dose to 50 mg q4 weeks at the investigator's discretion. This decision can be made at the subject's first or second major resupply visit (up until approximately 7 months) after implementation of Amendment 3 at the study site.

6.3 Timing and Study Agent Administration

Through the end of the study, it is recommended that both the visit and the SC study agent administration occur within 7 days of the scheduled visit day. The SC study agent administrations must always be at least 7 days apart.

6.4 DMARD/Oral Corticosteroid Initiation/Adjustment

Subjects may adjust or initiate DMARDs and/or oral corticosteroids at the investigator's discretion. Permitted DMARDs include methotrexate (MTX), sulfasalazine (SSZ), hydrochloroquine (HCQ), chloroquine (CQ), and bucillamine.

Prohibited medications listed in Section 8.2 may not be initiated by subjects as long as they are receiving study agent administrations.

6.5 Self-Administration

The SmartJect™ Autoinjector (PFS-AI) is expected to be used by the majority of subjects in study CNTO136ARA3004. In the event PFS-AIs are unavailable at the time of a subject's enrollment in this protocol, PFS-U will be provided until such times as the PFA-AIs become available.

Upon availability of PFS-AI trial supplies, subjects who are newly entering the CNTO136ARA3004 protocol will be trained on the operation of PFS-AI and perform self-administration of study agent using PFS-AI at the Week 2 study visit and return to the study site at Week 4 for self-administration with PFS-AI. The self-injection training consists of a face-to-face, "hands-on" training, with an explanation of each task in the Instructions For Use (IFU), a demonstration performed by the study site staff with the PFS-AI trainer device, followed by practice injections performed by the subject using the trainer device, until the study site staff and subject are satisfied that the injections can be performed as stated in the IFU. This mimics the typical training by a physician's office staff that is likely to be received by a patient for the prescribed marketed product, per the final product's labeling. The step-by-step Training Guide for investigators or site staff to follow when providing training of subjects will be provided in the Site IP Procedures Manual. If subjects are competent in using PFS-AI, they will subsequently be provided with study agent for self-administration at home and instructed how to transport and store medication for at-home use as indicated for this protocol. Subjects will be instructed to contact the investigator promptly in the event of any signs of an allergic reaction, infection, or bleeding.

Subjects may continue to administer the study agent at home for the duration of the study. Although additional face-to-face training sessions after the first training session are not scheduled, the site staff will be available to provide additional training if needed. If subjects or health care providers are uncertain about how to administer the study agent, the Sponsor recommends a review of the IFU and perform practice injections with the PFS-AI trainer device, and if necessary, to ask for retraining at the study site.

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Subjects unable or unwilling to self-administer will continue to have study agent injections performed by a health care professional at the study site. A caregiver may also be trained to administer study agent at home. In the event PFS-AIs are unavailable at the time of a subject's enrollment in this protocol, training on the use of a PFS-AI will be provided at the next study visit when the PFS-AI is available. Once the study becomes open-label, the Week 2 visit for training may be skipped by subjects who are to receive open label sirukumab 50 mg q4 weeks and training in the use of an PFS-AI will be provided at Week 4.

7 TREATMENT COMPLIANCE

Study agent will be administered subcutaneously by the subject or a trained care-giver. Subjects will maintain a log of all study agent administrations. Study agent supplies for each subject will be inventoried and accounted for.

Study personnel will maintain a log of all study agent administrations. Study agent supplies for each subject will be inventoried and accounted for.

When subjects begin self-administration at home, the investigator or designated study personnel will maintain a log of all study agents dispensed and returned and the amount of study agent dispensed will be recorded and compared with the amount returned.

Subjects will receive instructions on compliance with study treatment when they begin self-administration of study agent at home. During the course of the study, the investigator or designated study research personnel will be responsible for providing additional instruction to reeducate any subject who is not compliant with taking the study agent.

8 CONCOMITANT THERAPY AND PROCEDURES

8.1 Concomitant Therapy

All concomitant therapies must be recorded throughout the study, beginning at Week 0.

All therapies (prescription or over-the-counter medications, including vaccines, vitamins, herbal supplements) different from the study agent must be recorded in the concomitant therapy section of the eCRF.

The concomitant medication dose may be changed at the discretion of the investigator. Disease-modifying anti-rheumatic drug (DMARD) therapy is permitted at the discretion of the investigator (see Section 6.4), except for the specified prohibited medications (see Section 8.2).

8.1.1 Nonsteroidal Anti-inflammatory Drugs and Other Analgesics

Subjects treated with NSAIDs, including aspirin and selective cyclooxygenase-2 inhibitors, and other analgesics should receive the usual marketed doses approved in the country in which the study is being conducted. In this study, aspirin is considered an NSAID, except for low-dose aspirin prescribed for CV or cerebrovascular disease. The dose and the type of NSAIDs or other analgesics may be changed at the discretion of the investigator if the subject develops unacceptable side effects or a contraindication to their use.

8.1.2 Disease Modifying Antirheumatic Drugs/Systemic Immunosuppressives

Acceptable non-biologic DMARDs are MTX, SSZ, HCQ, chloroquine (CQ) or bucillamine.

DMARDs may be initiated or adjusted at the investigator's discretion.

Guidelines for MTX dose adjustment in the event of suspected MTX toxicity are provided in [Appendix C](#). The dose of MTX should be decreased 50% and/or a folic acid product should be started or increased in dose if AST/ALT increases ≥ 2 to < 3 times ULN during treatment. The MTX dose may be increased back to the baseline dose if the AST/ALT decreases to < 2 times ULN. The dose of MTX should be temporarily interrupted and a folic acid product should be started or increased in dose if AST/ALT increases to ≥ 3 times ULN and total bilirubin level is < 2 times ULN. See Section [10.3](#) for drug induced liver injury criteria that require permanent discontinuation of study agent administration.

All subjects using MTX at doses of ≥ 0.2 mg/kg weekly or who are at high risk of adverse reactions (eg, elderly age, renal impairment, chronic high-dose NSAIDs) should receive at least 5 mg oral folic acid or oral folinic acid weekly. Folic acid or folinic acid may also be initiated or increased for subjects using MTX for management of adverse events such as stomatitis, increased ALT/AST, leucopenia, or macrocytic anemia.

8.1.3 Corticosteroid Therapy

Oral Corticosteroids

The dose and the type of oral corticosteroid may be changed at the discretion of the investigator if the subject develops unacceptable side effects.

Intramuscular and Intravenous Corticosteroids

IM corticosteroids may be administered as needed throughout the course of the study, except not within 4 weeks prior to Weeks 52, 104, 156, and 208. Every attempt should be made to avoid the use of IV corticosteroids, however for conditions other than RA, corticosteroid therapy should be limited to situations in which, in the opinion of the treating physician, there are no adequate alternatives. Subjects may receive short courses (2 weeks or less) of oral or IV corticosteroids for reasons such as prophylactic therapy before surgery (stress-dose corticosteroids) or therapy for limited infections, exacerbation of asthma, or chronic obstructive pulmonary disease.

Intra-articular Corticosteroids

Intra-articular (IA) steroid injections should not be administered within 4 weeks prior to visits on Weeks 52, 104, 156, and 208.

8.1.4 Statin Therapy

Subjects are permitted to use statins (eg, pravastatin, rosuvastatin) for the treatment of hyperlipidemia as considered appropriate by National Cholesterol Education Program (NCEP) treatment guidelines (<http://www.nhlbi.nih.gov/guidelines/cholesterol/atp3full.pdf>) or other

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national cholesterol treatment guidelines. Some statins are metabolized by cytochrome P450 (CYP450) enzymes (see Section 8.1.5).

8.1.5 Drugs Metabolized by Cytochrome P450

Inflammatory cytokines, including IL-6, are known to down regulate activity and expression of multiple CYP450 enzymes. Hypothetically, IL-6 inhibition in a patient with an inflammatory condition will restore or increase the CYP enzyme activity, and, in turn, increase the hepatic metabolism and clearance of drugs that are substrates for those enzymes. Therefore, upon initiation or discontinuation of sirukumab in patients being treated with CYP450 substrates with a narrow therapeutic index, monitoring of the effect (eg, warfarin) or drug concentration (eg, theophylline) is recommended and the individual dose of the drug may be adjusted as needed. Since CYP3A4 is the major CYP enzyme and in vitro studies showed that IL-6 has a profound effect on CYP3A4, caution should also be exercised when sirukumab is coadministered with CYP3A4 substrate drugs, eg, oral contraceptives, certain statin medications (eg, simvastatin, atorvastatin, cerivastatin, lovastatin).

8.2 Prohibited Medications

The use of the following drugs is not permitted concomitantly with SC study agent administration:

- Systemic immunosuppressives or DMARDs (other than MTX, SSZ, HCQ, CQ, and bucillamine) including azathioprine, oral cyclosporine A, tacrolimus, mycophenolate mofetil, leflunomide, oral or parenteral gold, and IL-1ra (anakinra)
- Biologic agents targeted at reducing TNF α (including but not limited to infliximab, golimumab, certolizumab pegol, etanercept, yisaipu, and adalimumab)
- Tocilizumab (anti IL-6 receptor)
- B-cell depleting agents (eg, rituximab)
- Cytotoxic drugs such as cyclophosphamide, chlorambucil, nitrogen mustard, or other alkylating agents
- Abatacept (ORENCIA[®])
- Tofacitinib (XELJANZ[®])
- Any other biologic therapy for the treatment of RA
- Investigational drugs

8.3 Joint Procedures

Subjects undergoing a surgical joint procedure for the treatment of RA or receiving IA, tendon sheath, or bursal corticosteroid injections may continue to receive study agent administrations and undergo evaluations.

9 STUDY EVALUATIONS

9.1 Study Procedures

9.1.1 Overview

The Time and Events Schedule ([Table 1](#) and [Table 2](#)) summarizes the frequency and timing of efficacy, pharmacokinetic, immunogenicity, pharmacodynamics, pharmacogenetics, health economics, and safety measurements applicable to this study.

Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the subject's participation in the study. Also additional TB tests or tests for other infections may be performed as determined necessary by the medical monitor, study investigator or as required by local regulation.

All visit-specific PRO assessments should be conducted before any tests, procedures, or other consultations for that visit to prevent influencing subjects' perceptions. Every effort should be made to perform all other assessments in the order specified in the Time and Events Schedule unless logistically not feasible, and if possible, the same individual(s) should perform the assessments at each visit.

Health economics data will be collected. For details, see [Section 9.7](#).

Serum for the analysis of pharmacodynamic markers and whole blood (for gene expression analysis) will be collected through Week 156 for subjects coming from the CNTO136ARA3002 study and Week 208 from subjects coming from the CNTO136ARA3003 study. A single whole blood sample for DNA analysis will be collected only from subjects who have consented to participate in the optional pharmacogenetics (DNA) component of the study.

The total blood volume to be collected from each subject will be approximately 325 mL. Repeat or unscheduled samples may be taken for safety reasons.

Blood samples for RNA and DNA analyses will only be collected if permitted by local regulations.

9.1.2 Double-Blinded Treatment Phase

Subjects will receive blinded study agent treatments according to the Time and Events Schedule until the following 3 conditions have been met: the Week 52 DBL occurs in study CNTO136ARA3002, the Week 24 DBL occurs in study CNTO136ARA3003, and the last AI usability substudy subject completes the Week 16 visit or terminates from the study.

9.1.3 Open-Label Treatment Phase

The CNTO136ARA3004 study will become open-label after the following 3 conditions have been met: the Week 52 DBL occurs in study CNTO136ARA3002, the Week 24 DBL occurs in study CNTO136ARA3003, and the last AI usability substudy subject completes the Week 16 visit or terminates from the study.

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After a minimum of 1 year treatment in CNTO136ARA3004 for subjects from study CNTO136ARA3002, or a minimum of 2 years of treatment in CNTO136ARA3004 for subjects from CNTO136ARA3003, and after sirukumab is approved for the treatment of RA in the subject's country of residence, the Sponsor may no longer offer study treatment in CNTO136ARA3004 for those specific subjects. At that point the subject will have the opportunity to discuss treatment options with their treating physician.

9.1.4 Posttreatment Phase (Follow-Up)

At the end of the study, subjects will return for follow-up assessments through approximately 16 weeks after the last study agent administration. Subjects who discontinue study agent injections but do not terminate study participation will continue to have assessments performed for 16 weeks following last injection according to the Time and Events Schedule (Table 2).

Note: The visit that is approximately 16 weeks after the last study agent injection is referred to as the “final safety and efficacy follow-up visit” (Table 2).

In the event a subject discontinues study agent injections, the first safety and efficacy follow up visit should occur 4 weeks \pm 14 days after the date of the last administration of the study agent. The visit window for follow-up assessments is \pm 14 days.

9.2 Efficacy

9.2.1 Evaluations

9.2.1.1 Joint Assessments

Joint Assessor

Each of 68 joints will be evaluated for tenderness, and each of 66 joints will be evaluated for swelling (hips are excluded for swelling). All joints will be examined at visits as indicated in the Time and Events Schedule.

A joint assessor with adequate training and experience in performing joint assessments will be designated at each study site to perform all joint assessments. The joint assessor should preferably be a rheumatologist; however, if a rheumatologist is not available, the assessor should be a health care provider with at least 1 year of experience in performing joint assessments (for additional details, see Trial Center File). Health care providers with less than 1 year of experience may serve as a joint assessor based upon the discretion and approval of the Sponsor. It is required that the designated joint assessor identify an appropriate back-up joint assessor to provide coverage if the designated joint assessor is absent. However, it is strongly recommended that the joint assessor who performs the baseline joint assessments for a subject should also perform the joint assessments for that subject at every subsequent visit through the end of the study.

The Sponsor will provide training for each site's designated joint assessor prior to the [Week 0 visit] of the first subject at each site. A back-up joint assessor must complete training before performing a joint assessment for a subject's study visit. If an assessor was trained by the Sponsor in the primary studies (CNTO136ARA3002 and CNTO136ARA3003) or in a previous

clinical study within the last 3 years and there is adequate documentation of this training (certification), that training will be considered adequate for this study. Training documentation for each joint assessor should be maintained at the study site.

All joint assessors performing joint evaluations at a site must be listed on the Delegation Log at the study site and should be documented in the source documents at each visit.

Nonevaluable Joints

Joints should *only* be designated as “non-evaluable” by the joint assessor on the Joint Assessment Worksheet *if it is physically impossible to assess the joint* (ie, joint inaccessible due to a cast, joint not present due to an amputation, joint deformed so as to make it impossible to assess). In all other cases, the joint assessor should assess each joint for tenderness and swelling (hips are excluded for swelling) and complete the worksheet with their assessments. This should be completed regardless of any visual indications of prior surgeries (eg, scars) or knowledge they may have of a subject’s prior joint procedures/injections (eg, if the subject was the joint assessor’s patient prior to study participation).

9.2.1.2 Pain Assessment

Subjects will be asked to assess their average pain during the past week on a visual analogue scale (VAS). The scale ranges from “no pain” to “the worst possible pain”. This assessment should be completed prior to the joint examination. The validity of this assessment has been evaluated and reviewed extensively as it is a component of the ACR response score.^{8,15} Specific magnitudes of change in the VAS correspond to prespecified ACR score calculations (ie, a 20% improvement in the VAS corresponds to an ACR 20).

9.2.1.3 Patient’s and Physician’s Global Assessment of Disease Activity

The Patient’s and Physician’s Global Assessments of Disease Activity⁹ will be recorded on a VAS. The scale for the subject’s assessment ranges from “very well” to “very poor”. The scale for the physician’s assessment ranges from “no arthritis activity” to “extremely active arthritis”. The evaluating physician and subject must complete the global assessment independently of each other. The physician should preferably be the same person at every study visit for a given subject. The results of the joint assessment performed by the joint assessor will be available to the physician assessing the subject’s global disease.

9.2.1.4 Health Assessment Questionnaire – Disability Index

The functional status of the subject will be assessed using the HAQ-DI.¹² This 20-question instrument assesses the degree of difficulty a person has in accomplishing tasks in 8 functional areas (dressing, arising, eating, walking, hygiene, reaching, gripping, and activities of daily living). Responses in each functional area are scored from 0, indicating no difficulty, to 3, indicating inability to perform a task in that area.

9.2.1.5 Duration of Morning Stiffness

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

9.2.1.6 36-Item Short Form Questionnaire

The Medical Outcome Study health measure entitled the 36-item Short-Form (SF-36) health survey questionnaire was developed as part of the Rand Health Insurance Experiment and consists of 8 multi-item scales.

- Limitations in physical functioning due to health problems
- Limitations in usual role activities due to physical health problems
- Bodily pain
- General mental health (psychological distress and well-being)
- Limitations in usual role activities due to personal or emotional problems
- Limitations in social functioning due to physical or mental health problems
- Vitality (energy and fatigue)
- General health perception

These scales are scored from 0 to 100 with higher scores indicating better health. Another algorithm yields 2 summary scores, the Physical Component Score (PCS) and Mental Component Score (MCS). These summary scores are also scaled with higher scores indicating better health.⁴⁷ The concepts measured by the SF-36 are not specific to any age, disease, or treatment group, allowing comparison of relative burden of different diseases and the relative benefit of different treatments.⁴⁸

9.2.1.7 Work Limitations Questionnaire

The WLQ has been selected from existing instruments in order to generate estimates of work productivity and absenteeism. The WLQ is a brief, self-report questionnaire designed to enable investigators to obtain a sensitive measure of the degree to which employed individuals are experiencing limitations on-the-job due to their health problems and health-related productivity loss.²² The WLQ has 25 items that ask respondents to rate their level of difficulty or ability to perform specific job demands. The 25 items are aggregated into 4 scales, time management, physical demands, mental-interpersonal, and output. Scale scores range from 0 (limited none of the time) to 100 (limited all of the time) and represent the reported amount of time in the prior 2 weeks that respondents were limited on-the-job.

9.2.1.8 Multidimensional Personality Questionnaire (MPSQ)

The Placebell[™] technology will be explored in this study of rheumatoid arthritis. The Multidimensional Personality Questionnaire (MPSQ) is a questionnaire contributing to the evaluation of individual patient response to placebo by assessing patients's personality, well-being as well as attitudes and beliefs on disease therapies.^{35,36} It has been developed by

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Tools4patient SA. MPSQ is self-reported by patient and made of 114 items. Each of them is rated by patient on a 5-point scale ranging from 1 (strongly disagree) to 5 (strongly agree).

At selected sites, the MPSQ will be administered as an optional paper questionnaire to subjects who consent to participate after implementation of Amendment 3.

9.2.2 Definitions

9.2.2.1 American College of Rheumatology Responses

ACR responses are presented as the numerical measurement of improvement in multiple disease assessment criteria. For example, an ACR 20 response⁹ is defined as:

1. $\geq 20\%$ improvement from baseline in both swollen joint count (66 joints) and tender joint count (68 joints),

AND

2. $\geq 20\%$ improvement from baseline in 3 of the following 5 assessments:

Patient's assessment of pain (VAS)

Patient's Global Assessment of Disease Activity (VAS)

Physician's Global Assessment of Disease Activity (VAS)

Patient's assessment of physical function as measured by HAQ-DI

C-reactive protein (CRP)

ACR 50 and ACR 70 are similarly defined except improvement threshold from baseline is 50% and 70%, respectively.

9.2.2.2 Disease Activity Index Score 28

9.2.2.2.1 Disease Activity Index Score 28 Using CRP

The Disease Activity Index Score 28 using CRP [DAS28 (CRP)] is a derived score combining tender joints (28 joints), swollen joints (28 joints), CRP, and Patient's Global Assessment of Disease Activity (GH).⁴⁵ The DAS28 (CRP) is a continuous parameter and is defined as follows:

$$\text{DAS28 (CRP)} = 0.56 \times \text{SQRT}(\text{TEN28}) + 0.28 \times \text{SQRT}(\text{SW28}) + 0.36 \times \ln(\text{CRP} + 1) + 0.014 \times \text{GH} + 0.96$$
 where:

- The set of 28 joint count is based on evaluation of the shoulder, elbow, wrist, MCP1, MCP2, MCP3, MCP4, MCP5, PIP1, PIP2, PIP3, PIP4, PIP5 joints of both the upper right extremity and the upper left extremity as well as the knee joints of lower right and lower left extremities.
- TEN28 is 28 joint count for tenderness.
- SQRT (TEN28) is square root of TEN28.

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- SW28 is 28 joint count for swelling.
- SQRT (SW28) is square root of SW28
- Ln (CRP+1) is natural logarithm of (CRP value [mg/L] + 1).
- GH is Patient’s Global Assessment of Disease Activity on VAS.

9.2.2.2.1.1 DAS28 (CRP) Response

- DAS28 (CRP) response is defined in [Table 3](#).⁴⁵

Table 3: DAS28 (CRP) response criteria			
DAS28 (CRP) at the visit	Improvement from Baseline		
	> 1.2	> 0.6 – 1.2	≤ 0.6
• ≤ 3.2	• Good response	• Moderate response	• No response
• > 3.2 – 5.1	• Moderate response	• Moderate response	• No response
• > 5.1	• Moderate response	• No response	• No response

9.2.2.2.1.2 DAS28 (CRP) Remission

DAS28 (CRP) remission is defined as a DAS28 (CRP) value of < 2.6 at a visit.

9.2.2.3 Simplified Disease Activity Index Score

The Simplified Disease Activity Index (SDAI) score is a derived score combining tender joints (28 joints), swollen joints (28 joints), GH, Physician’s global assessments of disease activity (PGH), and CRP.²

SDAI is defined as follows:

SDAI = TEN28 + SW28 + GH + PGH + CRP (mg/dL) where:

- TEN28 and SW28 were defined the same as in Section [9.2.2.2.1](#)
- GH is Patient’s Global Assessment of Disease Activity on VAS.
- PGH is Physician’s Global Assessment of Disease Activity on VAS.

9.2.2.4 Clinical Disease Activity Index Score

Clinical Disease Activity Index (CDAI) score is a derived score combining tender joints (28 joints), swollen joints (28 joints), GH, and PGH.²

CDAI is defined as follows:

CDAI = TEN28 + SW28 + GH + PGH where:

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- TEN28 and SW28 were defined the same as in Section 9.2.2.2.1
- GH is Patient’s Global Assessment of Disease Activity on VAS.
- PGH is Physician’s Global Assessment of Disease Activity on VAS.

Note: CDAI is the same as SDAI, except that CRP is not included.

9.2.2.5 ACR/EULAR Remission

9.2.2.5.1 SDAI-Based ACR/EULAR Remission

SDAI-based ACR/EULAR remission is defined as a SDAI value of ≤ 3.3 at a visit¹⁰:

9.2.2.5.2 Boolean-Based ACR/EULAR Remission

A subject is considered as having achieved the Boolean-based ACR/EULAR remission at a visit if he/she meets all of the following 4 criteria at that visit¹⁰:

- Tender joint count (68 joints) ≤ 1 .
- Swollen joint count (66 joints) ≤ 1 .
- CRP ≤ 1 mg/dL
- Patient’s Global Assessment of Disease Activity on VAS ≤ 1 on a 0 to 10 scale.

9.2.3 Endpoints

Primary Endpoint

The primary endpoint is the number of subjects with each of the following long-term safety events through the end of the study: cardiovascular SAEs, malignancies, serious infections, and gastrointestinal perforations.

Major Secondary Endpoints

Laboratory parameters of interest (neutrophils, platelets, hepatobiliary parameters, and lipid parameters) will be observed.

Other secondary endpoints

- ACR responses
- DAS28
- HAQ-DI
- SF-36
- WLQ
- HECONQ
- Morning stiffness

9.3 Pharmacokinetics and Immunogenicity

9.3.1 Evaluations

Serum samples will be used to evaluate the pharmacokinetics, as well as the immunogenicity of sirukumab (antibodies to sirukumab). Serum collected for sirukumab serum concentration and antibodies to sirukumab analyses may additionally be used to evaluate safety or efficacy aspects that address concerns arising during or after the study period. Genetic analyses will not be performed on these serum samples. Subject confidentiality will be maintained. At visits where sirukumab serum concentration and antibodies to sirukumab will be evaluated, 1 blood draw of sufficient volume can be used. Venous blood samples will be collected and each serum sample will be divided into 3 aliquots (1 each for pharmacokinetics, antibodies to study agent, and a back-up). Subjects who discontinue study participation should have serum samples collected at the last safety follow-up visit.

Instructions for the collection, handling, and shipment of these samples are found in the Laboratory Manual.

9.3.2 Pharmacokinetics

9.3.2.1 Serum Collection and Handling

Blood samples for the measurement of serum sirukumab concentrations will be collected at visits as shown in the Time and Events Schedules ([Table 1](#) and [Table 2](#)). For subjects who had serum samples collected at earlier time points in study CNTO136ARA3002 (approximately 750 randomized subjects in CNTO136ARA3002) and all subjects who enrolled after participating in study CNTO136ARA3003, serum samples will be collected at Weeks 2, 4, 16, 28, 52, 104, 156 and the final safety and efficacy follow-up visit ([Table 1](#) and [Table 2](#)). One additional sample will be collected at Week 208 for subjects who enrolled after participating in study CNTO136ARA3003.

The exact dates and times of blood sampling must be recorded on the laboratory requisition form. Note that if the subject is to receive an administration of study agent at that visit, blood samples will be collected prior to study agent administration.

9.3.2.2 Analytical Procedures

Serum samples will be analyzed to determine concentrations of sirukumab using a validated, immunoassay method.

The Sponsor, or its designee, under conditions in which the subjects' identity remains blinded, will assay these samples.

9.3.2.3 Pharmacokinetic Parameters

Serum sirukumab concentration including C_{trough} will be summarized.

9.3.3 Immunogenicity Assessment (Antibodies to sirukumab)

To assess the immunogenicity of sirukumab, serum samples for the detection of antibodies to sirukumab will be collected at visits as shown in the Time and Events Schedules ([Table 1](#) and [Table 2](#)). For subjects who had serum samples collected at earlier time points in study

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CNTO136ARA3002 (approximately 750 randomized subjects in CNTO136ARA3002) and all subjects who enrolled after participating in study CNTO136ARA3003, serum samples will be collected at Weeks 16, 28, 52, 104, 156 and the final safety and efficacy follow-up visit. One additional sample will be collected at Week 208 for subjects who enrolled after participating in study CNTO136ARA3003.

Antibodies to sirukumab will be detected using a validated immunoassay method. Serum samples will be screened for antibodies binding to sirukumab and the titer of confirmed positive samples will be reported. Other analyses may be performed to verify the stability of antibodies to sirukumab and/or further characterize the immunogenicity of sirukumab. These samples will be analyzed by the Sponsor or its designee.

Subjects will be classified as positive for antibodies to sirukumab if any post-treatment samples tested positive for antibodies to sirukumab. Subjects will be classified as negative for antibodies to sirukumab if antibodies were not detected in any post-treatment samples.

9.4 Pharmacodynamic Evaluations

Serum and whole blood samples for the analysis of pharmacodynamic markers will be collected according to the Time and Events Schedule. These samples will be used to better understand the biology of RA, to analyze differences between responders and non-responders, and to assess loss of response. The samples to be collected include whole blood for RNA and serum for the evaluation of inflammation-associated proteins and other analytes such as but not limited to microRNAs.

9.5 Pharmacogenetics (DNA) Evaluations

Assessment of genetic factors such as DNA methylation will be completed. Only DNA research related to sirukumab or to the diseases for which this drug is developed will be performed. Subjects who agree to participate in this optional portion of the study must sign a separate pharmacogenetics informed consent. Further, a subject may withdraw such consent at any time without affecting their participation in other aspects of the study, or their future participation in the study.

9.6 SmartJect™ Autoinjector Usability Substudy

In this substudy, a select number of subjects at selected sites in English-speaking countries who are enrolled in CNTO136ARA3004 will be consented and enrolled in a SmartJect™ AI Usability substudy. Subjects will not be required to participate in the substudy, and can enter the CNTO136ARA3004 LTE study independent of participation in the substudy. Subjects completing the substudy will return to the LTE study for the remainder of their study treatments. Site personnel in the substudy will observe and document 2 scheduled self-administrations of study agent by subjects using the PFS-AI. All substudy subjects will also complete an e-diary regarding their experiences with at-home use of PFS-AI for an additional 12 weeks of study treatment. A subset of these subjects will also have a detailed interview at their final substudy visit regarding their at-home-use experience. For additional details, refer to the PFS-AI Usability Substudy Protocol.

9.7 Health Economics Evaluations

Health economics evaluations on employment status, impact of disease on daily productivity, and time lost from work will be collected. The impact of disease on patients' daily work productivity will be measured using a VAS. The scale ranges from “not at all affected” to “affected very much”.

9.8 Safety Evaluations

Details regarding the DMC and CEC are provided in Sections 11.10 and 11.11, respectively.

As noted in Section 3.2.6, AEs of interest have been identified. These are: hematologic laboratory abnormalities (decreases in neutrophils and platelets), hepatobiliary laboratory abnormalities, lipid parameter abnormalities, serious CV events, infections, malignancies, and gastrointestinal perforations.

The study will include the following evaluations of safety and tolerability according to the time points provided in the Time and Events Schedule:

Adverse Events

Adverse events will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally-acceptable representative) for the duration of the study. Adverse events will be followed by the investigator as specified in Section 12.

Clinical Laboratory Tests

Blood samples for serum chemistry and hematology will be collected. The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The following tests will be performed by the central laboratory:

- Hematology Panel
 - hemoglobin
 - hematocrit
 - RBC count
 - WBC count with differential
 - platelet count

- Serum Chemistry Panel
 - sodium
 - potassium
 - chloride
 - bicarbonate
 - AST
 - ALT
 - alkaline phosphatase
 - calcium

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- | | |
|-------------|--|
| - BUN | -phosphate |
| -creatinine | -albumin |
| -glucose | -total protein |
| | -total bilirubin, with fractionation if hyperbilirubinemia |
- Lipid Panel (fasting)

-total cholesterol	-high-density lipoprotein (HDL)
-low-density lipoprotein (LDL)	-triglycerides
 - Urine Pregnancy Testing for women of childbearing potential only.

Additional assays may be performed on lipid panel specimens to further characterize the changes in lipid profile following treatment with sirukumab. Additional laboratory tests may be performed as determined by the Sponsor for the further evaluation of subjects.

Subject Lab Data Access

Subjects at selected sites in the US will be offered the opportunity to consent to join a secure, web-based platform managed by a third party vendor so that they may access results to select clinical laboratory tests collected during the study (as defined above with the exception of RBC count). More details will be provided in the Informed Consent Form for these subjects.

Pathology

If a subject requires tissue sampling for the evaluation of an adverse event, the Sponsor may request that the sample be sent for additional central evaluation.

Vital Signs

Blood pressure and body weight will be measured.

Physical Examination

A general physical examination will be performed as indicated in [Table 1](#). Clinically significant findings should be reported as AEs.

Allergic Reactions

All subjects will be observed carefully for symptoms of allergic reactions for at least 30 minutes after the SC injection of study agent at the study site at least until the study becomes open-label. If mild or moderate allergic reaction is observed, acetaminophen 650 mg PO or NSAIDS and diphenhydramine 25 mg PO or IV may be administered. If the reaction is not severe, subsequent injections at the appropriate treatment intervals may be undertaken with caution. Subjects who self-inject the study agent away from the study site will receive detailed instructions on how to monitor and report AEs.

Subjects with severe reactions following an injection such as bronchospasm with wheezing and/or dyspnea requiring ventilator support, or symptomatic hypotension with a decrease in

systolic blood pressure greater than 40 mm Hg will not be permitted to receive any additional study agent injections. In the case of such reactions, appropriate medical treatment should be administered.

Injection Site Reactions

An injection site reaction is any unfavorable or unintended sign that occurs at the study agent injection site. All subjects must be carefully observed for symptoms of an injection site reaction. Subjects will be observed for at least 30 minutes after the SC injection of study agent for symptoms of an injection-site reaction at least until the study becomes open-label. If an injection site reaction is observed, the subject should be treated at the investigator's discretion. Any adverse reaction (eg, pain, erythema, and/or induration) should be noted on the AE page of the eCRF.

Early Detection of Active Tuberculosis

To aid in the early detection of TB reactivation or new TB infection during study participation, subjects must be evaluated for signs and symptoms of active TB at scheduled visits (refer to the Time and Events Schedule). The following series of questions is suggested for use during the evaluation:

- “Have you had a new cough of > 14 days’ duration or a change in a chronic cough?”
- “Have you had any of the following symptoms:
 - Persistent fever?
 - Unintentional weight loss?
 - Night sweats?”
- “Have you had close contact with an individual with active TB?” (If there is uncertainty as to whether a contact should be considered “close,” a physician specializing in TB should be consulted.)

If the evaluation raises suspicion that a subject may have TB reactivation or new TB infection, study agent administration should be interrupted and an immediate and thorough investigation should be undertaken, including, where possible, consultation with a physician specializing in TB.

Investigators should be aware that TB reactivation in immunocompromised subjects may present as disseminated disease or with extrapulmonary features. Subjects with evidence of active TB must immediately discontinue study agent and should be referred for appropriate treatment.

Subjects who experience close contact with an individual with active TB during the conduct of the study must have a repeat chest radiograph, a repeat QuantiFERON TB Gold test ([Appendix A](#)), a repeat tuberculin skin test ([Appendix B](#)) in countries in which the QuantiFERON-TB Gold test is not approved/registered, and, if possible, referral to a physician specializing in TB to determine the subject's risk of developing active TB and whether treatment for latent TB is warranted. Study agent administration should be interrupted during the

investigation. A positive QuantiFERON-TB Gold (or tuberculin skin) test result should be considered detection of latent TB. Appropriate treatment for latent TB is defined according to local country guidelines for immunocompromised patients. If no local country guidelines for immunocompromised patients exist, US guidelines must be followed or the subject must be excluded from the study. If recommended, treatment for latent TB must be initiated prior to or simultaneously with the administration of further study agent. Subjects who discontinue treatment for latent TB prematurely or who are noncompliant with therapy must immediately discontinue further administration of study agent and should return for all subsequent scheduled study visits (see Section 10.2). A subject whose first QuantiFERON-TB Gold test result is indeterminate should have the test repeated. In the event that the second QuantiFERON-TB Gold test result is also indeterminate, the subject should be excluded from the study.

Hepatitis B Monitoring

Subjects who are HBsAg- /HBcAb+ only, without detectable HBV DNA, should be monitored according to local guidelines. If local guidelines do not exist for HBV monitoring in these types of patients, monitoring should be performed following consultation with a hepatitis B specialist.

HBsAg- /HBsAb+ subjects who are HBcAb- or +, and without detectable HBV DNA, should be monitored if recommended under local guidelines related to HBV and biologic anti-rheumatic agents.

Hepatobiliary abnormalities

In the event of hepatobiliary abnormalities such as AST or ALT ≥ 3 times ULN, confirmatory testing should be repeated using a liver chemistry kit and clinical assessment for symptoms of hepatic dysfunction done as soon as possible. A liver chemistry kit will include the following tests: ALT, AST, alkaline phosphatase, total and direct bilirubin. If the hepatobiliary laboratory abnormality is confirmed, then a thorough evaluation should be performed, including the following, as appropriate:

- Medical and family history
- Review of medications, alcohol, and other substance use
- Physical examination (including vital signs, examination of liver and abdomen, other stigmata of hepatic disease)
- Abdominal ultrasound with consideration of further imaging (eg, CT, MRI, MRCP, ERCP, Doppler studies of hepatic vessels, etc., if indicated based on ultrasound findings or clinical situation)
- Laboratory evaluation using a hepatobiliary abnormalities kit: Complete blood counts with eosinophil count, international normalized ratio (INR), viral hepatitis serology testing (anti-Hepatitis A virus (HAV) IgM, HBsAg, anti-HBs, anti-HB core total, anti-HB core IgM, anti-HCV, HCV RNA, anti-Hepatitis E virus IgM, Epstein-Barr virus IgM and Cytomegalovirus IgM), total protein and globulins, antinuclear antibody, anti-smooth muscle antibody, iron markers (iron, TIBC, ferritin)

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Consultation with a specialist may be warranted. See Section 10.2 for specific instructions regarding discontinuation of treatment guidelines and evaluation of hepatobiliary abnormalities. Temporary or permanent discontinuation of study agent may be required (see Section 10.2). Temporary discontinuation or dose adjustment of MTX may be required (see Section 8.1.2).

9.9 Sample Collection and Handling

The actual dates and times of sample collection must be recorded on the laboratory requisition form.

Refer to the Time and Events Schedules for the timing and frequency of all sample collections.

Instructions for the collection, handling, and shipment of samples are found in the laboratory manual that will be provided for sample collection and handling.

10 SUBJECT COMPLETION/WITHDRAWAL

10.1 Completion

Subjects must remain in the study until the last scheduled visit followed by 16 weeks of safety and efficacy follow up to be considered as having completed participation in the study.

10.2 Discontinuation of Treatment

If a subject's study treatment must be discontinued before the end of the treatment regimen, this will not result in automatic withdrawal of the subject from the study.

Study agent administration to a subject must be permanently discontinued if any of the following occur:

1. The investigator (in consultation with the medical monitor) believes that for safety reasons (eg, adverse event) it is in the best interest of the subject to stop treatment.
2. Anaphylactic reaction resulting in bronchospasm with wheezing, or dyspnea requiring ventilatory support, or symptomatic hypotension with a greater than 40 mm Hg decrease in systolic blood pressure that occurs following a study agent administration.
3. Reaction suggestive of serum sickness occurring 1 to 14 days after study agent injection. These may be manifested by symptoms of myalgias, arthralgias, fever, rash, pruritus, facial, hand, or lip edema, dysphagia, urticaria, sore throat, and/or headache.
4. Opportunistic infection, ie, an infection by an organism that usually causes disease only in a host whose resistance is lowered (eg, *Pneumocystis jirovecii*, coccidioidomycosis, *Mycobacterium avium*).
5. TB
 - a. Active TB
 - b. Subject with latent TB who discontinues treatment for latent TB prematurely or is not compliant with treatment for latent TB
6. Malignancy, excluding nonmelanoma skin cancer.

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7. Demyelination, either central or peripheral.
8. Pregnancy during study participation.
9. Drug induced liver injury, including any one of the following:
 - a. Alanine transferase (ALT) or aspartate transferase (AST) $\geq 5 \times$ ULN but $< 8 \times$ ULN and cannot be monitored weekly for ≥ 2 weeks.
 - b. ALT or AST $\geq 8 \times$ upper limit of normal (ULN)
 - c. ALT or AST $\geq 5 \times$ ULN for 2 or more weeks
 - d. ALT or AST $\geq 3 \times$ ULN and total bilirubin $\geq 2 \times$ ULN (upper limit of normal) ($> 35\%$ direct bilirubin) (or ALT or AST $\geq 3 \times$ ULN **and** INR > 1.5 , if INR measured).

NOTE: if serum bilirubin fractionation is not immediately available, withdraw study drug for that subject if ALT or AST $\geq 3 \times$ ULN and total bilirubin $\geq 2 \times$ ULN. Serum bilirubin fractionation should be performed if testing is available. If testing is unavailable, record the presence of detectable urinary bilirubin on dipstick as indicative of direct bilirubin elevations and suggestive of liver injury.

- e. ALT or AST $\geq 3 \times$ ULN accompanied by clinical symptoms believed to be related to hepatitis or hypersensitivity such as new or worsening of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, or rash.

When any of the liver chemistry stopping criteria a-e is met, do the following:

- **Immediately** withdraw study agent for that subject
- Report the event to the Sponsor **within 24 hours** of learning its occurrence (see Section 12.4)
- Complete the Hepatobiliary Event Information Form and SAE form if the event also meets the criteria for an SAE. All events that meet criteria as described below **must be reported as an SAE**.
 - ALT or AST $\geq 3 \times$ ULN **and** total bilirubin $\geq 2 \times$ ULN ($> 35\%$ direct bilirubin) or
 - ALT or AST $\geq 3 \times$ ULN **and** INR > 1.5 (INR measurement is not required and the threshold value stated will not apply to patients receiving anticoagulants)
- Perform liver event follow up assessments, and monitor the subject until liver chemistries **resolve, stabilize, or return to baseline values as described below**.
- Do not restart study agent
- Make every reasonable attempt to have subjects meeting liver chemistry criteria a - e to return to clinic within 24 hours for repeat liver chemistries, liver event follow-up assessments (see below), and close monitoring.
- A specialist in hepatology consultation should be considered.

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- Make every reasonable attempt to monitor subjects twice weekly until liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) resolve, stabilize or return to within baseline values. Criterion e subjects should be monitored as frequently as possible.

Make every attempt to carry out the **liver event follow up assessments** described below:

- Viral hepatitis serology (anti-Hepatitis A virus (HAV) IgM, HBsAg, anti-HBs, anti-HB core total, anti-HB core IgM, anti-HCV, HCV RNA, anti-Hepatitis E virus IgM, Epstein-Barr virus IgM and Cytomegalovirus IgM).
 - If HBsAg or anti-HB core IgM is positive, or if anti-HBc total is the only positive test, a specialist in hepatology consultation should be obtained.
 - If HBsAg is positive, perform hepatitis delta antibody assay. NOTE: if hepatitis delta antibody assay cannot be performed, it can be replaced with a PCR of hepatitis D RNA virus – as outlined in: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1153793/>
- Blood sample for PK analysis, obtained within 24 hours of last dose. Record the date/time of the PK blood sample draw on the laboratory requisition form and the date/time of the last dose of study agent prior to blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the subject's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample.
- Serum creatine phosphokinase (CPK), lactate dehydrogenase (LDH) and albumin.
- Fractionate bilirubin, if total bilirubin $\geq 2 \times$ ULN
- Obtain complete blood count with differential to assess eosinophilia
- Record the appearance or worsening of clinical symptoms of hepatitis or hypersensitivity, such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia as relevant on the AE report form
- Record use of concomitant medications, acetaminophen, herbal remedies, other over the counter medications, or putative hepatotoxins, on the concomitant medications report form.
- Record alcohol use

The following are required for subjects that meet criteria of ALT or AST $\geq 3 \times$ ULN and bilirubin $\geq 2 \times$ ULN ($> 35\%$ direct) but are optional for subjects with other abnormal hepatobiliary chemistries as appropriate:

- Screen for other causes of liver disease: Total protein and globulins, ANA, ASMA (anti-smooth muscle antibodies), iron, TIBC, ferritin, alpha-1 anti-trypsin level, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG or gamma globulins). Additional testing should be performed if the following conditions are met:
 - If alkaline phosphatase $>$ ALT, AMA (anti-mitochondrial antibody) should be tested.
 - If patient is < 50 years of age, ceruloplasmin should also be tested.
 - If patient is sick enough to require hospitalization be hospitalized and is under age less than 50 years old, 24 hour urine copper should be tested.
 - Serum acetaminophen adduct HPLC assay (quantifies potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week)
 - Consider serum ethanol as clinically appropriate.
 - Liver ultrasound with consideration of further imaging (eg, CT, MRI, MRCP, ERCP, Doppler studies of hepatic vessels, etc., if indicated based on ultrasound findings or clinical situation)
10. Two confirmed consecutive absolute neutrophil counts of $< 0.5 \times 10^3/\mu\text{L}$ (SI: $< 0.5 \times 10^9$ cells/L).
 11. Two confirmed consecutive platelet counts $< 50,000/\mu\text{L}$ (SI: $< 50 \times 10^9$ cells/L).
 12. QTc > 500 msec* or uncorrected QT > 600 msec, Change from baseline: QTc > 60 msec*
*based on average QTc value of triplicate ECGs
 13. The initiation of protocol-prohibited medications. (see Section 8.2).
 14. Acute diverticulitis requiring antibiotic treatment
 15. Gastrointestinal perforation
 16. If sirukumab becomes approved in the subject's country of residence, it may no longer be offered by the Sponsor in CNTO136ARA3004. In this case, study agent administrations will be discontinued after 52 weeks of treatment for subjects who enrolled after completing participation in study CNTO136ARA3002, and after 104 weeks of treatment for subjects who enrolled after completing participation in CNTO136ARA3003. At that point the subject will have the opportunity to discuss treatment options with their treating physician.

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Subjects should not receive study agent administrations during the course of a serious infection. Discontinuation of study agent administration must be strongly considered for subjects who develop a serious infection such as sepsis or meningoenephalitis, and also should be considered for subjects who have serious infections requiring hospitalization or IV antibiotic therapy. Discontinuation of study agent administration should also be considered for severe injection-site reactions.

Subjects who discontinued study agent administration should continue participating in the study for safety and efficacy follow-up (Table 2).

10.2.1 Interruption of Study Agent Administration

Values for liver transaminase levels (AST, ALT), absolute neutrophil count (ANC), and platelet count that require study agent interruption and/or permanent discontinuation of study agent administration are listed below in Table 4.

Table 4: Values for liver transaminase levels, absolute neutrophil count, and platelet count that require study agent interruption and/or permanent discontinuation of study agent administration	
ALT or AST increased	
ALT or AST	Action
≥ 3 times the upper limit normal (≥ 3x ULN) for laboratory reference range.	Interrupt study agent administration, assess for symptoms, and repeat ALT/AST test as soon as possible using a liver chemistry kit as described in Section 9.8 Safety Evaluations below Hepatobiliary abnormalities.* May resume study agent when < 3x ULN**
Criteria for drug-induced liver injury (Section 10.2, #9)	Permanent discontinuation of study agent

Low Absolute Neutrophil Count (ANC)	
Neutrophil count	Action
0.5 to ≤ 1.0 x 10 ³ /μL (SI: 0.5 to ≤ 1.0 x 10 ⁹ cells/L)	Interrupt study agent administration, repeat ANC test as soon as possible* May resume study agent when > 1.0 x 10 ³ /μL**
< 0.5 x 10 ³ /μL (SI: < 0.5 x 10 ⁹ cells/L)	Interrupt study agent administration, repeat ANC test as soon as possible* If confirmed to be < 0.5 x 10 ³ /μL, discontinue study agent permanently (Section 10.2 #10)

Low Platelet Count	
Platelet count	Action
50,000 to ≤ 100,000/μL (SI: 50 to ≤ 100 x 10 ⁹ cells/L)	Interrupt study agent administration, repeat platelet count test as soon as possible* May resume study agent when platelet count > 100,000/μL **
< 50,000/μL (SI: < 50 x 10 ⁹ cells/L)	Interrupt study agent administration, repeat platelet count test as soon as possible* If confirmed to be < 50,000/μL, discontinue study agent permanently (Section 10.2 #11)
* Retesting should be done by Central laboratory	
** In case more than 3 subsequent injections are missed, and the PI wishes to resume study agent, please contact the Medical Monitor.	

10.3 Withdrawal from the Study

A subject will be withdrawn from the study for any of the following reasons:

- Lost to follow-up
- Withdrawal of consent
- Death

If a subject discontinues study agent administration before the end of the study, follow-up assessments should be obtained as per the Time and Events Schedule described in [Table 2](#).

If a subject is lost to follow-up, every reasonable effort must be made by the study site personnel to contact the subject and determine the reason for discontinuation/withdrawal. The measures taken to follow up must be documented.

When a subject withdraws before completing the study, the reason for withdrawal is to be documented in the CRF and in the source document. Study agent assigned to the withdrawn subject may not be assigned to another subject. Subjects who withdraw will not be replaced.

Withdrawal from Pharmacodynamic Research

The subject may withdraw consent for pharmacodynamics research while remaining in the clinical study. In such a case, any stored samples will be destroyed upon communication from the site to the Sponsor. No pharmacogenetics testing will be conducted on these samples. This does not include those samples specifically collected for pharmacogenetic analysis for which separate optional consent was obtained.

Withdrawal from Pharmacogenetics Research

The subject may withdraw consent for pharmacogenetics research while remaining in the clinical study. In such a case, any DNA extracted from the subject's blood will be destroyed upon communication from the site to the Sponsor. If requested, the investigator will receive written confirmation from the Sponsor that the sample has been destroyed.

11 STATISTICAL METHODS

Statistical analysis will be done by the Sponsor or under the authority of the Sponsor. Descriptive statistics (eg, mean, median, standard deviation, interquartile range, minimum, and maximum) will be used to summarize continuous variables. Counts and percentages will be used to summarize categorical variables.

Subjects will continue to receive the same treatment regimen administered in studies CNTO136ARA3002 and CNTO136ARA3003 at Weeks 104 and 52, respectively:

- Group 1: Sirukumab 100 mg SC q2 weeks
- Group 2: Sirukumab 50 mg SC q4 weeks

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After the study becomes open-label, subjects treated with SC sirukumab 100 mg q2 weeks will be offered the option to reduce the sirukumab dose to 50 mg q4 weeks at the investigator's discretion. This decision can be made at the subject's first or second major resupply visit (up until approximately 7 months) after implementation of Amendment 3 at the study site.

Since the treatment groups are not randomly assigned in this study, no formal hypothesis testing is planned. The efficacy, safety, and PK/PD/immunogenicity analyses will be performed separately for subjects who complete studies CNTO136ARA3002 and CNTO136ARA3003. The analyses will include all subjects enrolled by study and by treatment group above.

Additional data releases or locks may occur periodically as needed. The analyses based on these data releases or locks intend to integrate data from CNTO136ARA3002 and CNTO136ARA3003 with this study for the long-term PK, immunogenicity, safety and efficacy data of all subjects enrolled in these studies. A separate SAP for integration will be developed to specify the analyses and data handling rules.

An independent DMC will monitor the safety of the blinded portion of the study in unblinded fashion on a regular basis and whenever deemed necessary. Additional details are provided in Section 11.10.

11.1 Subject Information

Unless otherwise stated, in general, all subjects who enrolled this study will be included in analyses. Analyses will be performed based on the treatment groups defined in Section 11.

11.2 Efficacy and Safety Analyses

Baseline value in efficacy and safety is defined as the baseline value of study CNTO136ARA3002 or CNTO136ARA3003. No missing data imputation will be used.

11.2.1 Primary Endpoint

The number of subjects with each of the following long-term safety events through the end of study: cardiovascular SAEs, malignancies, serious infections, and gastrointestinal perforations will be summarized.

Serious cardiovascular events adjudicated by the CEC will be summarized by treatment group.

No hypothesis testing will be performed.

11.2.2 Major Secondary Endpoints

Laboratory parameters of interest (neutrophils, platelets, hepatobiliary parameters, and lipid parameters) will be observed. Toxicity grade will be summarized by treatment group over time through the end of the study.

11.2.3 Other Secondary Endpoints

In addition to the primary and major secondary efficacy endpoints, the following efficacy endpoints will be summarized by treatment group over time through the end of the study:

1. Proportion of subjects who achieve ACR 20 response
2. Proportion of subjects who achieve ACR 50 response
3. Proportion of subjects who achieve ACR 70 response
4. Proportion of subjects with DAS28 (CRP) response
5. Proportion of subjects with DAS28 (CRP) remission
6. Change from baseline in DAS28 (CRP)
7. Proportion of subjects with SDAI-based ACR/EULAR remission
8. Proportion of subjects with Boolean-based ACR/EULAR remission
9. Change from baseline in SDAI
10. Change from baseline in CDAI
11. Change from baseline in HAQ-DI
12. Proportion of HAQ-DI responders (ie, those who have a change from baseline of > 0.22 in HAQ-DI score)
13. Change from baseline in PCS and MCS and in domain scores of SF-36
14. Change from baseline in duration of morning stiffness

11.3 Pharmacokinetic Analyses

Blood samples for the measurement of serum sirukumab concentrations and the detection of antibodies to sirukumab will be collected and analyzed.

Serum sirukumab concentration data including C_{trough} will be summarized by visit. PK data may be displayed graphically. If sufficient samples are collected, steady-state trough serum sirukumab concentrations before and after switching from PFS-U to PFS-AI will be evaluated.

11.4 Immunogenicity Analyses

The incidence of antibodies to sirukumab will be summarized for all subjects who have appropriate samples. Additional analysis may be performed as needed.

11.5 Pharmacodynamic Analyses

Changes in the concentration of individual pharmacodynamic markers from baseline to the selected post treatment time points will be summarized. Association between baseline levels and changes from baseline in select biomarkers and clinical response will be explored. Baseline value is defined as the baseline value of study CNT0136ARA3002 or CNT0136ARA3003, respectively. The pharmacodynamic analysis will characterize the response of subjects to sirukumab, to determine if loss of response to sirukumab can be predicted, and to better understand RA. Data will be summarized in a separate technical report.

11.6 Pharmacogenetics (DNA) Analyses

Pharmacogenetics tests will be summarized by treatment group. Genetic factors and changes in expression of DNA methylation markers from baseline (CNTO136ARA3002 and CNTO136ARA3003 studies) to the collection time point in study CNTO136ARA3004 will also be summarized. The pharmacogenetic analyses will be summarized in a separate technical report.

11.7 Health Economics Analyses

Change from baseline in total and domain scores of the WLQ and HECONQ will be summarized over time. Baseline value is defined as the baseline value of study CNTO136ARA3002 or CNTO136ARA3003, respectively.

11.8 Safety Analyses

Adverse Events

The verbatim terms used in the eCRF by investigators to identify AEs will be coded using the MedDRA dictionary. All reported AEs with onset during the treatment phase (ie, treatment-emergent AEs and AEs that have worsened since baseline) will be included in the analysis. For each AE, the percentage of subjects who experience at least 1 occurrence of the given event will be summarized by treatment group. Other safety analyses include the proportion of subjects with infections, SAE, AE leading to discontinuation.

Summaries, listings, datasets, or subject narratives may be provided, as appropriate, for those subjects who die, who discontinue treatment due to an AE, or who experience a severe or a serious adverse event (SAE).

Additional analyses will be performed for the number of subjects with cardiovascular SAEs by cardiovascular type and the number of subjects with malignancies by malignancy type (eg, lymphoma, nonmelanoma skin cancers, and other malignancies).

Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test. NCI-CTCAE grades will be used in the summary of laboratory data. For some laboratory data, which are not covered in the NCI-CTCAE grading criteria, shift tables and/or other abnormal cutoff levels may be used for summaries. Descriptive statistics will be calculated for selected laboratory analyte at baseline and at each scheduled time point. A listing of subjects with post-baseline abnormal laboratory results based on NCI-CTCAE grades will also be provided.

Vital Signs

The proportion of subjects with markedly abnormal post-baseline values will be summarized.

11.9 Interim Analysis

No formal interim analyses are planned, though analyses based on interim releases and locks may be carried out for integrated PK, immunogenicity, safety and efficacy data.

11.10 Data Monitoring Committee

An independent DMC will be established to monitor data on an ongoing basis to ensure the continuing safety of the subjects enrolled in this study. The committee will meet periodically to review interim data. After the review, the DMC will make recommendations regarding the continuation of the study.

The DMC will have 3 to 6 members who are independent of the Sponsor. None of the members will be participating in the current study. The DMC will consist of at least 1 medical expert in the relevant therapeutic area and at least 1 statistician. The members of the committee will be specified prior to study initiation. The major function of this committee will be to monitor the safety of the study agent and to provide recommendations for placing the study on hold or stopping the study in the event that any unanticipated serious events occur.

The DMC will conduct periodic safety reviews that will occur every 4 months until at a minimum, the study becomes open-label. The DMC may change the frequency or number of reviews based on interim safety findings. The safety reviews will focus on particular AEs, SAEs, and mortality.

SAE reports will be provided to the DMC members on an ongoing basis. The DMC will have access to unblinded data and review tabulated safety summaries (if appropriate) and any additional data that the DMC may request during the conduct of the study. No formal statistical hypothesis testing is planned. In addition, during the study, the Sponsor's study responsible physician (or designee) will regularly review blinded safety data from the sites and notify the DMC and appropriate Sponsor personnel of any issues.

The content of the safety summaries, the DMC role and responsibilities, and the general procedures (including communications) and their recommendations on the study conduct will be defined and documented in the DMC charter prior to the first DMC review.

11.11 Clinical Events Committee

The CEC is an independent committee composed of external specialists, blinded to treatment assignment, which will be commissioned to review case information on serious CV events (myocardial infarction, stroke, death, hospitalization for angina, hospitalization for TIA). The operations, processes, and definitions to be employed by the committee will be defined in the CEC charter.

12 ADVERSE EVENT REPORTING

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of subjects, investigators, and the Sponsor, and are mandated by regulatory agencies worldwide. The Sponsor has established Standard Operating Procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of safety information; all clinical studies conducted by the Sponsor or its affiliates will be conducted in accordance with those procedures.

12.1 Definitions

12.1.1 Adverse Event Definitions and Classifications

Adverse Event

An adverse event is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. An adverse event does not necessarily have a causal relationship with the treatment. An adverse event 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 related to that medicinal (investigational or non-investigational) product. (Definition per ICH)

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.

Note: The Sponsor collects adverse events starting with the signing of the ICF (see Section 12.3.1, All Adverse Events, for time of last adverse event recording).

Serious Adverse Event

A SAE based on ICH is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
(The subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a suspected transmission of any infectious agent via a medicinal product
- Is medically important*

*Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An adverse event is considered as unlisted, if the nature or severity is not consistent with the applicable product reference safety information. For an investigational product, the

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expectedness of an adverse event will be determined by whether or not it is listed in the Investigator's Brochure.

Adverse Event Associated with the Use of the Drug

An adverse event is considered associated with the use of the drug if the attribution is possible, probable, or very likely by the definitions listed in Section 12.1.2.

12.1.2 Attribution Definitions

Not Related

An adverse event that is not related to the use of the drug.

Doubtful

An adverse event for which an alternative explanation is more likely, eg, concomitant drug(s), concomitant disease(s), or the relationship in time suggests that a causal relationship is unlikely.

Possible

An adverse event that might be due to the use of the drug. An alternative explanation, eg, concomitant drug(s), concomitant disease(s), is inconclusive. The relationship in time is reasonable; therefore, the causal relationship cannot be excluded.

Probable

An adverse event that might be due to the use of the drug. The relationship in time is suggestive (eg, confirmed by dechallenge). An alternative explanation is less likely, eg, concomitant drug(s), concomitant disease(s).

Very Likely

An adverse event that is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation, eg, concomitant drug(s), concomitant disease(s). The relationship in time is very suggestive (eg, it is confirmed by dechallenge and rechallenge).

12.1.3 Severity Criteria

An assessment of severity grade will be made using the following general categorical descriptors:

Mild: Awareness of symptoms that are easily tolerated, causing minimal discomfort and not interfering with everyday activities.

Moderate: Sufficient discomfort is present to cause interference with normal activity.

Severe: Extreme distress, causing significant impairment of functioning or incapacitation. Prevents normal everyday activities.

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The investigator should use clinical judgment in assessing the severity of events not directly experienced by the subject (eg, laboratory abnormalities).

12.2 Special Reporting Situations

Safety events of interest on a Sponsor medicinal product that may require expedited reporting and/or safety evaluation include, but are not limited to:

- Overdose of a Sponsor medicinal product
- Suspected abuse/misuse of a Sponsor medicinal product
- Inadvertent or accidental exposure to a Sponsor medicinal product
- Medication error involving a Sponsor product (with or without subject/patient exposure to the Sponsor medicinal product, eg, name confusion)
- Adverse events that require expedited reporting include: cardiovascular AEs (myocardial infarction, stroke, death, hospitalization for angina, and hospitalization for TIA), newly identified malignancies, active TB, gastrointestinal perforations, and certain hepatobiliary events (that meet the criteria described in Section 10.2). Adverse events of special interest will be reported in the same timeframe as an SAE, even if they do not meet the requirements to be an SAE. Of note, all hepatobiliary events that meet criteria as described below, **must be reported as an SAE (see Section 12.4)**.
 - ALT or AST $\geq 3 \times$ ULN **and** bilirubin $\geq 2 \times$ ULN ($> 35\%$ direct) or
 - ALT or AST $\geq 3 \times$ ULN **and** INR > 1.5 (INR measurement is not required and the threshold value stated will not apply to patients receiving anticoagulants)

Special reporting situations should be recorded in the CRF. Any special reporting situation that meets the criteria of a SAE should be recorded on the SAE page of the CRF.

12.3 Procedures

12.3.1 All Adverse Events

All adverse events and special reporting situations, whether serious or non-serious, will be reported from the time a signed and dated ICF is obtained until completion of the subject's last study visit (which may include contact for follow-up of safety). SAEs, including those spontaneously reported to the investigator within 4 months after the last dose of study agent, must be reported using the Serious Adverse Event Form. The Sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

All events that meet the definition of a SAE will be reported as SAEs, regardless of whether they are protocol-specific assessments. Anticipated events will be recorded and reported as described in [Attachment 2](#). All adverse events, regardless of seriousness, severity, or presumed relationship to study therapy, must be recorded using medical terminology in the source document and the CRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the CRF their opinion

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concerning the relationship of the adverse event to study therapy. All measures required for adverse event management must be recorded in the source document and reported according to Sponsor instructions.

The Sponsor assumes responsibility for appropriate reporting of adverse events to the regulatory authorities. The Sponsor will also report to the investigator all SAEs that are unlisted (unexpected) and associated with the use of the drug. The investigator (or Sponsor where required) must report these events to the appropriate IEC/IRB that approved the protocol unless otherwise required and documented by the IEC/IRB.

Subjects (or their designees, if appropriate) must be provided with a "study card" indicating the following:

- Subject number
- Study site number
- Study number
- Sponsor's emergency contact name and 24-hour telephone number (for medical staff only)
- Investigator's name and contact information
- Statement in the local language(s) that the subject is participating in a clinical trial.

12.3.2 Serious Adverse Events

All SAEs occurring during clinical studies must be reported to the appropriate Sponsor contact person by investigational staff within 24 hours of their knowledge of the event.

Information regarding SAEs will be transmitted to the Sponsor using the Serious Adverse Event Form, which must be completed and signed by a member of the investigational staff, and transmitted to the Sponsor within 24 hours. The initial and follow-up reports of a SAE should be made by facsimile (fax).

All SAEs that have not resolved by the end of the study, or that have not resolved upon discontinuation of the subject's participation in the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value/status is available
- The event can be attributed to agents other than the study agent or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

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Suspected transmission of an infectious agent by a medicinal product will be reported as a SAE.

Any event requiring hospitalization (or prolongation of hospitalization) that occurs during the course of a subject's participation in a clinical study must be reported as a SAE, except hospitalizations for the following:

- Social reasons in the absence of an adverse event
- Surgery or procedure planned before entry into the study (must be documented in the CRF)

The cause of death of a subject in a clinical study within 4 months of the last dose, whether or not the event is expected or associated with the investigational agent, is considered a SAE.

12.3.3 Pregnancy

All initial reports of pregnancy must be reported to the Sponsor by the investigational staff within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes (eg, spontaneous abortion, stillbirth, and congenital anomaly) are considered SAEs and must be reported using the Serious Adverse Event Form. Any subject who becomes pregnant during the study must discontinue further study treatment.

Because the effect of the study agent on sperm is unknown, pregnancies in partners of male subjects included in the study will be reported by the investigational staff within 24 hours of their knowledge of the event using the appropriate pregnancy notification form.

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required after the subject's consent has been obtained.

- For women: The study doctor will ask for your permission to stay in contact with you throughout the length of the pregnancy.
- For men: The study doctor will ask for your permission and your partner's to stay in contact with your partner throughout the pregnancy.

12.4 Adverse Events of Special Interest

All initial reports of cardiovascular AEs (myocardial infarction, stroke, death, hospitalization for angina, hospitalization for TIA), newly identified malignancies, active TB, hepatobiliary abnormalities (as defined below), and gastrointestinal perforations must be reported to the Sponsor by the investigational staff within 24 hours of their knowledge of the event even if these events do not meet the definition of an SAE.

Investigators are also advised that active TB is considered a reportable disease in most countries.

These events are to be considered serious only if they meet the definition of a SAE.

Hepatobiliary events:

All events that meet criteria as described below **must be reported as an SAE.**

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- ALT or AST $\geq 3 \times$ ULN **and** bilirubin $\geq 2 \times$ ULN (>35% direct) or
- ALT or AST $\geq 3 \times$ ULN **and** INR > 1.5 (INR measurement is not required and the threshold value stated will not apply to patients receiving anticoagulants)

The following conditions should be considered AEs of special interest and require expedited reporting:

- a. ALT or AST $\geq 8 \times$ ULN
- b. ALT or AST $\geq 5 \times$ ULN for 2 or more weeks
- c. ALT or AST $\geq 3 \times$ ULN and total bilirubin $\geq 2 \times$ ULN (> 35% direct bilirubin) (or ALT or AST $\geq 3 \times$ ULN **and** INR > 1.5 , if INR measured) (see above)
- d. ALT or AST $\geq 3 \times$ ULN accompanied by clinical symptoms believed to be related to hepatitis or hypersensitivity such new or as worsening of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, or rash.
- e. ALT or AST $\geq 5 \times$ ULN but $< 8 \times$ ULN and cannot be monitored at least weekly for ≥ 2 weeks.

12.5 Contacting Sponsor Regarding Safety

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding safety issues or questions regarding the study are listed on the Contact Information page(s), which will be provided as a separate document.

13 PRODUCT QUALITY COMPLAINT HANDLING

A product quality complaint (PQC) is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, ie, any dissatisfaction relative to the identity, quality, durability, or reliability of a product, including its labeling or package integrity. PQCs may have an impact on the safety and efficacy of the product. The timely, accurate, and complete reporting and analysis of PQC information from clinical studies are crucial for the protection of subjects, investigators, and the Sponsor, and are mandated by regulatory agencies worldwide. The Sponsor has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information; all clinical studies conducted by the Sponsor or its affiliates will be conducted in accordance with those procedures.

13.1 Procedures

All initial PQCs must be reported to the Sponsor by the investigational staff within 24 hours after being made aware of the event.

If the defect is combined with an SAE, the investigational staff must report the PQC to the Sponsor according to the SAE reporting timelines (see Section 12.3.2) in addition to reporting the SAE to the Sponsor. A sample of the suspected product should be maintained for further investigation if requested by the Sponsor.

13.2 Contacting Sponsor Regarding Product Quality

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding product quality issues are listed on the Contact Information page(s), which will be provided as a separate document.

14 STUDY AGENT INFORMATION

14.1 Physical Description of Study Agent(s)

The sirukumab drug product provided for this study is supplied in a 1 mL PFS fitted with either: (1) a passive safety needle guard (UltraSafe Passive™ Delivery System, Safety Syringes, Inc.) that is permanently assembled on the syringe or (2) a spring-powered, disposable autoinjector device for SC administration of liquid biologic drug products (SmartJect™ Autoinjector) that is permanently assembled on the syringe. The sirukumab PFS is aseptically filled to 50 mg/1.0 mL and 100 mg/1.0 mL of sirukumab in a Becton-Dickinson (BD) Hypak®, 1 mL glass SCF™ (presiliconized) syringe barrel with a 26 gauge (G) ½ inch fixed needle, a non-latex-based elastomeric needle shield, and a fluoropolymer coated elastomeric plunger stopper. For a list of excipients, refer to the Investigator's Brochure for sirukumab.

Until the study is unblinded, study agent will be supplied in a 1 mL PFS fitted with either: (1) a passive safety needle guard (UltraSafe Passive™ Delivery System, Safety Syringes, Inc.) that is permanently assembled on the syringe or (2) a spring-powered, disposable autoinjector device for SC administration of liquid biologic drug products (SmartJect™ Autoinjector) that is permanently assembled on the syringe. Placebo for sirukumab PFS is aseptically filled to 1.0 mL of placebo solution in a BD Hypak®, 1 mL glass SCF™ (presiliconized) syringe barrel with a 26 G ½ inch fixed needle, a non-latex-based elastomeric needle shield, and a fluoropolymer coated elastomeric plunger stopper. For a list of excipients, refer to the Investigator's Brochure for sirukumab.

14.2 Packaging

The sirukumab PFS-U will be supplied with a passive safety needle guard (UltraSafe Passive™ Delivery System, Safety Syringes, Inc.) that is permanently assembled on the syringe.

Once available, the sirukumab PFS-AI will be supplied with a spring-powered, disposable device for SC administration of liquid biologic drug products (SmartJect™ Autoinjector) that is permanently assembled on the syringe.

14.3 Labeling

Study agent labels will contain information to meet the applicable regulatory requirements.

14.4 Preparation, Handling, and Storage

All study agent presentations should be stored in a secured refrigerator at 2°C to 8°C (36°F to 46°F). Study agent should not be frozen or shaken. During extended storage, protect from excessive exposure to light. Protection from light is not required during administration.

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Parenteral drug products should be inspected visually for particulate matter and discoloration before administration, whenever solution and container permit. If visibly opaque particles, discoloration, or other foreign particles are observed, the solution should not be used.

Study agent should be administered according to the instructions provided in the Site Investigational Product Procedures Manual.

Subjects who are able and who have been appropriately trained in the self-administration of study agent may self-administer study agent at home in accordance with Section 6.5. Study personnel will instruct subjects on how to transport, store and administer medication for at-home use as indicated for this protocol. Details will be provided in the Site Investigational Product Procedures Manual.

14.5 Drug Accountability

The study agents are to be prescribed only by the principal investigator (PI) or a qualified physician listed as a subinvestigator on required forms (eg, FDA Form 1572). Records should be kept on the study agent accountability form provided by the Sponsor or its designee. Administration of the study agent must be recorded in the subject's permanent record. The study agent may not be used for any purpose other than that outlined in this protocol, including other human studies, animal investigations, or in vitro testing.

Upon termination of the study or at the request of the Sponsor or its designee, the investigator must return all unused study agent to the Sponsor or its designee or if approved by the Sponsor, unused study agent can be destroyed directly at the site or locally by an approved destruction unit as described in the Site Investigational Product Procedures Manual.

The investigator is responsible for ensuring that all study agent received at the site is inventoried and accounted for throughout the study. The dispensing of study agent to the subject, and the return of study agent from the subject (if applicable), must be documented on the drug accountability form. Subjects must be instructed to return all used or unused study agent, whether empty or containing study agent. Subjects will receive a sharps container to dispose of used PFS fitted with UltraSafe Passive™ or autoinjector. Subjects will be instructed to return the sharps container and/or unused cartons with PFS-UltraSafe Passive™ or autoinjector. The study agent administered to the subject must be documented on the drug accountability form. All study agents will be stored and disposed of according to the Sponsor's instructions. Site staff must not combine contents of the study agent containers.

Study agent must be handled in strict accordance with the protocol and the container label, and must be stored at the study site in a limited-access area or in a locked cabinet under appropriate environmental conditions. Unused study agent must be available for verification by the Sponsor's site monitor during on-site monitoring visits. The return to the Sponsor of unused study agent, or used returned study agent for destruction, will be documented on the drug return form. When the site is an authorized destruction unit and study agent supplies are destroyed on site, this must also be documented on the drug return form.

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Study agent should be dispensed under the supervision of the investigator or a qualified member of the investigational staff, or by a hospital/clinic pharmacist. Study agent will be supplied only to subjects participating in the study. Returned study agent must not be dispensed again, even to the same subject. Study agent may not be relabeled or reassigned for use by other subjects. The investigator agrees neither to dispense the study agent from, nor store it at, any site other than the study sites agreed upon with the Sponsor.

15 STUDY-SPECIFIC MATERIALS

The investigator will be provided with the following:

- Investigator Brochure
- Site Investigational Product Procedures Manual
- Central Laboratory Manual
- ePRO Device and Manual
- MTX Toxicity Guidelines ([Appendix C](#))
- IVRS/IWRS User Guides and Worksheets

16 ETHICAL ASPECTS

16.1 Study-Specific Design Considerations

Potential subjects will be fully informed of the risks and requirements of the study, and during the study, subjects will be given any new information that may affect their decision to continue participation. They will be told that their consent to participate in the study is voluntary and may be withdrawn at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled. Only subjects who are fully able to understand the risks, benefits, and potential AEs of the study, and provide their consent voluntarily will be enrolled.

16.2 Regulatory Ethics Compliance

16.2.1 Investigator Responsibilities

The investigator is responsible for ensuring that the clinical study is performed in accordance with the protocol, current ICH guidelines on GCP, and applicable regulatory and country-specific requirements.

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of study subjects are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the clinical study data are credible.

16.2.2 Independent Ethics Committee or Institutional Review Board

Before the start of the study, the investigator (or Sponsor where required) will provide the IEC/IRB with current and complete copies of the following documents:

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- Final protocol and, if applicable, amendments
- Sponsor-approved ICF (and any other written materials to be provided to the subjects)
- Investigator's Brochure (or equivalent information) and amendments/addenda
- Sponsor-approved subject recruiting materials
- Information on compensation for study-related injuries or payment to subjects for participation in the study, if applicable
- Investigator's curriculum vitae or equivalent information (unless not required, as documented by the IEC/IRB)
- Information regarding funding, name of the Sponsor, institutional affiliations, other potential conflicts of interest, and incentives for subjects (unless not required, as documented by the IEC/IRB)
- Any other documents that the IEC/IRB requests to fulfill its obligation

This study will be undertaken only after the IEC/IRB has given full approval of the final protocol, amendments (if any), ICF, applicable recruiting materials, and subject compensation programs, and the Sponsor has received a copy of this approval. This approval letter must be dated and must clearly identify the IEC/IRB and the documents being approved.

Approval for the pharmacogenetics research component of the clinical study and for the pharmacogenetics ICF must be obtained from the IEC/IRB. Approval for the protocol can be obtained independent of approval for pharmacogenetics research.

During the study the investigator (or Sponsor where required) will send the following documents and updates to the IEC/IRB for their review and approval, where appropriate:

- Protocol amendments
- Revisions to ICF and any other written materials to be provided to subjects
- If applicable, new or revised subject recruiting materials approved by the Sponsor
- Revisions to compensation for study-related injuries or payment to subjects for participation in the study, if applicable
- New edition(s) of the Investigator's Brochure and amendments/addenda
- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually)
- Reports of adverse events that are serious, unlisted/unexpected, and associated with the investigational drug
- New information that may adversely affect the safety of the subjects or the conduct of the study
- Deviations from or changes to the protocol to eliminate immediate hazards to the subjects
- Report of deaths of subjects under the investigator's care

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- Notification if a new PI is responsible for the study at the site
- Development Safety Update Report (DSUR) Line Listings, where applicable
- Any other requirements of the IEC/IRB

For all protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data, or trial conduct), the amendment and applicable ICF revisions must be submitted promptly to the IEC/IRB for review and approval before implementation of the change(s).

At least once a year, the IEC/IRB will be asked to review and reapprove this clinical study. The reapproval should be documented in writing (excluding the ones that are purely administrative, with no consequences for subjects, data, or study conduct).

At the end of the study, the investigator (or Sponsor where required) will notify the IEC/IRB about the study completion.

16.2.3 Informed 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 and by the reviewing IEC/IRB and be in a language that the subject can read and understand. 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 enrollment in the study, the investigator or an authorized member of the investigational staff must explain to potential subjects the aims, methods, reasonably anticipated 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 they may withdraw consent to participate at any time. They will be informed that choosing to not participate will not affect the care the subject will receive for the treatment of his or her disease. Subjects will be told that alternative treatments are available if they refuse to take part and that such refusal will not prejudice future treatment. 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 and authorized Sponsor staff or delegate(s) 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 or her study physician to recontact the subject for the purpose of obtaining consent for additional safety evaluations, if needed, and subsequent disease-related treatments, or to obtain information about his or her survival status.

The subject will be given sufficient time to read the ICF and the opportunity to ask questions. After this explanation and before entry into the study, consent should be appropriately recorded

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by means of the subject's personally dated signature. After having obtained the consent, a copy of the ICF must be given to the subject.

Subjects will be asked to consent to participate in a pharmacogenetics research component of the study where local regulations permit. After informed consent for the clinical study is appropriately obtained, the subject will be asked to sign and personally date a separate pharmacogenetics informed consent form indicating agreement to participate in optional pharmacogenetics research. A copy of the signed pharmacogenetics informed consent form will be given to the subject. Refusal to participate in the pharmacogenetics research component of the study will not result in ineligibility for the clinical study.

A limited number of subjects will be asked to consent to participate in the Subject Lab Data Access and/or to complete the Placebell Multidimensional Personality Questionnaire. Refusal to participate in either the Subject Lab Access program or to complete the Placebell Multidimensional Personality Questionnaire will not result in ineligibility for the clinical study.

16.2.4 Privacy of Personal Data

The collection and processing of personal data from subjects enrolled in this study will be limited to those data that are necessary to fulfill the objectives of the 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.

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 or her 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.

The subject has the right to request through the investigator access to his or her personal data and the right to request rectification of any data that are not correct or complete. Reasonable steps will be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

Exploratory DNA and biomarker research will not be conducted under standards appropriate for the return of data to subjects. In addition, the Sponsor cannot make decisions as to the significance of any findings resulting from exploratory research. Therefore, exploratory research data will not be returned to subjects or investigators, unless required by law. Privacy and confidentiality of data generated in the future on stored samples will be protected by the same standards applicable to all other clinical data.

16.2.5 Country Selection

This study will only be conducted in those countries where the intent is to launch or otherwise help ensure access to the developed product, unless explicitly addressed as a specific ethical consideration in Section 16.1.

17 ADMINISTRATIVE REQUIREMENTS

17.1 Protocol Amendments

Neither the investigator nor the Sponsor will modify this protocol without a formal amendment by the Sponsor. All protocol amendments must be issued by the Sponsor, and signed and dated by the investigator. Protocol amendments must not be implemented without prior IEC/IRB approval, or when the relevant competent authority has raised any grounds for non-acceptance, except when necessary to eliminate immediate hazards to the subjects, in which case the amendment must be promptly submitted to the IEC/IRB and relevant competent authority. Documentation of amendment approval by the investigator and IEC/IRB must be provided to the Sponsor or its designee. When the change(s) involves only logistic or administrative aspects of the study, the IRB (and IEC where required) only needs to be notified.

During the course of the study, in situations where a departure from the protocol is unavoidable, the investigator or other physician in attendance will contact the appropriate Sponsor representative (see Contact Information page(s) provided separately). Except in emergency situations, this contact should be made before implementing any departure from the protocol. In all cases, contact with the Sponsor must be made as soon as possible to discuss the situation and agree on an appropriate course of action. The data recorded in the CRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

17.2 Regulatory Documentation

17.2.1 Regulatory Approval/Notification

This protocol and any amendment(s) must be submitted to the appropriate regulatory authorities in each respective country, if applicable. A study may not be initiated until all local regulatory requirements are met.

17.2.2 Required Prestudy Documentation

The following documents must be provided to the Sponsor before shipment of study agent to the investigational site:

- Protocol and amendment(s), if any, signed and dated by the PI
- A copy of the dated and signed, written IEC/IRB approval of the protocol, amendments, ICF, any recruiting materials, and if applicable, subject compensation programs. This approval must clearly identify the specific protocol by title and number and must be signed by the chairman or authorized designee.
- Name and address of the IEC/IRB, including a current list of the IEC/IRB members and their function, with a statement that it is organized and operates according to GCP and the applicable laws and regulations. If accompanied by a letter of explanation, or equivalent,

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from the IEC/IRB, a general statement may be substituted for this list. If an investigator or a member of the investigational staff is a member of the IEC/IRB, documentation must be obtained to state that this person did not participate in the deliberations or in the vote/opinion of the study.

- Regulatory authority approval or notification, if applicable
- Signed and dated statement of investigator (eg, Form FDA 1572), if applicable
- Documentation of investigator qualifications (eg, curriculum vitae)
- Completed investigator financial disclosure form from the PI, where required
- Signed and dated clinical trial agreement, which includes the financial agreement
- Any other documentation required by local regulations

The following documents must be provided to the Sponsor before enrollment of the first subject:

- Completed investigator financial disclosure forms from all clinical subinvestigators
- Documentation of sub investigator qualifications (eg, curriculum vitae)
- Name and address of any local laboratory conducting tests for the study, and a dated copy of current laboratory normal ranges for these tests, if applicable
- Local laboratory documentation demonstrating competence and test reliability (eg, accreditation/license), if applicable

17.3 Subject Identification, Enrollment, and Screening Logs

The investigator agrees to complete a subject identification and enrollment log to permit easy identification of each subject during and after the study. This document will be reviewed by the Sponsor study site contact for completeness.

The subject identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure subject confidentiality, no copy will be made. All reports and communications relating to the study will identify subjects by subject ID and date of birth. In cases where the subject is not randomized into the study, the date seen and date of birth will be used.

The investigator must also complete a subject screening log, which reports all subjects who were seen to determine eligibility for inclusion in the study.

17.4 Source Documentation

At a minimum, source documentation must be available for the following to confirm data collected in the CRF: subject identification, eligibility, and study identification; study discussion and date of informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all AEs and follow-up of AEs; concomitant medication; drug receipt/dispensing/return records; study agent administration information; and date of study completion and reason for early discontinuation of study agent or withdrawal from the study, if applicable.

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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. Specific details required as source data for the study will be reviewed with the investigator before the study and will be described in the monitoring guidelines (or other equivalent document).

Data which may be recorded directly into the CRF, if in accordance with site capabilities and/or in compliance with local regulations, will be considered source data, and will include but not be limited to the following:

- Blood pressure
- Weight

The following subject- and investigator-completed RA scales and assessments designated by the Sponsor will be recorded directly into an electronic device and will be considered source data.

- Swollen and tender joint assessments
- Patient’s Global Assessment of Disease Activity
- Physician’s Global Assessment of Disease Activity
- Patient’s Assessment of Pain
- HAQ-DI
- SF-36
- Duration of Morning Stiffness
- WLQ
- HECONQ

Multidimensional Personality Questionnaire recorded on paper will also be considered source data.

During the “at home administration” (AHA) phase of the study, subjects will enter information on their study agent administration on a patient diary.

17.5 Case Report Form Completion

Case report forms are provided for each subject in electronic format.

Electronic Data Capture will be used for this study. The study data will be transcribed by study personnel from the source documents onto an electronic CRF (eCRF), and transmitted in a secure manner to the Sponsor within the timeframe agreed upon between the Sponsor and the site. The electronic file will be considered to be the eCRF.

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Worksheets may be used for the capture of some data to facilitate completion of the eCRF. Any such worksheets will become part of the subject's source documentation. All data relating to the study must be recorded in eCRFs prepared by the Sponsor. Data must be entered into eCRFs in English. Designated site personnel must complete the eCRF as soon as possible after a subject visit, and the forms should be available for review at the next scheduled monitoring visit.

The investigator must confirm that all data are accurate and correct.

All eCRF entries, corrections, and alterations must be made by the investigator or other authorized study-site personnel. If necessary, queries will be generated in the eDC tool. The investigator or an authorized member of the investigational staff must adjust the eCRF (if applicable) and complete the query.

If corrections to an eCRF are needed after the initial entry into the eCRF, this can be done in 3 different ways:

- Site personnel can make corrections in the eDC tool at their own initiative or as a response to an auto query (generated by the eDC tool)
- Site manager can generate a query for resolution by the investigational staff
- Clinical data manager can generate a query for resolution by the investigational staff

17.6 Data Quality Assurance/Quality Control

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and associated personnel before the study, and periodic monitoring visits by the Sponsor, and direct transmission of clinical laboratory data from a central laboratory into the Sponsor's designee's data base. Written instructions will be provided for collection, preparation, and shipment of samples.

Guidelines for CRF completion will be provided and reviewed with study personnel before the start of the study. Whenever possible, all subjective measurements (eg, pain scale information or other questionnaires) should be completed as consistently as possible and preferably by the same individual who made the initial baseline determinations. The Sponsor will review CRFs for accuracy and completeness during on-site monitoring visits and after transmission to the Sponsor; any discrepancies will be resolved with the investigator or designee, as appropriate. After upload of the data into the clinical study database they will be verified for accuracy and consistency with the data sources.

17.7 Record Retention

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all 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 Trial, 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 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 investigational product. 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.

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.

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.

17.8 Monitoring

The Sponsor will perform on-site monitoring visits as frequently as necessary. At these monitoring visits, the monitor will compare the data entered into the CRFs with the hospital or clinic records (source documents). The monitor will record dates of the visits in a study site visit log that will be kept at the site.

Although the data for all subjects is eligible to be monitored, a streamlined approach to monitoring may be implemented, whereby a subset of subjects and/or critical data points will be verified as defined in the monitoring plan. The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the 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 (medical records) must be allowed for the purpose of verifying that the data recorded in the CRF are consistent with the original source data. Findings from this review of CRFs and source documents will be discussed with the investigational staff. The Sponsor expects that, during 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.

17.9 Study Completion/Termination

17.9.1 Study Completion

The study is considered completed with the last visit for the last subject participating in the study. The final data from the investigational site will be sent to the Sponsor (or designee) after completion of the final subject visit at that site, in the time frame specified in the Clinical Trial Agreement.

17.9.2 Study Termination

The Sponsor reserves the right to close the investigational site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Investigational sites will be closed upon study completion or after a formal DBL if the site has no active subjects. An investigational site is considered closed when all required documents and study supplies have been collected and a site closure visit has been performed.

The investigator may initiate site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of an investigational site by the Sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IEC/IRB or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of the subjects by the investigator
- Discontinuation of further drug development

17.10 On-Site Audits

Representatives of the Sponsor's clinical quality assurance department may visit the site at any time during or after completion of the study to conduct an audit of the study in compliance with regulatory guidelines and company policy. These audits will require access to all study records, including source documents, for inspection and comparison with the CRFs. Subject privacy must, however, be respected. The investigator and staff are responsible for being present and available for consultation during routinely scheduled site audit visits conducted by the Sponsor or its designees.

Similar auditing procedures may also be conducted by agents of any regulatory body, either as part of a national GCP compliance program or to review the results of this study in support of a regulatory submission. The investigator should immediately notify the Sponsor if they have been contacted by a regulatory agency concerning an upcoming inspection.

17.11 Use of Information and Publication

All information, including but not limited to information regarding sirukumab or the Sponsor's operations (eg, patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the Sponsor to the investigator and not previously published, and any data, generated as a result of this study, are considered

confidential and remain the sole property of the Sponsor. The investigator agrees to maintain this information in confidence and use this information only to accomplish this study, and will not use it for other purposes without the Sponsor's prior written consent.

The investigator understands that the information developed in the clinical study will be used by the Sponsor in connection with the continued development of sirukumab, and thus may be disclosed as required to other clinical investigators or regulatory agencies. To permit the information derived from the clinical studies to be used, the investigator is obligated to provide the Sponsor with all data obtained in the study.

The results of the study will be reported in a CSR generated by the Sponsor and will contain CRF data from all investigational sites that participated in the study, clinical laboratory data from a central laboratory, and other data such as IVRS/IWRS data and x-ray data into the Sponsor's designee's database.

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the CSR. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at the Sponsor's site or other mutually-agreeable location.

The Sponsor will also provide all investigators with the summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate. The Sponsor will provide each investigator with the unblinding codes for their site only after completion of the full statistical analysis. Results of exploratory biomarker analyses performed after the CSR has been issued may be reported in a separate report and will not require a revision of the CSR. Study subject identifiers will not be used in publication of exploratory biomarker results. Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the investigator as provided for below) shall be the property of the Sponsor as author and owner of copyright in such work.

The Sponsor shall have the right to publish such data and information without approval from the investigator. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to the Sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the Sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the Sponsor will review these issues with the investigator. The Sponsor will not mandate modifications to scientific content and does not have the right to suppress information. For multicenter study designs and substudy approaches, secondary results generally should not be published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multicenter study by not submitting for publication data derived from the individual site until the combined results from the completed study have been submitted for publication, within 12 months of the availability of the final data (tables, listings, graphs), or the Sponsor confirms there will be no multicenter study publication. Authorship of publications

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resulting from this study will be based on the guidelines on authorship, such as those described in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, which state that the named authors must have made a significant contribution to the design of the study or analysis and interpretation of the data, provided critical review of the paper, and given final approval of the final version.

Registration of Clinical Studies and Disclosure of Results

The Sponsor will register and/or disclose the existence of and the results of clinical studies as required by law. The Sponsor aims to post results summary to the appropriate publicly available registers no later than 8 months after the last subject's last visit (LSLV). In addition, the aim is to submit a manuscript to a peer-reviewed journal for publication within 12 months of LSLV.

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ATTACHMENT 1: PROTOCOL HISTORY

- Original Protocol: 20 March 2012
- [Amendment 1](#): 06 Mar 2013
- [Amendment 2](#): 01 May 2014
- [Amendment 3](#): 06 Oct 2016

AMENDMENT 1 – 06 MARCH 2013

- The protocol has been revised to incorporate this amendment, which applies to all study centers. The rationale and description of the changes to the protocol are provided below. Minor formatting and typographical errors have also been corrected to improve the clarity and accuracy of the protocol text; these changes do not affect the overall conduct of the study.

1. The overall rationale for the study has been updated

An additional rationale for the study has been added.

Sections Affected	Original Content	Amended/New Content
1.2 Overall Rationale of the Study	This is a parallel-group long-term extension (LTE) trial of studies CNTO136ARA3002 and CNTO136ARA3003 to assess safety and efficacy of sirukumab in subjects with moderately to severely active RA.	This is a parallel-group long-term extension (LTE) trial of studies CNTO136ARA3002 and CNTO136ARA3003 to assess the long-term safety and efficacy of sirukumab in subjects with moderately to severely active RA.
	None	Additionally, a substudy of enrolled subjects in CNTO136ARA3004 will further assess the usability of the SmartJect™ Autoinjector (PFS-AI).
3.2 Study Design Rationale	None	Additionally, this study is designed to obtain experience in the use of the SmartJect™ Autoinjector (PFS-AI) in all subjects enrolled in CNTO136ARA3004. More data regarding the usability of the autoinjector will be evaluated in the PFS-AI substudy. Additional details are provided in Section 9.6.

2. Clarification of the primary objective has been made

Clarification of the primary objective has been made

Sections Affected	Original Content	Amended/New Content
Synopsis Primary Objective	To evaluate the long-term safety of sirukumab in subjects with RA.	To evaluate the long-term safety of sirukumab in subjects with RA who are refractory to DMARDs or anti-TNFα agents.
2.1 Primary Objective		

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3. The secondary objectives have been updated

An additional secondary objective has been added

Sections Affected	Original Content	Amended/New Content
Synopsis Secondary Objectives Synopsis Secondary Objectives	None None	Pharmacogenetics PFS-AI usability (as defined in a separate substudy protocol)
2.1 Primary Objective	None	PFS-AI usability (as defined in a separate substudy protocol)

4. The duration of blinded/open-label treatment has been described

Clarification of the duration of blinded/open-label treatment has been made.

Sections Affected	Original Content	Amended/New Content
Synopsis Overview of Study Design 3.1 Overview of Study design	Subjects will receive blinded treatment in this study until after the Week 52 DBL occurs in CNTO136ARA3002 and the Week 24 DBL occurs in CNTO136ARA3003.	Study treatment will remain blinded in CNTO136ARA3004 until the following 3 conditions have been met: the Week 52 DBL occurs in study CNTO136ARA3002, the Week 24 DBL occurs in study CNTO136ARA3003, and the last AI usability substudy subject completes the Week 16 visit or terminates from the study.
3.2.2 Treatment Groups, Dosage, and Dose Administration Interval	Subjects will continue to receive the dosing regimen they received at the Week 104 (CNTO136ARA3002) and at Week 52 visit (CNTO136ARA3003) in blinded fashion until after the Week 52 DBL in CNTO136ARA3002 and the Week 24 DBL in CNTO136ARA3003.	Subjects will continue to receive the same dosing regimen they received at the Week 104 (CNTO136ARA3002) and at Week 52 visit (CNTO136ARA3003) in blinded fashion until the following 3 conditions have been met: the Week 52 DBL occurs in study CNTO136ARA3002, the Week 24 DBL occurs in study CNTO136ARA3003, and the last AI usability substudy subject completes the Week 16 visit or terminates from the study. Thereafter the same treatment assignment will be continued, but the study will no longer be blinded and will become open-label.
3.2.4 Study Control, Randomization, and Blinding	Blinded matching placebo injections will be used to reduce potential bias during data collection and evaluation of clinical endpoints and will be maintained until after the	Blinded matching placebo injections will be used to reduce potential bias during data collection and evaluation of clinical endpoints and will be maintained until the

5.2 Blinding	<p>Week 52 DBL in CNTO136ARA3002 and the Week 24 DBL in CNTO136ARA3003.</p> <p>The study will remain blinded until after the Week 52 DBL in CNTO136ARA3002 and the Week 24 DBL in CNTO136ARA3003.</p>	<p>following 3 conditions have been met: the Week 52 DBL occurs in study CNTO136ARA3002, the Week 24 DBL occurs in study CNTO136ARA3003, and the last AI usability substudy subject completes the Week 16 visit or terminates from the study.</p> <p>The study will remain blinded until the following 3 conditions have been met: the Week 52 DBL occurs in study CNTO136ARA3002, the Week 24 DBL occurs in study CNTO136ARA3003, and the last AI usability substudy subject completes the Week 16 visit or terminates from the study.</p>
9.1.2 Double-Blinded Treatment Phase	<p>Subjects will have clinic visits per the Time and Events Schedule until after the Week 52 DBL in CNTO136ARA3002 and the Week 24 DBL in CNTO136ARA3003 to receive blinded active study agent treatment.</p>	<p>Subjects will receive blinded study agent treatments according to the Time and Events Schedule until the following 3 conditions have been met: the Week 52 DBL occurs in study CNTO136ARA3002, the Week 24 DBL occurs in study CNTO136ARA3003, and the last AI usability substudy subject completes the Week 16 visit or terminates from the study.</p>
9.1.3 Open-Label Treatment Phase	<p>After the Week 52 DBL in CNTO136ARA3002 and the Week 24 DBL in CNTO136ARA3003 subjects will receive open-label study agent treatment through the end of study.</p>	<p>The CNTO136ARA3004 study will become open-label after the following 3 conditions have been met: the Week 52 DBL occurs in study CNTO136ARA3002, the Week 24 DBL occurs in study CNTO136ARA3003, and the last AI usability substudy subject completes the Week 16 visit or terminates from the study.</p>

5. A short summary of the SmartJect™ autoinjector has been added

A short summary of the SmartJect™ autoinjector to be introduced in this study has been added.

Sections Affected	Original Content	Amended/New Content
<p>Synopsis Overview of Study design Synopsis Self-administration 3.1 Overview of Study Design</p>	<p>None</p>	<p>The SmartJect™ Autoinjector (PFS-AI) is expected to be used by the majority of subjects in study CNTO136ARA3004. In the event PFS-AIs are unavailable at the time of a subject’s enrollment in this protocol, sirukumab PFS-UltrSAFE (PFS-U), the same device used in the CNTO136ARA3002 and CNTO136ARA3003 studies, will be provided until such time as the PFS-AIs become available. Upon</p>

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		availability of PFS-AI trial supplies, subjects who are newly entering the CNTO136ARA3004 protocol will be trained on the operation of PFS-AI and perform self-administration of study agent using PFS-AI at the Week 2 study visit and return to the study site at Week 4 for self-administration with PFS-AI. In the event PFS-AIs are unavailable at the time of a subject's enrollment in this protocol, training on the use of a PFS-AI will be provided at the next study visit when the PFS-AI is available.
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6. Clarification on the overview of the study design have been made

Clarifications on the overview of the study design have been made.

Sections Affected	Original Content	Amended/New Content
Synopsis Overview of Study Design	In study CNTO136ARA3002, after the completion of the Week 104 visit (evaluations and study agent administration), the subject will sign the informed consent form (ICF) and enter the long-term extension (LTE) study CNTO136ARA3004. As a result, the Week 104 visit in study CNTO136ARA3002 will correspond to the Week 0 visit in the CNTO136ARA3004 study. The duration of study CNTO136ARA3002 is 2 years and the duration of study CNTO136ARA3004 is approximately 3 years for a total of 5 years.	During the Week 104 visit in CNTO136ARA3002 or the Week 52 visit in CNTO136ARA3003, subjects will sign the informed consent form (ICF) to enter the LTE study CNTO136ARA3004. As a result, the Week 104 visit in study CNTO136ARA3002 and the Week 52 visit in study CNTO136ARA3003 will correspond to the Week 0 visit in the CNTO136ARA3004 study.
3.1 Overview of Study Design	The long-term extension (LTE) study will start after subjects have completed participation in studies CNTO136ARA3002 or CNTO136ARA3003. The purpose of this LTE study is to evaluate the safety, efficacy, and pharmacologic effects of sirukumab for a minimum duration of 3 years and a maximum duration of approximately 5 years. In study CNTO136ARA3002, after the completion of the Week 104 visit (evaluations and study agent	Subjects will become eligible to participate in this LTE study when they have completed participation in studies CNTO136ARA3002 (104 weeks) or CNTO136ARA3003 (52 weeks). The purpose of this LTE study is to evaluate the safety, efficacy, and pharmacologic effects of sirukumab for a minimum duration of 1 to 4 additional years and a maximum total duration of approximately 5 years across the combined protocols (CNTO136ARA3002 (2 years) or CNTO136ARA3003 (1 year) + CNTO136ARA3004 (1 to 4 years) = maximum of 5 years treatment). During the Week 104 visit in CNTO136ARA3002 or the Week 52 visit in CNTO136ARA3003, subjects will sign

	<p>administration), the subject will sign the informed consent form (ICF) and enter the long-term extension (LTE) study CNTO136ARA3004. As a result, the Week 104 visit in study CNTO136ARA3002 will correspond to the Week 0 visit in the CNTO136ARA3004 study. The duration of study CNTO136ARA3002 is 2 years and the duration of study CNTO136ARA3004 is approximately 3 years for a total of 5 years.</p> <p>Similarly, in study CNTO136ARA3003, after the completion of the Week 52 visit (evaluations and study agent administration), the subject will sign the ICF and enter the LTE study CNTO136ARA3004. As a result, the Week 52 visit in study CNTO136ARA3003 will correspond to the Week 0 visit in the CNTO136ARA3004 study. The duration of study CNTO136ARA3003 is 1 year and the duration of study CNTO136ARA3004 is approximately 4 years for a total of 5 years.</p> <p>If sirukumab becomes approved and available for use for RA in the subject's country of residence, the subject may be discontinued from study agent administrations and will have the opportunity to discuss treatment options with their treating physician under the following conditions:</p> <ul style="list-style-type: none"> • For subjects from study CNTO136ARA3002, after a minimum of 1 year in this study • For subjects from study CNTO136ARA3003, after a minimum of 2 years in this study <p>The maximum duration of this study is expected to be 208 weeks, followed by approximately 16 weeks of safety and efficacy follow-up after the administration of the final study agent injection of sirukumab.</p>	<p>the informed consent form (ICF) to enter the LTE study CNTO136ARA3004. As a result, the Week 104 visit in study CNTO136ARA3002 and the Week 52 visit in study CNTO136ARA3003 will correspond to the Week 0 visit in the CNTO136ARA3004 study.</p> <p>After a minimum of 1 year treatment in CNTO136ARA3004 for subjects from study CNTO136ARA3002, or a minimum of 2 years of treatment in CNTO136ARA3004 for subjects from CNTO136ARA3003, and after sirukumab is approved for the treatment of RA in the subject's country of residence, the Sponsor may no longer offer study treatment in CNTO136ARA3004 for those specific subjects. At that point the subject will have the opportunity to discuss treatment options with their treating physician.</p> <p>The maximum duration of participation in this study is 208 weeks, followed by approximately 16 weeks of safety and efficacy follow-up after the administration of the final study agent injection of sirukumab.</p>
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7. Clarification on pharmacogenetics blood sample has been made

Clarification on pharmacogenetics blood sample has been made.

Sections Affected	Original Content	Amended/New Content
3.1 Overview of Study Design	A pharmacogenetics blood sample to assess DNA methylation will be collected from subjects who consent separately to the pharmacogenetics component of the study where local regulations permit. Participation in the pharmacogenetics research is optional.	A pharmacogenetics blood sample to assess genetic factors such as DNA methylation patterns will be collected from subjects who consent separately to the pharmacogenetics component of the study where local regulations permit. Participation in the pharmacogenetics research component of this study is optional.

8. Figure 1 representing the study design has been updated

Panel A in Figure 1 describing the study design has been updated.

Sections Affected	Original Content	Amended/New Content
3.1 Overview of Study Design	CNTO136ARA3004 will become an open-label study after the 52-Week DBL in CNTO136ARA3002 and the 24-Week DBL in CNTO136ARA3003 have occurred.	Deleted.

9. Clarification on the study phases and duration of treatment have been made

Clarifications on the study phases and duration of treatment have been made.

Sections Affected	Original Content	Amended/New Content
3.2.3 Study Phases and Duration of Treatment	<p>There will be 3 phases of this LTE study: Blinded active treatment, open-label treatment, and safety and efficacy follow-up.</p> <p>The blinded active treatment phase of the study will be from Week 0 until after the Week 52 DBL in CNTO136ARA3002 and the Week 24 DBL in CNTO136ARA3003.</p> <p>The open-label treatment phase of the study will begin after the Week 52 DBL in CNTO136ARA3002 and the Week 24 DBL in CNTO136ARA3003.</p> <p>The safety and efficacy follow-up phase of the study will be approximately 16 weeks from the last administration of study agent or is discontinued permanently from study agent (early). The safety and efficacy follow-up allows for</p>	<p>There will be 3 phases of this LTE study: Blinded active treatment, open-label treatment, and safety and efficacy follow-up.</p> <p>As described in Section 3.2.2, the blinded active treatment phase will continue until following 3 conditions have been met: the Week 52 DBL occurs in study CNTO136ARA3002, the Week 24 DBL occurs in study CNTO136ARA3003, and the last AI usability substudy subject completes the Week 16 visit or terminates from the study.</p> <p>The open-label treatment phase of the study will begin after those 3 conditions have been met, and will continue through the last scheduled dose for all subjects. The safety and efficacy follow-up will include</p>

	<p>monitoring of the subject for a period of equivalent to at least 5 times the half-life of sirukumab.</p> <p>The duration of the study is expected to be 156 weeks for subjects enrolling after participation in CNTO136ARA3002 and 208 weeks for subjects enrolling after participation in CNTO136ARA3003, followed by approximately 16 weeks of safety and efficacy follow-up after the administration of the final study agent injection of sirukumab.</p>	<p>approximately 16 weeks of study evaluations following the last administration of study agent, including follow-up for patients who discontinued study treatment prior to their last scheduled dose. The safety and efficacy follow-up allows for monitoring of the subject for a period of equivalent to at least 5 times the half-life of sirukumab.</p> <p>The maximum duration of the study is expected to be 156 weeks for subjects enrolling after participation in study CNTO136ARA3002 and 208 weeks for subjects enrolling after participation in study CNTO136ARA3003, followed by approximately 16 weeks of safety and efficacy follow-up after the administration of the final study agent injection of sirukumab.</p> <p>After a minimum of 1 year treatment in CNTO136ARA3004 for subjects from study CNTO136ARA3002, or a minimum of 2 years of treatment in CNTO136ARA3004 for subjects from CNTO136ARA3003, and after sirukumab is approved for the treatment of RA in the subject’s country of residence, the Sponsor may no longer offer study treatment in CNTO136ARA3004 for those specific subjects. At that point the subject will have the opportunity to discuss treatment options with their treating physician.</p>
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9. Figure 1 representing the study design has been updated

Panel A in Figure 1 describing the study design has been updated.

Sections Affected	Original Content	Amended/New Content
3.1 Overview of Study Design	CNTO136ARA3004 will become an open-label study after the 52-Week DBL in CNTO136ARA3002 and the 24-Week DBL in CNTO136ARA3003 have occurred.	Deleted.

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10. Clarification of study status for the CNTO136ARA3002 and CNTO136ARA3003

Clarification of the status for the CNTO136ARA3002 and CNTO136ARA3003 has been made

Sections Affected	Original Content	Amended/New Content
3.2.5 Efficacy Evaluations	The efficacy evaluations chosen for this study are consistent with those in main studies CNTO136ARA3002 and CNTO136ARA3003.	The efficacy evaluations chosen for this study are consistent with those in primary studies CNTO136ARA3002 and CNTO136ARA3003.
Synopsis Dosing Regimen 6.1 Dosing Regimen	Subjects will continue to receive the sirukumab dosing regimen they received at the end of the main primary studies (CNTO136ARA3002, CNTO136ARA3003).	Subjects will continue to receive the sirukumab dosing regimen they received at the end of the primary studies (CNTO136ARA3002, CNTO136ARA3003).
9.2.1.1 Joint Assessments	If an assessor was trained by the Sponsor in the main studies (CNTO136ARA3002 and CNTO136ARA3003) or in a previous clinical study within the last 3 years and there is adequate documentation of this training (certification), that training will be considered adequate for this study.	If an assessor was trained by the Sponsor in the primary studies (CNTO136ARA3002 and CNTO136ARA3003) or in a previous clinical study within the last 3 years and there is adequate documentation of this training (certification), that training will be considered adequate for this study.

11. The paragraph detailing the CEC has been deleted

A paragraph regarding the CEC has been deleted as the information and consolidated under the heading ‘Cardiovascular events’

Sections Affected	Original Content	Amended/New Content
3.2.6 Safety Evaluations	The CEC is an independent committee composed of external specialists, blinded to treatment assignment, which will be commissioned to review case information on serious CV events (myocardial infarction, stroke, death, hospitalization for angina, hospitalization for TIA). The operations, processes, and definitions to be employed by the committee will be defined in the CEC charter.	Deleted.
Cardiovascular events	None.	The operations, processes, and definitions to be employed by the committee will be defined in the CEC charter.

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12. Additional details regarding the PFS-AI are provided

Additional details about the PFS-AI have been added.

Sections Affected	Original Content	Amended/New Content
3.2.11 Self-Administration	None.	The SmartJect™ AI platform technology device, referred to as PFS-AI, is a prefilled, spring-powered, single use, disposable device for the SC administration of a single dose of a liquid biologic drug product. The PFS-AI was designed as a platform device for several liquid biologic drug products and has a simple, universal design that is suitable for use by clinicians, caregivers, and patients, including those with hand impairment and pain in the hands and wrists resulting from diseases such as rheumatoid arthritis (RA), and psoriatic arthritis (PsA). The PFS-AI is designed to operate effectively in a number of hand orientations. Since the needle is shielded from sight at all times, the PFS-AI also accommodates those patients with a needle phobia who cannot tolerate seeing injections administered.

13. Inclusion criteria #3 has been deleted

Inclusion criteria #3 has been deleted.

Sections Affected	Original Content	Amended/New Content
4.1 Inclusion Criteria #3	Must be willing and able to complete the subject diaries correctly.	Deleted.
4.1 Inclusion Criteria#4	Sign the informed consent form (ICF) for pharmacogenetics research indicating willingness to participate in the pharmacogenetics component of the study (in order to participate in the optional pharmacogenetics component of this study) where local regulations permit. Refusal to give consent for this component does not exclude a subject from participation in the clinical study.	Sign an informed consent form (ICF) for pharmacogenetics research in order to participate in the optional pharmacogenetics component of this study, where local regulations permit. Refusal to give consent for this component does not exclude a subject from participation in this clinical study. The numbering has been appropriately cascaded.

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14. Prohibitions and Restrictions #1, #2, and #5 have been revised

Clarifications of Prohibitions and Restrictions #1, #2, and #5 have been made.

Sections Affected	Original Content	Amended/New Content
4.3 Prohibitions and Restrictions #1	If a woman of childbearing potential, she must remain on a highly effective method of birth control during the study and for 4 months after receiving the last study agent. If she is using hormonal contraceptives, she must use an additional non-hormonal birth control method. The exception to this restriction is if the subject or her male partner is sterilized; this situation does not require birth control.	If a woman of childbearing potential, she must remain on a highly effective method of birth control during the study and for 4 months after receiving the last study agent. If she is using hormonal contraceptives, she must use an additional non-hormonal birth control method. The exception to this restriction is if the subject or her male partner is sterilized; this situation does not require birth control. A woman must not to donate eggs (ova, oocytes) for the purposes of assisted reproduction during the study and for 4 months after receiving the last dose of study agent.
4.3 Prohibitions and Restrictions#2	If a man, he is to use an effective method of birth control and not donate sperm during the study and for 4 months after receiving the last dose of study agent. The exception to this is if the subject or his female partner is sterilized; this situation does not require birth control (see inclusion criteria #11).	Men must use an effective method of birth control during the study and for 4 months after receiving the last dose of study agent. The exception to this is if the subject or his female partner is sterilized. Also, men must not donate sperm during the study and for 4 months after receiving the last dose of study agent.
4.3 Prohibitions and Restrictions#5	Must agree not to receive an investigational medical device.	Must agree not to receive an investigational medical device or other investigational drugs.

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15. Clarifications to the dosing regimen have been made

Clarifications to the dosing regimen have been made.

Sections Affected	Original Content	Amended/New Content
6.1 Dosing Regimen	<p>Group 1: Sirukumab 100 mg SC at Weeks 0, 2, and q2 weeks through Week 156 for subjects who enrolled after completing participation in CNTO136ARA3002 and through Week 208 for subjects who enrolled after completing participation in CNTO136ARA3003.</p> <p>Group 2: Sirukumab 50 mg SC at Weeks 0, 4, and q4 weeks through Week 156 for subjects who enrolled after completing participation in CNTO136ARA3002 and through Week 208 for subjects who enrolled after completing participation in CNTO136ARA3003. Between sirukumab injections, placebo SC at Weeks 2, 6, and q4 weeks until the study becomes open-label.</p> <p>None</p>	<p>Group 1: Sirukumab 100 mg SC at Weeks 0 (administered as the last dose in CNTO136ARA3002 or CNTO136ARA3003), 2, and q2 weeks through Week 156 for subjects who enrolled after completing participation in CNTO136ARA3002 and through Week 208 for subjects who enrolled after completing participation in CNTO136ARA3003.</p> <p>Group 2: Sirukumab 50 mg SC at Weeks 0 (administered as the last dose in CNTO136ARA3002 or CNTO136ARA3003), 4, and q4 weeks through Week 156 for subjects who enrolled after completing participation in CNTO136ARA3002 and through Week 208 for subjects who enrolled after completing participation in CNTO136ARA3003. Between sirukumab injections, placebo SC injections will be administered at Weeks 2, 6, and q4 weeks until the study becomes open-label and placebo injections will be discontinued.</p> <p>After a minimum of 1 year treatment in CNTO136ARA3004 for subjects from study CNTO136ARA3002, or a minimum of 2 years of treatment in CNTO136ARA3004 for subjects from CNTO136ARA 3003, and after sirukumab is approved for the treatment of RA in the subject's country of residence, the Sponsor may no longer offer study treatment in CNTO136ARA3004 for those specific subjects. At that point the subject will have the opportunity to discuss treatment options with their treating physician.</p>

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16. Details regarding the training in the use of the PFS-AI have been added

Additional details regarding the training in the use of the PFS-AI have been made.

Sections Affected	Original Content	Amended/New Content
<p>Synopsis</p> <p>6.5 Self-Administration</p>	<p>Subjects who enrolled after completing participation in CNTO136ARA3002 may continue to administer the study agent at home for the duration of the study. Subjects who enrolled after participation in CNTO136ARA3003 may start at home administration (AHA) of the study agent after Week 0.</p> <p>Subjects unable or unwilling to self-administer will continue to have study agent injections performed by a health care professional at the study site. A caregiver may also be trained to administer study agent at home.</p> <p>Study personnel will instruct subjects on how to self-administer and on how to transport and store medication for at-home use as indicated for this protocol.</p>	<p>The SmartJect™ Autoinjector (PFS-AI) is expected to be used by the majority of subjects in study CNTO136ARA3004. In the event PFS-AIs are unavailable at the time of a subject’s enrollment in this protocol, PFS-U will be provided until such times as the PFS-AIs become available.</p> <p>Upon availability of PFS-AI trial supplies, subjects who are newly entering the CNTO136ARA3004 protocol will be trained on the operation of PFS-AI and perform self-administration of study agent using PFS-AI at the Week 2 study visit and return to the study site at Week 4 for self-administration with PFS-AI. The self-injection training consists of a face-to-face, “hands-on” training, with an explanation of each task in the Instructions For Use (IFU), a demonstration performed by the study site staff with the PFS-AI trainer device, followed by practice injections performed by the subject using the trainer device, until the study site staff and subject are satisfied that the injections can be performed as stated in the IFU. The step-by-step Training Guide for investigators or site staff to follow when providing training of subjects will be provided in the Site IP Procedures Manual. If subjects are competent in using PFS-AI, they will subsequently be provided with study agent for self-administration at home and instructed how to transport and store medication for at-home use as indicated for this protocol.</p> <p>Subjects may continue to administer the study agent at home for the duration of the study. Although additional face-to-face training sessions after the first training session are not scheduled, the site staff will be available to provide additional training if needed. If subjects or health care providers are uncertain about how to administer the study agent, the Sponsor recommends a review of the IFU and perform practice</p>

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		<p>injections with the PFS-AI trainer device, and if necessary, to ask for retraining at the study site. Subjects unable or unwilling to self-administer will continue to have study agent injections performed by a health care professional at the study site. A caregiver may also be trained to administer study agent at home. In the event PFS-AIs are unavailable at the time of a subject's enrollment in this protocol, training on the use of a PFS-AI will be provided at the next study visit when the PFS-AI is available. Once the study becomes open-label, the Week 2 visit for training may be skipped by subjects who are to receive open label sirukumab 50 mg q4 weeks and training in the use of an PFS-AI will be provided at Week 4.</p>
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17. The subsection on autoinjectors has been deleted

The section on autoinjectors has been deleted and the content been added to Section 6.5.

Sections Affected	Original Content	Amended/New Content
6.6 Autoinjector	At selected sites, study agent packaged in an autoinjector will be introduced for use in the study. At the Week 4 visit, a selected number of subjects (who have not been previously trained in one of the main studies) will be trained in the use of an autoinjector for the self-administration of the study agent.	Deleted.

18. Clarification on the coadministration of certain class of drugs has been made

Clarification on the coadministration of CYP3A4 substrate drugs has been made.

Sections Affected	Original Content	Amended/New Content
8.1.5 Drugs Metabolized by Cytochrome P450	Caution should also be exercised when sirukumab is coadministered with CYP3A4 substrate drugs, eg, oral contraceptives, certain statin medications (eg, simvastatin, atorvastatin, cerivastatin, lovastatin).	Since CYP3A4 is the major CYP enzyme and <i>in vitro</i> studies showed that IL-6 has a profound effect on CYP3A4, caution should also be exercised when sirukumab is coadministered with CYP3A4 substrate drugs, eg, oral contraceptives, certain statin medications (eg, simvastatin, atorvastatin, cerivastatin, lovastatin).

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19. The total blood volume to be collected has been revised

As a result of content change in Table 1, the total blood volume to be collected has been revised.

Sections Affected	Original Content	Amended/New Content
9.1.1 Overview	Also additional TB tests may be performed as determined necessary by the investigator or as required by local regulation. The total blood volume to be collected from each subject will be approximately 235 mL.	Also additional TB tests or tests for other infections may be performed as determined necessary by the medical monitor, study investigator or as required by local regulation. The total blood volume to be collected from each subject will be approximately 325 mL.

20. Clarifications on the posttreatment phase have been made

Clarifications on the posttreatment phase have been made.

Sections Affected	Original Content	Amended/New Content
9.1.4 Posttreatment Phase (Follow-Up) Paragraph 1	Subjects who discontinue study agent injections but do not terminate study participation, should also return for follow-up assessments through approximately 16 weeks after the last study agent injection as specified below.	Subjects who discontinue study agent injections but do not terminate study participation will continue to have assessments performed for 16 weeks following last injection according to the Time and Events Schedule (Table 2).
Paragraph 3	Subjects who discontinue study agent injections will have assessments performed according to the Time and Events Schedule (Table 2).	Deleted.

21. Clarification on the training for the joint assessor and back-up joint assessor have been made

Clarifications on training for the JA and back-up JA have been made.

Sections Affected	Original Content	Amended/New Content
9.2.1.1 Joint Assessments Joint Assessor	The Sponsor will provide training for each site's joint assessors and back-up joint assessors prior to the Week 0 visit of the first subject at each site.	The Sponsor will provide training for each site's designated joint assessor prior to the Week 0 visit of the first subject at each site. A back-up joint assessor must complete training before performing a joint assessment for a subject's study visit.
9.2.1.3 Patient's and Physician's Global Assessment of Disease Activity	In addition, the physician performing the global assessment cannot be the joint assessor described in Section 9.2.1.1.	Deleted.

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22. Clarification on the Work Limitations Questionnaire have been made

Questions in addition to the Work Limitations Questionnaire will not be added.

Sections Affected	Original Content	Amended/New Content
9.2.1.7 Work Limitations Questionnaire	The WLQ has been selected from existing instruments in order to generate estimates of work productivity and absenteeism. The WLQ is a brief, self-report questionnaire designed to enable investigators to obtain a sensitive measure of the degree to which employed individuals are experiencing limitations on-the-job due to their health problems and health-related productivity loss. ²² The WLQ has 25 items that ask respondents to rate their level of difficulty or ability to perform specific job demands. The 25 items are aggregated into 4 scales, time management, physical demands, mental-interpersonal, and output. Scale scores range from 0 (limited none of the time) to 100 (limited all of the time) and represent the reported amount of time in the prior 2 weeks that respondents were limited on-the-job. Additionally, 3 questions added to the beginning of the WLQ collect information on the amount of time in hours that an individual typically works per week and whether any time in hours was missed from work due to health problems.	The WLQ has been selected from existing instruments in order to generate estimates of work productivity and absenteeism. The WLQ is a brief, self-report questionnaire designed to enable investigators to obtain a sensitive measure of the degree to which employed individuals are experiencing limitations on-the-job due to their health problems and health-related productivity loss.²² The WLQ has 25 items that ask respondents to rate their level of difficulty or ability to perform specific job demands. The 25 items are aggregated into 4 scales, time management, physical demands, mental-interpersonal, and output. Scale scores range from 0 (limited none of the time) to 100 (limited all of the time) and represent the reported amount of time in the prior 2 weeks that respondents were limited on-the-job.

23. Clarifications on the collection of the last sample have been made

Clarifications on the timing of the collection of the last serum sample have been made.

Sections Affected	Original Content	Amended/New Content
9.3.1 Evaluations	Subjects who discontinue study participation should have serum samples collected at the final safety and efficacy follow-up visit.	Subjects who discontinue study participation should have serum samples collected at the last safety follow-up visit.

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24. Clarifications on the schedule for collection of blood samples have been made

Clarifications on the schedule for collection of blood samples have been made.

Sections Affected	Original Content	Amended/New Content
Synopsis Pharmacokinetic and Immunogenicity Evaluations	Blood samples for the measurement of serum sirukumab concentrations and the detection of antibodies to sirukumab will be collected from subjects who also had samples collected at earlier time points in studies CNTO136ARA3002 and CNTO136ARA3003 according to the Time and Events Schedule (Table 1).	Blood samples for the measurement of serum sirukumab concentrations and the detection of antibodies to sirukumab will be collected according to the Time and Events Schedule (Table 1).
9.3.2.1 Serum Collection and Handling	<p>Blood samples for the measurement of serum sirukumab concentrations will be collected as follows:</p> <ul style="list-style-type: none"> • For subjects who enrolled after participating in study CNTO136ARA3002 and had samples collected at earlier time points in that study will have a sample collected at Week 156 and the final safety and efficacy follow-up visit; • For subjects who enrolled after participating in study CNTO136ARA3003, samples will be collected at Weeks 4, 16, 28, 52, 208, and the final safety and efficacy follow-up visit. <p>The exact dates and times of blood sampling must be recorded on the laboratory requisition form. Note that if the subject is to receive an administration of study agent at that visit, blood samples will be collected prior to study agent administration.</p>	<p>Blood samples for the measurement of serum sirukumab concentrations will be collected at visits as shown in the Time and Events Schedules (Table 1 and Table 2). For subjects who had serum samples collected at earlier time points in study CNTO136ARA3002 (approximately 50% of randomized subjects in CNTO136ARA3002) and all subjects who enrolled after participating in study CNTO136ARA3003, serum samples will be collected at Weeks 2, 4, 16, 28, 52, 104, 156 and the final safety and efficacy follow-up visit (Table 1 and Table 2). One additional sample will be collected at Week 208 for subjects who enrolled after participating in study CNTO136ARA3003.</p>

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25. Clarifications on the collection of blood samples for immunogenicity evaluation have been made

Clarifications on the collection of blood samples for immunogenicity evaluation have been made.

Sections Affected	Original Content	Amended/New Content
9.3.3 Immunogenicity Assessment (Antibodies to Sirukumab)	<p>To assess the immunogenicity of sirukumab, blood samples for the detection of antibodies to sirukumab will be collected as follows:</p> <ul style="list-style-type: none"> For subjects who enrolled after participating in study CNTO136ARA3002 and had samples collected at earlier time points in that study will have a sample collected at Week 156 and the final safety and efficacy follow-up visit; For subjects who enrolled after participating in study CNTO136ARA3003, samples will be collected at Weeks 52, 208, and the final safety and efficacy follow-up visit. 	<p>To assess the immunogenicity of sirukumab, serum samples for the detection of antibodies to sirukumab will be collected at visits as shown in the Time and Events Schedules (Tables 1 and 2). For subjects who had serum samples collected at earlier time points in study CNTO136ARA3002 (approximately 50% of randomized subjects in CNTO136ARA3002) and all subjects who enrolled after participating in study CNTO136ARA3003, serum samples will be collected at Weeks 16, 28, 52, 104, 156 and the final safety and efficacy follow-up visit. One additional sample will be collected at Week 208 for subjects who enrolled after participating in study CNTO136ARA3003.</p>

26. Clarification on the planned pharmacodynamics evaluations have been made

Clarifications on the planned pharmacodynamics evaluations have been made.

Sections Affected	Original Content	Amended/New Content
Synopsis Pharmacodynamic Evaluations 9.4 Pharmacodynamic Evaluations	<p>The samples will be used to better understand the biology of RA, to provide a biological assessment of the response of patients to treatment with sirukumab, to analyze responders and to determine if the markers can be used to classify patients as potential responders to treatment.</p>	<p>Serum and whole blood samples for the analysis of pharmacodynamic markers will be collected according to the Time and Events Schedule. These samples will be used to better understand the biology of RA, to analyze differences between responders and non-responders, and to assess loss of response. The samples to be collected include whole blood for RNA, and serum for the evaluation of inflammation-associated proteins and other analytes such as but not limited to microRNAs.</p>

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27. Clarification on the planned pharmacogenetics evaluations have been made

Clarifications on the planned pharmacogenetics evaluations have been made

Sections Affected	Original Content	Amended/New Content
Synopsis Pharmacogenetics (DNA) Evaluations	DNA methylation testing will be performed to better understand the response of subjects to treatment with sirukumab. A whole blood sample will be collected for DNA methylation testing. Only DNA research related to sirukumab or to the diseases for which this drug is developed will be performed. Pharmacogenetic testing will be undertaken in this study in consenting subjects only.	Pharmacogenetic testing will be undertaken in this study for only those subjects who have provided voluntary consent. Assessment of genetic factors such as DNA methylation testing will be performed to better understand the response of subjects to treatment with sirukumab. A whole blood sample will be collected for DNA methylation testing. Only DNA research related to sirukumab or to the diseases for which this drug is developed will be performed.
9.5 Pharmacogenetics (DNA) Evaluations	Assessment of DNA methylation will be completed. Only DNA research related to sirukumab or to the diseases for which this drug is developed will be performed. Subjects participating in this portion of the study must sign a separate pharmacogenetics informed consent.	Assessment of genetic factors such as DNA methylation will be completed. Only DNA research related to sirukumab or to the diseases for which this drug is developed will be performed. Subjects who agree to participate in this optional portion of the study must sign a separate pharmacogenetics informed consent.

28. Details regarding the SmartJect™ Autoinjector substudy have been added

Details regarding the SmartJect™ Autoinjector substudy have been added.

Sections Affected	Original Content	Amended/New Content
Synopsis SmartJect™ Autoinjector substudy	None	In this substudy, a select number of subjects at selected sites in English-speaking countries who are enrolled in CNTO136ARA3004 will be consented and enrolled in the SmartJect™ AI Usability substudy. Site personnel in this substudy will observe and document 2 scheduled self-administrations of study agent by subjects using the PFS-AI. All substudy subjects will also complete an e-diary regarding their experiences with at-home use of PFS-AI.
9.6 SmartJect™ Autoinjector substudy	None	In this substudy, a select number of subjects at selected sites in English-speaking countries who are enrolled in CNTO136ARA3004 will be consented and enrolled in a SmartJect™ AI Usability substudy. Subjects will not

		<p>be required to participate in the substudy, and can enter the CNTO136ARA3004 LTE study independent of participation in the substudy. Subjects completing the substudy will return to the LTE study for the remainder of their study treatments. Site personnel in the substudy will observe and document 2 scheduled self-administrations of study agent by subjects using the PFS-AI. All substudy subjects will also complete an e-diary regarding their experiences with at-home use of PFS-AI for an additional 12 weeks of study treatment. A subset of these subjects will also have a detailed interview at their final substudy visit regarding their at-home-use experience. For additional details, refer to the PFS-AI Usability Substudy Protocol.</p>
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29. Clarifications on safety evaluations have been added

Clarifications on hepatitis B monitoring have been added.

Sections Affected	Original Content	Amended/New Content
9.8 Safety Evaluations	None	<p>Hepatitis B Monitoring</p> <p>Subjects who are HBsAg- /HBcAb+ only, without detectable HBV DNA, should be monitored according to local guidelines. If local guidelines do not exist for HBV monitoring in these types of patients, monitoring should be performed following consultation with a hepatitis B specialist.</p> <p>HBsAg- /HBsAb+ subjects who are HBcAb- or +, and without detectable HBV DNA, should be monitored if recommended under local guidelines related to HBV and biologic anti-rheumatic agents.</p>

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30. Clarification on the withdrawal from the pharmacodynamics and pharmacogenetics research

Clarifications on the withdrawal from the pharmacodynamics and pharmacogenetics research have been made.

Sections Affected	Original Content	Amended/New Content
10.3 Withdrawal from the Study	The samples may be used in method development or to better understand processes in the underlying disease. No pharmacogenetics testing will be conducted on these samples. This does not include those samples specifically collected for pharmacogenetic analysis for which separate optional consent was obtained.	<p>Withdrawal from Pharmacodynamic Research</p> <p>The subject may withdraw consent for pharmacodynamics research while remaining in the clinical study. In such a case, any stored samples will be destroyed upon communication from the site to the Sponsor. No pharmacogenetics testing will be conducted on these samples. This does not include those samples specifically collected for pharmacogenetic analysis for which separate optional consent was obtained.</p> <p>Withdrawal from Pharmacogenetics Research</p> <p>The subject may withdraw consent for pharmacogenetics research while remaining in the clinical study. In such a case, any DNA extracted from the subject's blood will be destroyed upon communication from the site to the Sponsor. If requested, the investigator will receive written confirmation from the Sponsor that the sample has been destroyed.</p>

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31. Clarifications on the pharmacokinetic analyses have been made

Clarifications on the pharmacokinetic analyses have been made.

Sections Affected	Original Content	Amended/New Content
Synopsis Pharmacokinetic and Immunogenicity Analyses	Serum sirukumab concentration data will be summarized by visit for each study. PK data may be displayed graphically. If sufficient samples are collected, trough serum sirukumab concentrations before and after switching from PFS to Autoinjector will be evaluated.	Serum sirukumab concentration data including C _{trough} will be summarized by visit . PK data may be displayed graphically. If sufficient samples are collected, steady-state trough serum sirukumab concentrations before and after switching from PFS-U to PFS-AI will be evaluated.
11.3 Pharmacokinetic Analyses	<p>Blood samples for the measurement of serum sirukumab concentrations and the detection of antibodies to sirukumab will be collected from subjects who had samples collected at earlier time points in studies CNTO136ARA3002 and CNTO136ARA3003 as delineated in the Time and Events Schedule (Table 1).</p> <p>Serum sirukumab concentration data will be summarized by visit for each study. PK data may be displayed graphically. If sufficient samples are collected, trough serum sirukumab concentrations before and after switching from pre-filled syringe (PFS) to Autoinjector will be evaluated.</p>	<p>Blood samples for the measurement of serum sirukumab concentrations and the detection of antibodies to sirukumab will be collected and analyzed.</p> <p>Serum sirukumab concentration data including C_{trough} will be summarized by visit. PK data may be displayed graphically. If sufficient samples are collected, steady-state trough serum sirukumab concentrations before and after switching from PFS-U to PFS-AI will be evaluated.</p>

32. Clarifications on the immunogenicity analyses have been made

Clarifications on the immunogenicity analyses have been made.

Sections Affected	Original Content	Amended/New Content
11.4 Immunogenicity Analyses	The incidence of antibodies to sirukumab will be summarized through the end of study for all subjects who have appropriate samples.	The incidence of antibodies to sirukumab will be summarized for all subjects who have appropriate samples. Additional analysis may be performed as needed.

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33. Clarifications on the pharmacodynamic analyses have been made

Clarifications on the pharmacodynamic analyses have been made.

Sections Affected	Original Content	Amended/New Content
Synopsis Pharmacodynamic Analyses 11.5 Pharmacodynamic Analyses	The pharmacodynamic analysis will characterize the response of subjects to sirukumab, loss of response, to determine if response to sirukumab can be predicted, and to understand RA. The analysis, along with the RNA analysis will be summarized in a separate technical report.	The pharmacodynamic analysis will characterize the response of subjects to sirukumab, to determine if loss of response to sirukumab can be predicted, and to better understand RA. Data will be summarized in a separate technical report.

34. Clarifications on the pharmacogenetics (DNA) analyses have been made

Clarifications on the pharmacogenetics (DNA) analyses have been made.

Sections Affected	Original Content	Amended/New Content
Synopsis Pharmacogenetics Analyses 11.6 Pharmacogenetics (DNA) Analyses	Pharmacogenetics data will be descriptively summarized by treatment group. Results will be presented in a separate technical report.	Pharmacogenetics tests will be summarized by treatment group. Genetic factors and changes in expression of DNA methylation markers from baseline (CNTO136ARA3002 and CNTO136ARA3003 studies) to the collection time point in study CNTO136ARA3004 will also be summarized. The pharmacogenetic analyses will be summarized in a separate technical report.

35. Clarifications on source documentation have been made

Clarifications on source documentation have been made.

Sections Affected	Original Content	Amended/New Content
17.4 Source Documentation	The following data may be recorded directly into the CRF, if in accordance with site capabilities and/or in compliance with local regulations, and will be considered source data: <ul style="list-style-type: none"> • Race • History of smoking • Blood pressure • Height and weight 	Deleted.

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36. Clarifications on data quality assurance and quality control have been made

Clarifications data quality assurance and quality control have been made

Sections Affected	Original Content	Amended/New Content
17.6 Data Quality Assurance/Quality Control	None	Whenever possible, all subjective measurements (eg, pain scale information or other questionnaires) should be completed as consistently as possible and preferably by the same individual who made the initial baseline determinations.

37. Clarifications on monitoring have been made

Clarifications on monitoring have been made

Sections Affected	Original Content	Amended/New Content
17.8 Monitoring	The Sponsor will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a study site visit log that will be kept at the site. The first post-initiation visit will be made as soon as possible after enrollment has begun. At these visits, the monitor will compare the data entered into the CRFs with the hospital or clinic records (source documents).	The Sponsor will perform on-site monitoring visits as frequently as necessary. At these monitoring visits, the monitor will compare the data entered into the CRFs with the hospital or clinic records (source documents). The monitor will record dates of the visits in a study site visit log that will be kept at the site. Although the data for all subjects is eligible to be monitored, a streamlined approach to monitoring may be implemented, whereby a subset of subjects and/or critical data points will be verified as defined in the monitoring plan.

38. Revisions in Table 1 have been summarized

Revisions within Table 1 and the accompanying legends are summarized.

Sections Affected	Original Content	Amended/New Content
Table 1 Times and Events in Long-term Extension	<p>a. All assessments are to be completed prior to study agent administration, unless otherwise specified. For subjects who discontinue study agent injections, see Table 2 for required follow-up assessments. Administration of study agent and visit windows will be within 7 days for all visits. Administration of study agent must occur no less than 7 days apart throughout the study.</p> <p>b. Last study agent administration for subjects who enrolled after participating in CNT0136ARA3002. These subjects will then have assessments as described in Table 2.</p> <p>c. For a select number of subjects, training in the use of an autoinjector will be provided for the self-administration of study agent.</p> <p>d. Urine pregnancy testing during the study for women of childbearing potential only.</p> <p>e. RA assessments include the following: patient pain assessment; patient global assessment of disease activity, physician global assessment of disease activity, Health Assessment Questionnaire-Disability Index, and duration of morning stiffness.</p> <p>f. Pharm serum samples (sirukumab concentration and antibodies to sirukumab) will be collected only from those subjects who enrolled after participating in study CNT0136ARA3003.</p> <p>g. On days of study agent administration, Pharm serum samples (sirukumab concentration and antibodies to sirukumab) must be collected prior to administration. Blood collected from one venipuncture will be divided into multiple aliquots of serum for Pharm serum (sirukumab concentration and antibodies to sirukumab) and backup samples. Refer to the Central Laboratory Manual for more detailed instructions.</p>	<p>a. All assessments are to be completed prior to study agent administration, unless otherwise specified. For subjects who discontinue study agent injections, see Table 2 for required follow-up assessments. Administration of study agent and visit windows should be within 7 days for all visits. Administration of study agent must occur no less than 7 days apart throughout the study.</p> <p>b. Once the study becomes open-label, the Week 2 visit will not be conducted for subjects in treatment Group 2. The training session for these subjects will occur at Week 4 or at a subsequent visit following the availability of the PFS-AI.</p> <p>c. Last study agent administration for subjects who enrolled after participating in CNT0136ARA3002. These subjects will then have follow-up assessments as described in Table 2.</p> <p>d. Last study agent administration for subjects who enrolled after participating in CNT0136ARA3003. These subjects will then have follow-up assessments as described in Table 2.</p> <p>e. Training in the use of a PFS-AI will be provided at the first scheduled visit that the subject receives the PFS-AI for the self-administration of study agent.</p> <p>f. Urine pregnancy testing during the study for women of childbearing potential only. Additional pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the subject's participation in the study.</p> <p>g. RA assessments include the following: patient pain assessment; patient global assessment of disease activity, physician global assessment of disease</p>

	<p>h. Pharm serum samples (sirukumab concentration and antibodies to sirukumab) will be collected only from those subjects who enrolled after participating in study CNTO136ARA3002 and had samples collected at earlier time points in study CNTO136ARA3002.</p> <p>i. An optional pharmacogenetics blood sample will be collected from those subjects who sign a separate consent form (where local regulations permit).</p>	<p>activity, Health Assessment Questionnaire-Disability Index, and duration of morning stiffness.</p> <p>h. Pharm serum samples (sirukumab concentration and antibodies to sirukumab) will be collected from subjects who had pharm serum samples collected at earlier time points in study CNTO136ARA3002 (approximately 50% of randomized subjects in CNTO136ARA3002) and from all subjects enrolled after participating in study CNTO136ARA3003.</p> <p>i. On days of study agent administration, Pharm serum samples (sirukumab concentration and antibodies to sirukumab) must be collected prior to administration. Blood collected from one venipuncture will be divided into 3 serum aliquots (1 each sirukumab concentration, antibodies to sirukumab and a backup sample). Refer to the Central Laboratory Manual for more detailed instructions.</p> <p>j. Pharm serum samples (sirukumab concentration and antibodies to sirukumab) will be collected only from those subjects who enrolled after participating in study CNTO136ARA3003.</p> <p>k. An optional pharmacogenetics blood sample will be collected from those subjects who sign a separate consent form (where local regulations permit).</p> <p>The legend alphabets were cascaded appropriately.</p> <p>Xs for urine pregnancy test, TB testing, and blood pressure evaluations have been removed from Week 2 and placed in Week 4. Additional Xs have been inserted for pharm serum samples for sirukumab concentration at Week 104 and for antibodies to sirukumab at Weeks 16, 28, and 104.</p>
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<p>Table 2 Times and Events in Safety and Efficacy Follow-up After Last Study Agent Injection or after Discontinuation of Study Agent</p>	<p>c Pharm serum samples (sirukumab concentration and antibodies to sirukumab) will be collected at the final safety and efficacy follow up visit only from those subjects who had samples collected at earlier time points in studies CNTO136ARA3002 and CNTO136ARA3003.</p> <p>d Blood collected from one venipuncture will be divided into multiple aliquots of serum for Pharm serum (sirukumab concentration and antibodies to sirukumab) and backup samples. Refer to the Central Laboratory Manual for more detailed instructions.</p>	<p>c Pharm serum samples (sirukumab concentration and antibodies to sirukumab) will be collected at the final safety and efficacy follow up visit only from those subjects who had pharm serum samples collected at earlier time points in study CNTO136ARA3002 (approximately 50% of randomized subjects in CNTO136ARA3002) and from all subjects enrolled after participating in study CNTO136ARA3003.</p> <p>d Blood collected from one venipuncture will be divided into 3 serum aliquots (1 each for sirukumab concentration, antibodies to sirukumab and a backup sample). Refer to the Central Laboratory Manual for more detailed instructions.</p>
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39. Editorial changes made throughout the protocol

A substantial number of editorial changes have been made throughout the protocol for clarity. These changes do not alter the meaning of the original text.

Sections Affected	Original Content	Amended/New Content
<p>Title page</p> <p>Synopsis</p> <p>Synopsis</p> <p>3.1 Overview of Study Design</p>	<p>A Multicenter, Parallel-group Study of Long-term Safety and Efficacy of CNTO 136 (sirukumab) for Rheumatoid Arthritis in Subjects Completing Treatment in CNTO136ARA3002 and CNTO136ARA3003</p> <p>The long-term extension (LTE) study will start after subjects have completed participation in studies CNTO136ARA3002 or CNTO136ARA3003. The purpose of this LTE study is to evaluate the safety, efficacy, and pharmacologic effects of sirukumab for a minimum duration of 3 years and a maximum duration of approximately 5 years.</p>	<p>A Multicenter, Parallel-group Study of Long-term Safety and Efficacy of CNTO 136 (sirukumab) for Rheumatoid Arthritis in Subjects Completing Treatment in Studies CNTO136ARA3002 (SIRROUND-D) and CNTO136ARA3003 (SIRROUND-T)</p> <p>Subjects will become eligible to participate in this LTE study when they have completed participation in studies CNTO136ARA3002 (104 weeks) or CNTO136ARA3003 (52 weeks). The purpose of this LTE study is to evaluate the safety, efficacy, and pharmacologic effects of sirukumab for a minimum duration of 1 additional year and a maximum total duration of approximately 5 years across the combined protocols (CNTO136ARA3002 (2 years) or CNTO136ARA3003 (1 year) + CNTO136ARA3004 (1 to 4 years) = maximum of 5 years treatment).</p>

<p>3.1 Overview of Study Design</p>	<p>Thereafter this study (CNTO136ARA3004) becomes open-label. Once this study becomes open-label, subjects in this study will receive unblinded study agent through IVRS/IWRS. However, when this study becomes open-label, those subjects who remain in studies CNTO136ARA3002 and CNTO136ARA3003 due to staggered enrollment will continue to receive blinded treatment until they complete participation in those studies.</p> <p>Serum samples will be used to evaluate PK and antibodies to sirukumab. Samples to be collected include serum and whole blood RNA for the evaluation of inflammation-associated proteins and other analytes. These samples will be used to better understand the biology of RA, to provide a biological assessment of the response of subjects to treatment with sirukumab, to analyze differences between responders and non-responders, to assess loss of response, and to determine if the markers can be used to classify patients as potential responders prior to treatment.</p> <p>Only 1 DBL (at the end of the study) is planned. Additional data releases or locks may occur periodically as needed.</p>	<p>Thereafter study CNTO136ARA3004 will become open-label and placebo injections are discontinued in the SC sirukumab 50 mg treatment group. Once study CNTO136ARA3004 becomes open-label, study subjects in this study will receive open-label study agent through IVRS/IWRS. However, when this study becomes open-label, any subjects who still remain in studies CNTO136ARA3002 and CNTO136ARA3003 due to staggered enrollment will continue to receive blinded treatment until they complete participation in those studies.</p> <p>Serum samples will be collected for the evaluation of sirukumab PK and antibodies to sirukumab. Other samples to be collected include serum and whole blood RNA for the evaluation of inflammation-associated proteins and other analytes. These samples will be used to better understand the biology of RA, to analyze differences between responders and non-responders, and to assess loss of response.</p> <p>Only 1 DBL (at the end of the study) is planned. Additional data releases or locks may occur as needed.</p>
<p>3.2.7 Pharmacokinetic Evaluations</p>	<p>Serum samples will be collected for evaluation of pharmacokinetics of sirukumab in subjects with RA according to the Time and Events Schedules.</p>	<p>To evaluate the PK of sirukumab in subjects with RA following long-term treatment, serum samples for the measurement of sirukumab concentrations will be collected according to the Time and Events Schedules.</p>
<p>Synopsis Blinding</p>	<p>To maintain the blind, all subjects will receive each administration of study agent as 1 SC injection as follows:</p>	<p>To maintain the blind, all subjects will receive study agent as 1 SC injection as follows:</p>
<p>6.2 Blinding</p>	<p>Group 1 (sirukumab 100 mg): 1.0 mL sirukumab 100 mg injection q2 weeks until the study becomes open-label. Group 2 (sirukumab 50 mg): 1.0 mL sirukumab 50 mg</p>	<p>Group 1 (sirukumab 100 mg): 1.0 mL sirukumab 100 mg injection q2 weeks</p>

<p>Synopsis Timing and Study Agent Administration 6.3 Timing and Study Agent Administration</p> <p>7 Treatment Compliance Paragraph 3</p> <p>8.1 Concomitant Therapy Paragraph 1 Paragraph 3</p> <p>8.1.3 Intra-articular Corticosteroids 9.1.1 Overview</p>	<p>injection q4 weeks until the study becomes open-label. Between sirukumab injections, placebo SC at Weeks 2, 6, and q4 weeks until the study becomes open-label.</p> <p>Through the end of the study, it is recommended that both the visit and the SC study agent administration be within 7 days from the scheduled visit day. The SC study agent administrations must always be at least 7 days apart.</p> <p>When subjects begin self-administration at home, the investigator or designated study personnel will maintain a log of all study agent dispensed and returned. When study agent is self-administered by subjects at home, the amount of study agent dispensed will be recorded and compared with the amount returned.</p> <p>All concomitant therapies must be recorded throughout the study, beginning with the administration of the first dose of the study agent at Week 0.</p> <p>The concomitant medication dose may be changed at the discretion of the investigator. Disease-modifying anti-rheumatic drug (DMARD) therapy is permitted at the discretion of the investigator (see Section 6.4), except for the specified prohibited medications (biologic immunosuppressive agents, cytotoxic drugs, and investigational agents; see Section 8.2).</p> <p>No intra-articular (IA) steroid injections should be administered between Weeks 48 and 52, between Weeks 100 and 104, between Weeks 152 and 156, and between Weeks 204 and 208 of this study.</p>	<p>Group 2 (sirukumab 50 mg): 1.0 mL sirukumab 50 mg injection q4 weeks until the study becomes open-label. Between sirukumab injections, placebo SC injections will be administered at Weeks 2, 6, and q4 weeks until the study becomes open-label, and placebo injections will be discontinued.</p> <p>Through the end of the study, it is recommended that both the visit and the SC study agent administration occur within 7 days of the scheduled visit day. The SC study agent administrations must always be at least 7 days apart.</p> <p>When subjects begin self-administration at home, the investigator or designated study personnel will maintain a log of all study agent dispensed and returned and the amount of study agent dispensed will be recorded and compared with the amount returned.</p> <p>All concomitant therapies must be recorded throughout the study, beginning at Week 0.</p> <p>The concomitant medication dose may be changed at the discretion of the investigator. Disease-modifying anti-rheumatic drug (DMARD) therapy is permitted at the discretion of the investigator (see Section 6.4), except for the specified prohibited medications (see Section 8.2).</p> <p>Intra-articular (IA) steroid injections should not be administered within 4 weeks prior to visits on Weeks 52, 104, 156, and 208.</p>
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<p>9.1.1 Overview Paragraph 5</p>	<p>At Week 0, a single whole blood sample for DNA analysis will be collected only from subjects who have consented to participate in the optional pharmacogenetics (DNA) component of the study.</p> <p>No intra-articular (IA) steroid injections should be administered between Weeks 48 and 52, between Weeks 100 and 104, between Weeks 152 and 156, and between Weeks 204 and 208 of this study.</p>	<p>A single whole blood sample for DNA analysis will be collected only from subjects who have consented to participate in the optional pharmacogenetics (DNA) component of the study.</p> <p>Intra-articular (IA) steroid injections should not be administered within 4 weeks prior to visits on Weeks 52, 104, 156, and 208.</p>
<p>9.1.3 Open-label Treatment Phase</p>	<p>Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the subject's participation in the study. Also additional TB tests may be performed as determined necessary by the investigator or as required by local regulation.</p> <p>After the Week 52 DBL in CNTO136ARA3002 and the Week 24 DBL in CNTO136ARA3003 subjects will receive open-label study agent treatment through the end of study. If sirukumab becomes approved and available for use for RA in the subject's country of residence, the subject may be discontinued from study agent administrations and will have the opportunity to discuss treatment options with their treating physician under the following conditions:</p> <ul style="list-style-type: none"> • For subjects from study CNTO136ARA3002, after a minimum of 1 year in this study • For subjects from study CNTO136ARA3003, after a minimum of 2 years in this study 	<p>Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the subject's participation in the study. Also additional TB tests or tests for other infections may be performed as determined necessary by the medical monitor, study investigator or as required by local regulation.</p> <p>The CNTO136ARA3004 study will become open-label after the following 3 conditions have been met: the Week 52 DBL occurs in study CNTO136ARA3002, the Week 24 DBL occurs in study CNTO136ARA3003, and the last AI usability substudy subject completes the Week 16 visit or terminates from the study.</p> <p>After a minimum of 1 year treatment in CNTO136ARA3004 for subjects from study CNTO136ARA3002, or a minimum of 2 years of treatment in CNTO136ARA3004 for subjects from CNTO136ARA3003, and after sirukumab is approved for the treatment of RA in the subject's country of residence, the Sponsor may no longer offer study treatment in CNTO136ARA3004 for those specific subjects. At that point the subject will have the opportunity to discuss treatment options with their treating physician.</p>

<p>9.7 Health Economics Evaluations</p>	<p>Health economics evaluations on employment status, impact of disease on daily productivity, and time lost from work will be collected at Weeks 28, 52, 76, 104, 128, 156, and 208. The impact of disease on patients’ daily work productivity will be measured using a VAS. The scale ranges from “not at all affected” to “affected very much”.</p>	<p>Health economics evaluations on employment status, impact of disease on daily productivity, and time lost from work will be collected. The impact of disease on patients’ daily work productivity will be measured using a VAS. The scale ranges from “not at all affected” to “affected very much”.</p>
<p>10.3 Withdrawal from the Study</p>	<p>If a subject discontinues study agent administration before the end of the study, follow-up assessments should be obtained as per the Time and Events Schedule described in Table 2. For details, see Section 10.3.</p>	<p>If a subject discontinues study agent administration before the end of the study, follow-up assessments should be obtained as per the Time and Events Schedule described in Table 2.</p>
<p>11 Statistical Methods Paragraph 3</p>	<p>Since the treatment groups are not randomly assigned in this study, no formal hypothesis testing is planned. The efficacy, safety, and PK/PD/immunogenicity analyses will be performed separately for subjects who complete each study of CNTO136ARA3002 and CNTO136ARA3003. The analyses will include all subjects enrolled in this study by study and by treatment group above.</p>	<p>Since the treatment groups are not randomly assigned in this study, no formal hypothesis testing is planned. The efficacy, safety, and PK/PD/immunogenicity analyses will be performed separately for subjects who complete studies CNTO136ARA3002 and CNTO136ARA3003. The analyses will include all subjects enrolled by study and by treatment group above.</p>
<p>Paragraph 4</p>	<p>Additional data releases or locks may occur periodically as needed. The analyses based on these data releases or locks intend to integrate data from CNTO136ARA3002 and CNTO136ARA3003 with this study for the long-term safety and efficacy data of all subjects enrolled in these studies. A separate SAP for integration will be developed to specify the analyses and data handling rules.</p>	<p>Additional data releases or locks may occur periodically as needed. The analyses based on these data releases or locks intend to integrate data from CNTO136ARA3002 and CNTO136ARA3003 with this study for the long-term PK, immunogenicity, safety and efficacy data of all subjects enrolled in these studies. A separate SAP for integration will be developed to specify the analyses and data handling rules.</p>
<p>Synopsis Interim Analysis 11.9 Interim Analyses</p>	<p>No formal interim analyses are planned, though analyses based on interim releases and locks may be carried out for integrated safety and efficacy data.</p>	<p>No formal interim analyses are planned, though analyses based on interim releases and locks may be carried out for integrated PK, immunogenicity, safety and efficacy data.</p>

CNTO 136 (sirukumab): Clinical Protocol CNTO136ARA3004 – Amendment 3

11.10 Data Monitoring Committee Paragraph 3	The DMC will conduct periodic safety reviews that will occur every 4 months until the study becomes open-label. The DMC may change the frequency or number of reviews based on interim safety findings. The safety reviews will focus on particular AEs, SAEs, and mortality.	The DMC will conduct periodic safety reviews that will occur every 4 months until at a minimum , the study becomes open-label. The DMC may change the frequency or number of reviews based on interim safety findings. The safety reviews will focus on particular AEs, SAEs, and mortality.
14.1 Physical Description of Study Agent	The sirukumab drug product provided for this study is supplied in a 1 mL PFS fitted with either: (1) a passive safety needle guard (UltraSafe Passive™ Delivery System, Safety Syringes, Inc.) that is permanently assembled on the syringe or (2) a spring-powered, disposable autoinjector device for SC administration of liquid biologic drug products (SmartJect™ Autoinjector) that is permanently assembled on the syringe.	Until the study is unblinded, study agent will be supplied in a 1 mL PFS fitted with either: (1) a passive safety needle guard (UltraSafe Passive™ Delivery System, Safety Syringes, Inc.) that is permanently assembled on the syringe or (2) a spring-powered, disposable autoinjector device for SC administration of liquid biologic drug products (SmartJect™ Autoinjector) that is permanently assembled on the syringe.
14.2 Packaging	The sirukumab PFS will be supplied with a passive safety needle guard (UltraSafe Passive™ Delivery System, Safety Syringes, Inc.) that is permanently assembled on the syringe. Once available, the sirukumab PFS may also be supplied with a spring-powered, disposable device for SC administration of liquid biologic drug products (SmartJect™ Autoinjector) that is permanently assembled on the syringe.	The sirukumab PFS-U will be supplied with a passive safety needle guard (UltraSafe Passive™ Delivery System, Safety Syringes, Inc.) that is permanently assembled on the syringe. Once available, the sirukumab PFS-AI will be supplied with a spring-powered, disposable device for SC administration of liquid biologic drug products (SmartJect™ Autoinjector) that is permanently assembled on the syringe.
14.4 Preparation, Handling, and Storage Paragraph 1	All sirukumab and sirukumab placebo study agent presentations should be stored in a secured refrigerator at 2°C to 8°C (36°F to 46°F). Sirukumab should not be frozen or shaken. During extended storage, protect from excessive exposure to light. Protection from light is not required during administration.	All study agent presentations should be stored in a secured refrigerator at 2°C to 8°C (36°F to 46°F). Study agent should not be frozen or shaken. During extended storage, protect from excessive exposure to light. Protection from light is not required during administration.
Paragraph 3	Sirukumab should be administered according to the instructions provided in the Site Investigational Product Binder.	Study agent should be administered according to the instructions provided in the Site Investigational Product Binder.

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17.5 Case Report Form Completion Paragraph 4	All subjective measurements (eg, pain scale information or other questionnaires) will be completed by the same individual who made the initial baseline determinations whenever possible. The investigator must confirm that all data entries in the CRFs are accurate and correct.	The investigator must confirm that all data are accurate and correct.
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AMENDMENT 2 – 01 MAY 2014

The protocol has been revised to incorporate this amendment, which applies to all study centers. The rationale and description of the changes to the protocol are provided below. Minor formatting and typographical errors have also been corrected to improve the clarity and accuracy of the protocol text; these changes do not affect the overall conduct of the study.

1. A change from percent to a number of randomized subjects for PK and immunogenicity analyses has been made.

Pharmacokinetic and immunogenicity analyses will be performed in approximately 750 randomized subjects from study CNTO136ARA3002.

Sections Affected	Original Content	Amended/New Content
Table 1 Times and Events in Long-term Extension Footnote h	Pharm serum samples (sirukumab concentration and antibodies to sirukumab) will be collected from subjects who had pharm serum samples collected at earlier time points in study CNTO136ARA3002 (approximately 50% of randomized subjects in CNTO136ARA3002) and from all subjects enrolled after participating in study CNTO136ARA3003.	Pharm serum samples (sirukumab concentration and antibodies to sirukumab) will be collected from subjects who had pharm serum samples collected at earlier time points in study CNTO136ARA3002 (approximately 750 randomized subjects in CNTO136ARA3002) and from all subjects enrolled after participating in study CNTO136ARA3003.
Table 2 Times and Events in Safety and Efficacy Follow-up After Last Study Agent Injection or after Discontinuation of Study Agent Footnote c	Pharm serum samples (sirukumab concentration and antibodies to sirukumab) will be collected at the final safety and efficacy follow up visit only from those subjects who had pharm serum samples collected at earlier time points in study CNTO136ARA3002 (approximately 50% of randomized subjects in CNTO136ARA3002) and from all subjects enrolled after participating in study CNTO136ARA3003.	Pharm serum samples (sirukumab concentration and antibodies to sirukumab) will be collected at the final safety and efficacy follow up visit only from those subjects who had pharm serum samples collected at earlier time points in study CNTO136ARA3002 (approximately 750 randomized subjects in CNTO136ARA3002) and from all subjects enrolled after participating in study CNTO136ARA3003.
9.3.2.1 Serum Collection and Handling	For subjects who had serum samples collected at earlier time points in study CNTO136ARA3002 (approximately 50% of randomized subjects in CNTO136ARA3002) and all subjects who enrolled after participating in study CNTO136ARA3003, serum samples will be collected at Weeks 2, 4, 16, 28, 52, 104, 156 and the final safety and efficacy follow-up visit (Table 1 and Table 2).	For subjects who had serum samples collected at earlier time points in study CNTO136ARA3002 (approximately 750 randomized subjects in CNTO136ARA3002) and all subjects who enrolled after participating in study CNTO136ARA3003, serum samples will be collected at Weeks 2, 4, 16, 28, 52, 104, 156 and the final safety and efficacy follow-up visit (Table 1 and Table 2).

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9.3.3 Immunogenicity Assessment (Antibodies to Sirukumab)	For subjects who had serum samples collected at earlier time points in study CNTO136ARA3002 (approximately 50% of randomized subjects in CNTO136ARA3002) and all subjects who enrolled after participating in study CNTO136ARA3003, serum samples will be collected at Weeks 16, 28, 52, 104, 156 and the final safety and efficacy follow-up visit.	For subjects who had serum samples collected at earlier time points in study CNTO136ARA3002 (approximately 750 randomized subjects in CNTO136ARA3002) and all subjects who enrolled after participating in study CNTO136ARA3003, serum samples will be collected at Weeks 16, 28, 52, 104, 156 and the final safety and efficacy follow-up visit.
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2. Efficacy assessments at Week 180 have been added.

Efficacy assessments (joint assessment, RA assessments, SF-36, WLQ, and health economics) have been added at Week 180.

Sections Affected	Original Content	Amended/New Content
Table 1 Times and Events in Long-term Extension	None	Xs noted for: <ul style="list-style-type: none"> • Joint assessment • RA assessments • SF-36 • WLQ • Health economics

3. The guidelines for the discontinuation of treatment have been revised.

Per DMC recommendation, GI perforation and acute diverticulitis have been added to the list of conditions that would result in the permanent discontinuation of study agent administrations.

Sections Affected	Original Content	Amended/New Content
10.2 Discontinuation of Treatment	None	14. Acute diverticulitis requiring antibiotic treatment 15. Gastrointestinal perforation

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4. Clarification on subject study card content.

The subject's name and date of birth are not included on the study card.

Sections Affected	Original Content	Amended/New Content
12.3.1 All Adverse Events Paragraph 4	Subjects (or their designees, if appropriate) must be provided with a "study card" indicating the following: <ul style="list-style-type: none"> • Subject's name • Subject number • Subject's date of birth • Study site number • Investigator's name and 24-hour contact information • Statement that the subject is participating in a clinical trial. 	Subjects (or their designees, if appropriate) must be provided with a "study card" indicating the following: <ul style="list-style-type: none"> • Subject number • Study site number • Study number • Sponsor's emergency contact name and 24-hour telephone number (for medical staff only) • Investigator's name and contact information • Statement in the local language(s) that the subject is participating in a clinical trial.

5. Prohibited medications have been revised.

Additions have been made to the list of prohibited medications.

Sections Affected	Original Content	Amended/New Content
8.2 Prohibited Medications	None	<ul style="list-style-type: none"> • Tofacitinib (XELJANZ®) • Any other biologic therapy for the treatment of RA

6. The time frame for reporting all initial PQCs has been revised.

A clarification on the time frame for the reporting all initial PQCs has been revised.

Sections Affected	Original Content	Amended/New Content
13.1 Procedures	All initial PQCs must be reported to the Sponsor by the investigational staff as soon as possible after being made aware of the event.	All initial PQCs must be reported to the Sponsor by the investigational staff within 24 hours after being made aware of the event.

CNTO 136 (sirukumab): Clinical Protocol CNTO136ARA3004 – Amendment 3

7. Criteria for planned statistical analyses for clinical laboratory data have been revised.

Clarifications on the criteria for the planned statistical analyses of clinical laboratory data have been made.

Sections Affected	Original Content	Amended/New Content
11.8 Safety Analyses Clinical Laboratory Tests	Laboratory data will be summarized by type of laboratory test. NCI-CTCAE grades will be used in the summary of laboratory data. Descriptive statistics will be calculated for selected laboratory analyte at baseline and at each scheduled time point. A listing of subjects with any markedly abnormal laboratory results will also be provided.	Laboratory data will be summarized by type of laboratory test. NCI-CTCAE grades will be used in the summary of laboratory data. For some laboratory data, which are not covered in the NCI-CTCAE grading criteria, shift tables and/or other abnormal cutoff levels may be used for summaries. Descriptive statistics will be calculated for selected laboratory analyte at baseline and at each scheduled time point. A listing of subjects with post-baseline abnormal laboratory results based on NCI-CTCAE grades will also be provided.

8. Clarifications for contacting the investigator by subjects who self-administer study agent have been made.

Clarifications for contacting the investigator by subjects who upon self-administration study agent experience any signs of allergic reaction, infection, or bleeding have been made.

Sections Affected	Original Content	Amended/New Content
Synopsis Self Administration Paragraph 2 6.5 Self Administration	None	Subjects will be instructed to contact the investigator promptly in the event of any signs of an allergic reaction, infection, or bleeding.

AMENDMENT 3 – 06 OCT 2016

The protocol has been revised to incorporate this amendment, which applies to all study centers. The rationale and description of the changes to the protocol are provided below. Minor formatting and typographical errors have also been corrected to improve the clarity and accuracy of the protocol text; these changes do not affect the overall conduct of the study.

1. Language has been included for optional dose reduction from 100 mg SC q2 weeks to 50 mg SC q4 weeks.

Based on data from Phase 3 studies, subjects treated with SC sirukumab 100 mg q2 weeks will be offered the option to reduce the sirukumab dose to 50 mg q4 weeks after the study becomes open-label. Figure 1 was also updated accordingly.

Sections Affected	Original Content	Amended/New Content
Synopsis (Dosing and Administration: Dosing Regimen)	None	After the study becomes open-label, subjects treated with SC sirukumab 100 mg q2 weeks will be offered the option to reduce the dose to 50 mg q4 weeks at the investigator's discretion. This decision can be made at the subject's first or second major resupply visit (up until approximately 7 months) after implementation of Amendment 3 at the study site. Once a subject's dose is reduced to 50 mg q4 weeks, the subject will receive that dose for the remainder of the trial (ie, a return to 100 mg q2 weeks will not be allowed). If a subject opts to remain on the sirukumab 100 mg q2 weeks dose, he or she will remain on that dose for the duration of their participation in the study (ie, the subject will not have the option to reduce the dose at a subsequent timepoint).
Synopsis (Statistical Methods)	None	After the study becomes open-label, subjects in Group 1 will be offered the option (at the discretion of the investigator) to reduce the sirukumab dose to 50 mg q4 weeks for the remainder of the trial.
1.2 Overall Rationale for the Study (paragraph 2)	None	Following the database lock for the primary endpoint, analysis of CNTO136ARA3002 and CNTO136ARA3003 PK and efficacy data showed that there was no clear dose response between the sirukumab SC 50 mg q4 weeks and sirukumab SC 100 g q2 weeks dose groups across efficacy endpoints. Furthermore, there were a greater proportion of subjects with hypersensitivity reactions and injection

<p>3.1 Overview of Study Design (Figure 1)</p>	<p><i>[Figure labels as follows]</i> Wk 0** Wk 156* Wk 208* Group 1 <i>[Footnotes as follows]</i> *Subjects from study CNTO136ARA3002 will have completed 104 weeks of study agent treatment prior to enrolling in this study. Subjects from study CNTO136ARA3003 will have completed 52 weeks of study agent treatment prior to enrolling in this study. **Subjects from study CNTO136ARA3002 will receive the last study agent administration at Week 156 and subjects from study CNTO136ARA3003 will receive the last study agent administration at Week 208.</p>	<p>site reactions in the sirukumab 100 mg q2 weeks dose group compared with the sirukumab 50 mg q4 weeks dose group. Therefore, to allow for minimization of the exposure to this immunosuppressant biologic agent, subjects treated with SC sirukumab 100 mg q2 weeks will be offered the option to reduce the sirukumab dose to 50 mg q4 weeks at the investigator's discretion after the study becomes open-label. This decision can be made at the subject's first or second major resupply visit (up until approximately 7 months) after implementation of Amendment 3 at the study site. Once a subject's dose is reduced to 50 mg q4 weeks, the subject will receive that dose for the remainder of the trial (ie, a return to 100 mg q2 weeks will not be allowed). If a subject opts to remain on the sirukumab 100 mg q2 weeks dose, he or she will remain on that dose for the duration of their participation in the study (ie, the subject will not have the option to reduce the dose at a subsequent timepoint).</p> <p><i>[Asterisks corrected for the footnotes; one footnote added:]</i> Wk 0±* Wk 156** Wk 208** Group 1 † *Subjects from study CNTO136ARA3002 will have completed 104 weeks of study agent treatment prior to enrolling in this study. Subjects from study CNTO136ARA3003 will have completed 52 weeks of study agent treatment prior to enrolling in this study. **Subjects from study CNTO136ARA3002 will receive the last study agent administration at Week 156 and subjects from study CNTO136ARA3003 will receive the last study agent administration at Week 208. †After the study becomes open-label, subjects in Group 1 will be offered the option (at the discretion of the investigator) to reduce the sirukumab dose to 50 mg q4 weeks for the remainder of the trial.</p>
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<p>3.2.2 Treatment Groups, Dosage, and Dose Administration Interval (paragraph 3)</p>	<p>None</p>	<p>Following the database lock for the primary endpoint, analysis of CNTO136ARA3002 and CNTO136ARA3003 PK and efficacy data showed that there was no clear dose response between the sirukumab SC 50 mg q4 weeks and sirukumab SC 100 mg q2 weeks dose groups across efficacy endpoints. Furthermore, there were a greater proportion of subjects with hypersensitivity reactions and injection site reactions in the sirukumab 100 mg q2 weeks dose group compared with the sirukumab 50 mg q4 weeks dose group. Therefore, to allow for minimization of the exposure to this immunosuppressant biologic agent, subjects treated with SC sirukumab 100 mg q2 weeks will be offered the option to reduce the sirukumab dose to 50 mg q4 weeks at the investigator's discretion after the study becomes open-label. This decision can be made at the subject's first or second major resupply visit (up until approximately 7 months) after implementation of Amendment 3 at the study site.</p>
<p>5.1 Treatment Allocation (paragraph 4); 6.2 Blinding (paragraph 4); 11 Statistical Methods (paragraph 4)</p>	<p>None</p>	<p>After the study becomes open-label, subjects treated with SC sirukumab 100 mg q2 weeks will be offered the option to reduce the sirukumab dose to 50 mg q4 weeks at the investigator's discretion. This decision can be made at the subject's first or second major resupply visit (up until approximately 7 months) after implementation of Amendment 3 at the study site.</p>
<p>6.1 Dosing Regimen (paragraph 4)</p>	<p>None</p>	<p>After the study becomes open-label, subjects treated with SC sirukumab 100 mg q2 weeks will be offered the option to reduce the sirukumab dose to 50 mg q4 weeks at the investigator's discretion. This decision can be made at the subject's first or second major resupply visit (up until approximately 7 months) after implementation of Amendment 3 at the study site. Once a subject's dose is reduced to 50 mg q4 weeks, the subject will receive that dose for the remainder of the trial (ie, a return to 100 mg q2 weeks will not be allowed). If a subject opts to remain on the sirukumab 100 mg q2 weeks dose, he or she will remain on that</p>

		dose for the duration of their participation in the study (ie, the subject will not have the option to reduce the dose at a subsequent timepoint).
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2. Additional mentions of Patient Reported Outcome (PRO) evaluations and endpoints were added to the appropriate sections for completeness throughout the document.

The additional mentions of the PRO evaluations and endpoints (eg, Health Economics Questionnaire and morning stiffness) were added to various sections of the document for clarity and completeness.

Sections Affected	Original Content	Amended/New Content
<p>Synopsis (Efficacy Evaluations), 3.2.5 Efficacy Evaluations (paragraph 3)</p> <p>Synopsis (Statistical Methods – Medical Resource Usage and Health Economics)</p> <p>9.2.3 Endpoints (Other secondary endpoints)</p> <p>11.2.3 Other Secondary Endpoints</p>	<p>Patient Reported Outcome (PRO) evaluations include:</p> <ul style="list-style-type: none"> • 36-Item Short Form (SF-36) • Work Limitations Questionnaire (WLQ) <p>WLQ data will be summarized over time.</p> <p>Other secondary endpoints</p> <ul style="list-style-type: none"> • ACR responses • DAS28 • HAQ-DI • SF-36 • WLQ <p>In addition to the primary and major secondary efficacy endpoints, the following efficacy endpoints will be summarized by treatment group over time through the end of the study:</p> <ol style="list-style-type: none"> 1. Proportion of subjects who achieve ACR 20 response 2. Proportion of subjects who achieve ACR 50 response 3. Proportion of subjects who achieve ACR 70 response 4. Proportion of subjects with DAS28 (CRP) response 5. Proportion of subjects with DAS28 (CRP) remission 6. Change from baseline in DAS28 (CRP) 	<p>Patient Reported Outcome (PRO) evaluations include:</p> <ul style="list-style-type: none"> • 36-Item Short Form (SF-36) • Work Limitations Questionnaire (WLQ) • Health Economic Questionnaire (HECONQ) <p>WLQ and HECONQ data will be summarized over time.</p> <p>Other secondary endpoints</p> <ul style="list-style-type: none"> • ACR responses • DAS28 • HAQ-DI • SF-36 • WLQ • HECONQ • Morning stiffness <p>In addition to the primary and major secondary efficacy endpoints, the following efficacy endpoints will be summarized by treatment group over time through the end of the study:</p> <ol style="list-style-type: none"> 1. Proportion of subjects who achieve ACR 20 response 2. Proportion of subjects who achieve ACR 50 response 3. Proportion of subjects who achieve ACR 70 response 4. Proportion of subjects with DAS28 (CRP) response 5. Proportion of subjects with DAS28 (CRP) remission 6. Change from baseline in DAS28 (CRP)

<p>11.7 Health Economics Analyses</p>	<p>7. Proportion of subjects with SDAI-based ACR/EULAR remission 8. Proportion of subjects with Boolean-based ACR/EULAR remission 9. Change from baseline in SDAI 10. Change from baseline in CDAI 11. Change from baseline in HAQ-DI 12. Proportion of HAQ-DI responders (ie, those who have a change from baseline of > 0.22 in HAQ-DI score) 13. Change from baseline in PCS and MCS and in domain scores of SF-36</p> <p>Change from baseline in total and domain scores of WLQ will be summarized over time.</p>	<p>7. Proportion of subjects with SDAI-based ACR/EULAR remission 8. Proportion of subjects with Boolean-based ACR/EULAR remission 9. Change from baseline in SDAI 10. Change from baseline in CDAI 11. Change from baseline in HAQ-DI 12. Proportion of HAQ-DI responders (ie, those who have a change from baseline of > 0.22 in HAQ-DI score) 13. Change from baseline in PCS and MCS and in domain scores of SF-36 14. Change from baseline in duration of morning stiffness.</p> <p>Change from baseline in total and domain scores of WLQ and HECONQ will be summarized over time.</p>
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3. Placebell[®]™ technology for RA was incorporated into the study.

Language regarding the incorporation of the Placebell[®]™ technology was added to account for its exploration in this study.

Sections Affected	Original Content	Amended/New Content
<p>Time and Events Schedule (Table 1)</p> <p>9.2.1.8 Multidimensional Personality Questionnaire (MPSQ)</p>	<p>None</p> <p>None</p>	<p>Exploration of Placebell[®]™ technology for RA Placebell Multidimensional Personality Questionnaire^h: optional at selected sites for consenting subjects at a single visit after implementation of Amendment 3; Wk 16 through Wk 208</p> <p>h. At selected sites, the MPSQ will be administered as an optional paper questionnaire to subjects who consent to participate after implementation of Amendment 3 at the study site.</p> <p>The Placebell[®]™ technology will be explored in this study of rheumatoid arthritis. The Multidimensional Personality Questionnaire (MPSQ) is a questionnaire contributing to the evaluation of individual patient response to placebo by assessing patients's personality, well-being as well as attitudes and beliefs on disease therapies. It has been developed by Tools4patient SA. MPSQ is self-reported by patient and made of 114 items. Each of them is rated by patient on a 5-point</p>

<p>9.8 Safety Evaluations</p>	<p>None</p>	<p>scale ranging from 1 (strongly disagree) to 5 (strongly agree). At selected sites, the MPSQ will be administered as an optional paper questionnaire to subjects who consent to participate after implementation of Amendment 3.</p> <p>Subject Lab Data Access Subjects at selected sites in the US will be offered the opportunity to consent to join a secure, web-based platform managed by a third party vendor so that they may access results to select clinical laboratory tests collected during the study (as defined above with the exception of RBC count). More details will be provided in the Informed Consent Form for these subjects.</p>
<p>16.2.3 Informed Consent (paragraph 5)</p>	<p>None</p>	<p>A limited number of subjects will be asked to consent to participate in the Subject Lab Data Access and/or to complete the Placebell Multidimensional Personality Questionnaire. Refusal to participate in either the Subject Lab Access program or to complete the Placebell Multidimensional Personality Questionnaire will not result in ineligibility for the clinical study.</p>

4. Specifying language was added regarding what is considered source data during source documentation.

Language was added to the source documentation section to specify the data that will be considered source data.

Sections Affected	Original Content	Amended/New Content
<p>17.4 Source Documentation (paragraph 4)</p>	<p>None</p>	<p>Data which may be recorded directly into the CRF, if in accordance with site capabilities and/or in compliance with local regulations, will be considered source data, and will include but not be limited to the following:</p> <ul style="list-style-type: none"> • Blood pressure • Weight <p>The following subject- and investigator-completed RA scales and assessments designated by the Sponsor will be recorded directly into an electronic device and will be considered source data.</p>

		<ul style="list-style-type: none"> • Swollen and tender joint assessments • Patient’s Global Assessment of Disease Activity • Physician’s Global Assessment of Disease Activity • Patient’s Assessment of Pain • HAQ-DI • SF-36 • Duration of Morning Stiffness • WLQ • HECONQ <p>Multidimensional Personality Questionnaire recorded on paper will also be considered source data.</p>
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5. Clarification was made in the Time & Events Schedules regarding the timing of the collection of pharm serum samples.

A cut-off date for randomization was added to provide further specification of the subject population from CNTO136ARA3002 from which samples will be collected.

Sections Affected	Original Content	Amended/New Content
<p>Time and Events Schedule (Table 1)</p>	<p>i. Pharm serum samples (sirukumab concentration and antibodies to sirukumab) will be collected from subjects who had pharm serum samples collected at earlier time points in study CNTO136ARA3002 (approximately 750 randomized subjects in CNTO136ARA3002) and from all subjects enrolled after participating in study CNTO136ARA3003.</p>	<p>i. Pharm serum samples (sirukumab concentration and antibodies to sirukumab) will be collected from subjects who had pharm serum samples collected at earlier time points in study CNTO136ARA3002 (approximately 750 randomized subjects randomized in CNTO136ARA3002 before 18 November 2013) and from all subjects enrolled after participating in study CNTO136ARA3003.</p>
<p>Time and Events Schedule (Table 2)</p>	<p>c. Pharm serum samples (sirukumab concentration and antibodies to sirukumab) will be collected at the final safety and efficacy follow up visit only from those subjects who had pharm serum samples collected at earlier time points in study CNTO136ARA3002 (approximately 750 randomized subjects in CNTO136ARA3002) and from all subjects enrolled after participating in study CNTO136ARA3003.</p>	<p>c. Pharm serum samples (sirukumab concentration and antibodies to sirukumab) will be collected at the final safety and efficacy follow up visit only from those subjects who had pharm serum samples collected at earlier time points in study CNTO136ARA3002 (approximately 750 randomized subjects randomized in CNTO136ARA3002 before 18 November 2013) and from all subjects enrolled after participating in study CNTO136ARA3003.</p>

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6. A clarification regarding joint assessors was made.

The joint assessors are not required to be independent.

Sections Affected	Original Content	Amended/New Content
9.2.1.1 Joint Assessments (Joint Assessor paragraph 3)	The Sponsor will provide training for each site's designated IJA prior to the [Week 0 visit] of the first subject at each site. A back-up IJA must complete training before performing a joint assessment for a subject's study visit.	The Sponsor will provide training for each site's designated IJA joint assessor prior to the [Week 0 visit] of the first subject at each site. A back-up IJA joint assessor must complete training before performing a joint assessment for a subject's study visit.

7. A specification was made regarding how long subjects are required to be monitored for allergic and injection site reactions throughout the study.

Clarifying language was added to the Safety Evaluations to specify that subjects only need to undergo monitoring for symptoms of allergic reactions and injection site reactions at least until the study becomes open-label.

Sections Affected	Original Content	Amended/New Content
9.8 Safety Evaluations (Allergic Reactions)	All subjects will be observed carefully for symptoms of allergic reactions for at least 30 minutes after the SC injection of study agent at the study site.	All subjects will be observed carefully for symptoms of allergic reactions for at least 30 minutes after the SC injection of study agent at the study site at least until the study becomes open-label.
9.8 Safety Evaluations (Injection Site Reactions)	An injection site reaction is any unfavorable or unintended sign that occurs at the study agent injection site. All subjects must be carefully observed for symptoms of an injection site reaction. Subjects will be observed for at least 30 minutes after the SC injection of study agent for symptoms of an injection-site reaction.	An injection site reaction is any unfavorable or unintended sign that occurs at the study agent injection site. All subjects must be carefully observed for symptoms of an injection site reaction. Subjects will be observed for at least 30 minutes after the SC injection of study agent for symptoms of an injection-site reaction at least until the study becomes open-label.

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8. A criterion was added to the Subject Completion / Withdrawal criteria for completeness.

A criterion for discontinuation of study treatment was added to address the potential future approval of sirukumab in the subject's country of residence. This is already mentioned earlier in the document, but is being added to this list for completeness.

Sections Affected	Original Content	Amended/New Content
10.2 Discontinuation of Treatment	None	16. If sirukumab becomes approved in the subject's country of residence, it may no longer be offered by the Sponsor in CNTO136ARA3004. In this case, study agent administrations will be discontinued after 52 weeks of treatment for subjects who enrolled after completing participation in study CNTO136ARA3002, and after 104 weeks of treatment for subjects who enrolled after completing participation in CNTO136ARA3003. At that point the subject will have the opportunity to discuss treatment options with their treating physician.

9. The list of anticipated events was updated and language was moved to an attachment at the end of the protocol.

Language was added to include synovitis in the list of anticipated events, which was moved from section 12.3.2 to a new attachment (Attachment 2) at the end of the protocol. A reference to this attachment was included in section 12.3.1 (All Adverse Events).

Sections Affected	Original Content	Amended/New Content
12.3.1 All Adverse Events (paragraph 2)	All events that meet the definition of a SAE will be reported as SAEs, regardless of whether they are protocol-specific assessments. All adverse events, regardless of seriousness, severity, or presumed relationship to study therapy, must be recorded using medical terminology in the source document and the CRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the CRF their opinion concerning the relationship of the adverse event to study therapy. All measures required for adverse event management must be recorded in the source document and reported according to Sponsor instructions.	All events that meet the definition of a SAE will be reported as SAEs, regardless of whether they are protocol-specific assessments. Anticipated events will be recorded and reported as described in Attachment 2. All adverse events, regardless of seriousness, severity, or presumed relationship to study therapy, must be recorded using medical terminology in the source document and the CRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the CRF their opinion concerning the relationship of the adverse event to study therapy. All measures required for adverse event management must be recorded in the source document and reported according to Sponsor instructions.

<p>12.3.2 Serious Adverse Events (paragraphs 7, 8)</p>	<p>SAEs related to the disease under study will be collected per protocol but will not be unblinded and expedited if they fall into the following categories:</p> <ul style="list-style-type: none"> • Exacerbations of RA • Worsening joint pain or swelling due to RA <p>These events will be reviewed periodically at the time of database locks in an unblinded fashion, if unblinded data is available. In addition, the DMC will review unblinded data during the blinded portions of the study (Section 11.10). If the review finds an association with the use of the drug to be a reasonable possibility, the assessment and all single cases not yet reported will be sent to FDA in an expedited manner.</p>	<p>SAEs related to the disease under study will be collected per protocol but will not be unblinded and expedited if they fall into the following categories:</p> <ul style="list-style-type: none"> • Exacerbations of RA • Worsening joint pain or swelling due to RA <p>These events will be reviewed periodically at the time of database locks in an unblinded fashion, if unblinded data is available. In addition, the DMC will review unblinded data during the blinded portions of the study (Section 11.10). If the review finds an association with the use of the drug to be a reasonable possibility, the assessment and all single cases not yet reported will be sent to FDA in an expedited manner.</p>
<p>Attachment 2: Anticipated Events</p>	<p>None</p>	<p>An anticipated event is an adverse event (serious or non-serious) that commonly occurs as a consequence of the underlying disease or condition under investigation (disease related) or background regimen. For the purposes of this study the following events will be considered anticipated events:</p> <ul style="list-style-type: none"> • Exacerbations of rheumatoid arthritis (RA) • Worsening joint pain or swelling due to RA • Synovitis <p>Reporting of Anticipated Events These events will be captured on the CRF and in the database, and will be reported to the sponsor as described in Section 12.3.1, All Adverse Events. Any event that meets serious adverse event criteria will be reported to the sponsor within the appropriate timeline as described in Section 12.3.2, Serious Adverse Events. These anticipated events are exempt from expedited reporting as individual single cases to Health Authorities. However, if based on an aggregate review, it is determined that an anticipated event is possibly related to study drug, the sponsor will report these events in an expedited manner.</p>

		<p>Anticipated Event Review Committee (ARC) An Anticipated Event Review Committee (ARC) will be established to perform reviews of pre-specified anticipated events at an aggregate level. The ARC is a safety committee within the sponsor’s organization that is independent of the sponsor’s study team. The ARC will meet to aid in the recommendation to the sponsor’s study team as to whether there is a reasonable possibility that an anticipated event is related to the study drug.</p> <p>Statistical Analysis Details of statistical analysis of anticipated events, including the frequency of review and threshold to trigger an aggregate analysis of anticipated events will be provided in a separate Anticipated Events Safety Monitoring Plan (ASMP).</p>
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10. Language for consent regarding pregnancy was updated for greater specification.

Language was added regarding consent guidelines for male and female subjects involved in pregnancy during the study.

Sections Affected	Original Content	Amended/New Content
<p>12.3.3 Pregnancy (paragraph 3)</p>	<p>Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.</p>	<p>Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required after subject’s consent has been obtained.</p> <ul style="list-style-type: none"> • For women: The study doctor will ask for your permission to stay in contact with you throughout the length of the pregnancy. • For men: The study doctor will ask for your permission and your partner’s to stay in contact with your partner throughout the pregnancy.

11. Updates were made to the Study Specific Materials.

As this is an outsourced study, “Site Investigational Product Binder” is not being used. “Binder” was replaced with “Procedures Manual” for consistency with other related Phase 3 studies. Updates were also made for some of the names of the Study Specific Materials that are provided to the investigator.

Sections Affected	Original Content	Amended/New Content
14.4 Preparation, Handling, and Storage (paragraphs 3 and 4)	Study agent should be administered according to the instructions provided in the Site Investigational Product Binder. Subjects who are able and who have been appropriately trained in the self-administration of study agent may self-administer study agent at home in accordance with Section 6.5. Study personnel will instruct subjects on how to transport, store and administer medication for at-home use as indicated for this protocol. Details will be provided in the Site Investigational Product Binder.	Study agent should be administered according to the instructions provided in the Site Investigational Product Binder Procedures Manual . Subjects who are able and who have been appropriately trained in the self-administration of study agent may self-administer study agent at home in accordance with Section 6.5. Study personnel will instruct subjects on how to transport, store and administer medication for at-home use as indicated for this protocol. Details will be provided in the Site Investigational Product Binder Procedures Manual .
14.5 Drug Accountability (paragraph 2)	Upon termination of the study or at the request of the Sponsor or its designee, the investigator must return all unused study agent to the Sponsor or its designee or if approved by the Sponsor, unused study agent can be destroyed directly at the site or locally by an approved destruction unit as described in the Site Investigational Product Binder.	Upon termination of the study or at the request of the Sponsor or its designee, the investigator must return all unused study agent to the Sponsor or its designee or if approved by the Sponsor, unused study agent can be destroyed directly at the site or locally by an approved destruction unit as described in the Site Investigational Product Binder Procedures Manual .
15 Study Specific Materials	The investigator will be provided with the following: <ul style="list-style-type: none"> Investigator Brochure Site Investigational Product Binder Central Laboratory Manual PRO Questionnaires MTX Toxicity Guidelines (Appendix C) IVRS/IWRS Manual Electronic Data Capture (eDC) Manual 	The investigator will be provided with the following: <ul style="list-style-type: none"> Investigator Brochure Site Investigational Product Binder Procedures Manual Central Laboratory Manual PRO Questionnaires ePRO Device and Manual MTX Toxicity Guidelines (Appendix C) IVRS/IWRS Manual User Guides and Worksheets Electronic Data Capture (eDC) Manual

ATTACHMENT 2: ANTICIPATED EVENTS

An anticipated event is an adverse event (serious or non-serious) that commonly occurs as a consequence of the underlying disease or condition under investigation (disease related) or background regimen.

For the purposes of this study the following events will be considered anticipated events:

- Exacerbations of rheumatoid arthritis (RA)
- Worsening joint pain or swelling due to RA
- Synovitis

Reporting of Anticipated Events

These events will be captured on the CRF and in the database, and will be reported to the sponsor as described in Section 12.3.1, All Adverse Events. Any event that meets serious adverse event criteria will be reported to the sponsor within the appropriate timeline as described in Section 12.3.2, Serious Adverse Events. These anticipated events are exempt from expedited reporting as individual single cases to Health Authorities. However, if based on an aggregate review, it is determined that an anticipated event is possibly related to study drug, the sponsor will report these events in an expedited manner.

Anticipated Event Review Committee (ARC)

An Anticipated Event Review Committee (ARC) will be established to perform reviews of pre-specified anticipated events at an aggregate level. The ARC is a safety committee within the sponsor's organization that is independent of the sponsor's study team. The ARC will meet to aid in the recommendation to the sponsor's study team as to whether there is a reasonable possibility that an anticipated event is related to the study drug.

Statistical Analysis

Details of statistical analysis of anticipated events, including the frequency of review and threshold to trigger an aggregate analysis of anticipated events will be provided in a separate Anticipated Events Safety Monitoring Plan (ASMP).

APPENDIX A QUANTIFERON®-TB GOLD TESTING

The QuantiFERON-TB Gold test is one of the interferon- γ (IFN- γ) based blood assays for TB screening (Cellestis, 2009). It utilizes the recently identified *M. tuberculosis*-specific antigens ESAT-6 and CFP-10 in the standard format, as well as TB7.7 (p4) in the In-Tube format, to detect in vitro cell-mediated immune responses in infected individuals. The QuantiFERON-TB Gold assay measures the amount of IFN-g produced by sensitized T-cells when stimulated with the synthetic *M. tuberculosis*-specific antigens. In *M. tuberculosis*-infected persons, sensitized T lymphocytes will secrete IFN- γ in response to stimulation with the *M. tuberculosis*-specific antigens and, thus, the QuantiFERON-TB Gold test should be positive. Because the antigens used in the test are specific to *M. tuberculosis* and not found in BCG, the test is not confounded by BCG vaccination, unlike the tuberculin skin test. However, there is some cross-reactivity with the 3 Mycobacterium species, *M. kansasii*, *M. marinum*, and *M. szulgai*. Thus, a positive test could be the result of infection with one of these 3 species of Mycobacterium, in the absence of *M. tuberculosis* infection.

In a study of the QuantiFERON-TB Gold test (standard format) in subjects with active TB, sensitivity has been shown to be approximately 89% (Mori et al, 2004). Specificity of the test in healthy BCG-vaccinated individuals has been demonstrated to be more than 98%. In contrast, the sensitivity and specificity of the tuberculin skin test was noted to be only about 66% and 35% in a study of Japanese patients with active TB and healthy BCG-vaccinated young adults, respectively. However, sensitivity and specificity of the tuberculin skin test depend on the population being studied, and the tuberculin skin test performs best in healthy young adults who have not been BCG-vaccinated.

Data from a limited number of published studies examining the performance of the QuantiFERON-TB Gold assay in immunosuppressed populations suggest that the sensitivity of the QuantiFERON-TB Gold test is better than the tuberculin skin test even in immunosuppressed patients (Ferrara et al, 2005; Kobashi et al, 2007; Matulis et al, 2008). The ability of IFN- γ -based tests to detect latent infection has been more difficult to study due to the lack of a gold standard diagnostic test; however, several TB outbreak studies have demonstrated that the tests correlated better than the tuberculin skin test with the degree of exposure that contacts had to the index TB case (Brock et al, 2004; Ewer et al, 2003). In addition, TB contact tracing studies have shown that patients who had a positive QuantiFERON-TB Gold test result and were not treated for latent TB infection were much more likely to develop active TB during longitudinal follow-up than those who had a positive tuberculin skin test and a negative QuantiFERON-TB Gold test result (Higuchi et al, 2007; Diel et al, 2008).

Although the performance of the new IFN- γ -based blood tests for active or latent *M. tuberculosis* infection have not been well validated in the immunosuppressed population, experts believe these new tests will be at least as, if not more, sensitive, and definitely more specific, than the tuberculin skin test (Barnes, 2004; personal communication, April, 2008 TB Advisory Board).

Performing the QuantiFERON-TB Gold In Tube Test

The QuantiFERON-TB Gold test In-Tube format will be provided for this study. The In-Tube format contains 1 additional *M. tuberculosis*-specific antigen, TB7.7 (p4), which is thought to increase the specificity of the test.

To perform the test using the In-Tube format, blood is drawn through standard venipuncture into supplied tubes that already contain the *M. tuberculosis*-specific antigens. Approximately 3 tubes will be needed per subject, each requiring 1 mL of blood. One tube contains the *M. tuberculosis*-specific antigens, while the remaining tubes contain positive and negative control reagents.

Thorough mixing of the blood with the antigens is necessary prior to incubation. The blood is then incubated for 16 to 24 hours at 37°C, after which tubes are centrifuged for approximately 15 minutes at 2000 to 3000g. Following centrifugation, plasma is harvested from each tube, frozen, and shipped on dry ice to the central laboratory. The central laboratory will perform an ELISA to quantify the amount of IFN- γ present in the plasma using spectrophotometry and computer software analysis.

The central laboratory will analyze and report results for each subject, and sites will be informed of the results. Subjects who have an indeterminate result should have the test repeated.

Adherence to Local Guidelines

Local country guidelines for immunocompromised patients should be consulted for acceptable antituberculous treatment regimens for latent TB. If no local country guidelines for immunocompromised patients exist, US guidelines must be followed.

In countries in which the QuantiFERON-TB Gold test is not considered approved/registered, a tuberculin skin test is additionally required.

References

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APPENDIX B TUBERCULIN SKIN TESTING

Administering the Mantoux Tuberculin Skin Test

The Mantoux tuberculin skin test (CDC, 2000) is the standard method of identifying persons infected with *Mycobacterium tuberculosis*. Multiple puncture tests (Tine and Heaf) should not be used to determine whether a person is infected because the amount of tuberculin injected intradermally cannot be precisely controlled. Tuberculin skin testing is both safe and reliable throughout the course of pregnancy. The Mantoux tuberculin test is performed by placing an intradermal injection of 0.1 mL of tuberculin into the inner surface of the forearm. The test must be performed with tuberculin that has at least the same strength as either 5 tuberculin units (TU) of standard purified protein derivative (PPD) S or 2 TU of PPD RT 23, Statens Seruminstitut, as recommended by the World Health Organization. PPD strengths of 1 TU or 250 TU are not acceptable (Menzies, 2000). Using a disposable tuberculin syringe with the needle bevel facing upward, the injection should be made just beneath the surface of the skin. This should produce a discrete, pale elevation of the skin (a wheal) 6 mm to 10 mm in diameter. To prevent needle-stick injuries, needles should not be recapped, purposely bent or broken, removed from disposable syringes, or otherwise manipulated by hand. After they are used, disposable needles and syringes should be placed in puncture-resistant containers for disposal. Institutional guidelines regarding universal precautions for infection control (eg, the use of gloves) should be followed. A trained health care worker, preferably the investigator, should read the reaction to the Mantoux test 48 to 72 hours after the injection. Subjects should never be allowed to read their own tuberculin skin test results. If a subject fails to show up for the scheduled reading, a positive reaction may still be measurable up to 1 week after testing. However, if a subject who fails to return within 72 hours has a negative test, tuberculin testing should be repeated. The area of induration (palpable raised hardened area) around the site of injection is the reaction to tuberculin. For standardization, the diameter of the induration should be measured transversely (perpendicular) to the long axis of the forearm. Erythema (redness) should not be measured. All reactions should be recorded in millimeters, even those classified as negative.

Interpreting the Tuberculin Skin Test Results

In the US and many other countries, the most conservative definition of positivity for the tuberculin skin test is reserved for immunocompromised patients, and this definition is to be applied in this study to maximize the likelihood of detecting latent TB, even though the subjects may not be immunocompromised at baseline.

In the US and Canada, an induration of 5 mm or greater in response to the intradermal tuberculin skin test is considered to be a positive result and evidence for either latent or active TB.

In countries outside the US and Canada, country-specific guidelines for immunocompromised patients should be consulted for the interpretation of tuberculin skin test results. If no local country guidelines for immunocompromised patients exist, US guidelines must be followed.

Treatment of Latent Tuberculosis

Local country guidelines for immunocompromised patients should be consulted for acceptable antituberculous treatment regimens for latent TB. If no local country guidelines for immunocompromised patients exist, US guidelines must be followed.

References

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Menzies RI. Tuberculin skin testing. In: Reichman LB, Hershfield ES (eds). Tuberculosis, a comprehensive international approach. 2nd ed. New York, NY: Marcel Dekker, Inc; 2000:279-322.

APPENDIX C GUIDELINES FOR MTX DOSE ADJUSTMENTS FOR MTX-TOXICITY

- The following algorithm will be used to make the dose adjustments in the event of MTX-induced toxicities (see Section 8.1.2):

1. Mild toxicity

- *Labs*: liver function test results (AST or ALT) < 2 x upper normal limit (ULN) central laboratory, leukocyte count $\geq 3.5 \times 10^9$ cells per liter
- *Symptoms*: mild nausea, mild abdominal distress, and occasional mild headaches, no rash, and no oral ulceration
- *Adjustment*: confirm relevant laboratory findings and continue with the current dosing algorithm

2. Moderate toxicity

- *Labs*: liver function test results (AST or ALT) ≥ 2 x ULN but < 3 x ULN and a leukocyte count of $\geq 2.0 \times 10^9$ cells per liter but < 3.5×10^9 cells per liter
- *Symptoms*: moderate nausea, moderate abdominal distress, minimal macular erythematous rash, and minor oral ulceration
- *Adjustment*: confirm the laboratory findings, decrease the dose of MTX by 50%, and repeat the laboratory tests 2 weeks following the dose reduction
- If the liver function tests return to < 2 x ULN, and the leukocyte count returns to values between normal and 3.5×10^9 cells per liter, and nausea or headaches improve and rash and oral ulceration resolve, the MTX dose may be increased to the baseline dose at the investigator's discretion.
- If the liver function tests remain elevated (≥ 2 x ULN and < 3 x ULN) or the leukocyte count remains $\geq 2.0 \times 10^9$ cells per liter but < 3.5×10^9 cells per liter, or the nausea does not improve, the MTX dose should be decreased again by 50%.

3. Severe toxicity

- *Labs*: liver function tests results (AST and/or ALT) ≥ 3 x ULN, and the leukocyte count is < 2.0×10^9 cells per liter
- *Symptoms*: severe nausea and vomiting, severe abdominal pain, severe headaches, and diffuse rash or major oral ulceration
- *Adjustment*: confirm the laboratory findings and withhold MTX therapy for 2 weeks, then repeat laboratory tests
- If, after 2 weeks, the repeat liver function test results are between ULN and < 3 x ULN, the leukocyte count is $\geq 2.0 \times 10^9$ cells per liter, and nausea or headaches or rash and oral ulceration have improved, MTX can be restarted at 50% of the baseline dose, at the investigator's discretion.
- If after 2 weeks, the repeat laboratory tests continue to demonstrate severe toxicity or the nausea or headaches, rash, or oral ulceration remain severe, MTX therapy should be withheld an additional 2 weeks and the laboratory tests repeated after that time.

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- If the subject improves after an additional 2 weeks off MTX, the MTX should be restarted at 50% of baseline dose, at the investigator's discretion.
- If after an additional 2 weeks off MTX, there has been no improvement in the subject, MTX should be discontinued permanently.

INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study drug, the conduct of the study, and the obligations of confidentiality.

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

Signature: _____ Date: _____
(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

Telephone Number: _____

Signature: _____ Date: _____
(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): Elizabeth Hsia, MD

Institution: Janssen Research & Development

Signature: _____ Date: 06 Oct 2016
(Day Month Year)

Note: If the address or telephone number of the investigator changes during the course of the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.