Janssen Research & Development *

Clinical Protocol

A Double-Blind, Placebo-Controlled, Multicenter Study of Sirukumab as Adjunctive Treatment to a MonoAminergic antidepressant in Adults with Major Depressive Disorder

Protocol CNTO136MDD2001; Phase 2a

Amendment INT-5

CNTO136 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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PROTOCOL AMENDMENTS

Protocol Version	Issue Date
Original Protocol	16 Feb 2015
Amendment INT-1	2 Apr 2015
Amendment INT-2	13 May 2015
Amendment INT-3	8 June 2015
Amendment INT-4	3 Feb 2016
Amendment INT-5	22 Jan 2018

Amendments below are listed beginning with the most recent amendment.

Amendment 5 (22 Jan 2018)

This amendment is considered to be nonsubstantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union, in that it does not significantly impact the safety or physical/mental integrity of subjects, nor the scientific value of the study.

The overall reason for the amendment: The overall reason for the amendment is to have a first database lock when all subjects have completed the 12-week double-blind treatment phase for the primary efficacy analyses.

Applicable Section(s)	Description of Change(s)
Rationale: Section about analyses for primary efficacy added to the statistical methods	
Synopsis	Section about analyses for primary efficacy added to the statistical methods
Rationale: Randomization codes will be disclosed fully for sponsor staff for the primary efficacy analyses	
5. Treatment allocation and blinding	Specified that randomization codes will be disclosed fully for sponsor staff for the primary efficacy analyses
Rationale: Section added to describe the first database lock for the primary efficacy analyses	
11. Statistical Methods	Section added to describe the first database lock for the primary efficacy analyses

Amendment INT-4 (3 Feb 2016)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

The overall reason for the amendment: The overall reason for the amendment is to include subjects who may be more reflective of the general population of subjects with Major Depressive Disorder (MDD) by updating the list of allowed antidepressants and concomitant therapies and comorbidities in subjects with MDD. Another reason is to add 50 subjects with hsCRP < 0.300 mg/dL (SI <3.00 mg/L).

Applicable Section(s)	Description of Change(s)
Rationale: To add mirtazapine, fluvoxamine, agomelatine, imipramine, nortriptyline and amitriptyline as allowed antidepressants	

Synopsis –Overview of Study Design; 3.1 Overview of Study Design; 4.1 Inclusion Criteria; 8. Prestudy and Concomitant Therapy; 9.1.2 Screening Phase	Mirtazapine, fluvoxamine, agomelatine, imipramine, nortriptyline and amitriptyline added as allowed antidepressants.
Rationale: Due to time consuming nature of the screening assessments of the first screening visit, they may be divided over 2 days.	
Synopsis –Overview of Study Design; T&E schedule; 3.1 Overview of Study Design; 9.1.2 Screening Phase	Screening assessments of the first screening visit may be divided over 2 days. However, C-SSRS, IDS-C30 and $HDRS_{17}$ must be performed on the same day.
Rationale: Allow improvement of up to and including 25% on the $HDRS_{17}$ total score from the screening visit to the baseline visit to reflect the most commonly used criteria for minimal response.	
Synopsis –Overview of Study Design; 3.1 Overview of Study Design; 4.1 Inclusion Criteria; 9.1.3 Double-Blind Treatment Phase	Acceptable improvement on $HDRS_{17}$ total score from the screening to baseline visit increased from $< 20\%$ to $\leq 25\%$
Rationale: Study drug has no effect on blood pressure	
T&E schedule; 9.6 Safety Evaluations; 11.9 Safety Analyses	Orthostatic vital signs removed.
Rationale: To have criteria for interruption of study agent administration	
10.2 Discontinuation of Study Treatment	Section with criteria for interruption of study agent administration added.
Rationale: Have a better reflection of the general population of subjects with Major Depressive Disorder	
4.1 Inclusion Criteria	- Comorbid Persistent Depressive Disorder and ADHD allowed; specified that Panic Disorder can be with or without agoraphobia. - Acceptable improvement on $HDRS_{17}$ total score from the screening to baseline visit increased from $< 20\%$ to $\leq 25\%$ - Mirtazapine, fluvoxamine, agomelatine, imipramine, nortriptyline and amitriptyline added to allowed antidepressants. - After completion of the hsCRP < 0.300 mg/dL cohort, retesting for CRP will be allowed, but only for subjects who have hsCRP ≥ 0.250 mg/dL (SI 2.50 mg/L) and < 0.300 mg/dL (SI 3.00 mg/L) at screening. Retesting for CRP is only allowed once.
4.2 Exclusion criteria	- Comorbid Persistent Depressive Disorder and ADHD allowed; specified that Panic Disorder can be with or without agoraphobia. - Length of current major depressive episode increased to 60 months. - Supine systolic blood pressure increased to 150 mmHg.

	- One-time repeat urine drug screen allowed for positive drug screen for barbiturates or opioids.
8. Prestudy and Concomitant Therapy	- Use of prophylactic use of low dose aspirin allowed. - Involuntarily commitment to psychiatric hospitalization limited to the current episode. - Benzodiazepines up to the equivalent of 2 mg of lorazepam per day allowed at intake if administered fixed daily dose for at least 2 weeks prior to screening. - Phenazepam up to 1.5 mg daily allowed. - Zoplicone and melatonin allowed as sleep medications. - Continuous fixed dose or PRN use of sleep medications is allowed. - Trazodone allowed (not exceeding 150 mg/day) given as a sleep aid or for sexual dysfunction). - PRN use of specific NSAIDs allowed. - Requirement for stable frequency of psychotherapy decreased to last 3 months prior to screening. - Psychostimulants for ADHD are prohibited, but cognitive behavioral therapy is allowed.
Rationale: To achieve a better understanding of the relationship between CRP (and potentially other inflammatory biomarkers) and clinical response, by studying 50 additional subjects with hsCRP levels <0.300 mg/dL.	
Synopsis – secondary objectives; 2.1 Objectives;	Four secondary objectives added.
4.1 Inclusion criteria	Inclusion criterion #4 removed.
Synopsis – Statistical Methods; 3. Study Design and Rationale; 4.1 Inclusion Criteria; 5. Treatment Allocation and Blinding; 9.1.3 Double-Blind Treatment Phase; 9.2.2. Endpoints; 11.2 Sample Size Determination; 11.3 Efficacy Analyses	- Figure 1 adjusted - Sample size determination adjusted. - Analyses for additional secondary objectives added. - Group of 50 subjects with screening hsCRP<0.300 mg/dL (SI 3.00 mg/L) added. - 4th stratum with hsCRP level 0.000 to <0.300 mg/dL (SI 0.00 to <3.00 mg/L) added.
Rationale: Administrative: correction MGH-ATRQ	
Attachment 4	Updated version of MGH-ATRQ added, with minimal dose for fluoxetine corrected to 20mg/d and agomelatine, nefazodone, tianeptine and reboxetine added.
Rationale: Administrative: ADR table adjusted	
Section 1.1.2.2.2 Safety	Column with frequency added, to be consistent with IB ED 10 addendum 2

Amendment INT-3 (8 June 2015)

This amendment is considered to be nonsubstantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union, in that it does not significantly impact the safety or physical/mental integrity of subjects, nor the scientific value of the study.

The overall reason for the amendment: The overall reason for the amendment is feedback from the Health Canada to add risk of sepsis according to the Investigator's Brochure.

Applicable Section(s)	Description of Change(s)
Rationale: Sepsis added as an adverse drug reaction.	
1.1.2 Clinical Studies 1.1.2.2.2 Safety	Sepsis added in text and in Table 1. Adverse Drug Reactions with Sirukumab (CNTO136)
Rationale: Administrative: correction text Attachment 3	
Attachment 3	Global improvement section has been deleted as only the Clinical Global Impression Questionnaire-Severity (CGI-S) is used in this study.

Amendment INT-2 (13 May 2015)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

The overall reason for the amendment: The overall reason for the amendment is feedback from the FDA to add an additional clinical laboratory assessment (to monitor neutrophils, platelets, and liver enzymes) at the Week 4 visit, as hematologic effects and effects on liver enzymes occurred within the first 4 weeks of treatment in the Phase 2 RA study (C1377T04), according to the Investigator's Brochure.

Applicable Section(s)	Description of Change(s)
Rationale: To add an additional clinical laboratory assessment at the Week 4 visit.	
Time & Events schedule	Clinical laboratory assessment added on W4 visit.
Rationale: Administrative: Clarification of timing of MGH-ATRQ	
Time & Events schedule	Clarified that MGH –ATRQ is to be done at the first screening visit.
Rationale: Clarify that the Structured Interview Guide for the Hamilton Depression Scale (SIGH-D) will be used for $HDRS_{17}$ assessment.	
Synopsis; 9.2.1 Evaluations	Clarification and rationale added that Structured Interview Guide for the Hamilton Depression Scale (SIGH-D) will be used.
Rationale: Administrative: correction of typo	
Synopsis; 9.2.1 Evaluations	Score for 'nearly every day' for PHQ-9 corrected from '4=Nearly every day' to '3=Nearly every day'
Rationale: Administrative: correction discontinuation of treatment criteria	
10.2 Discontinuation of Study Treatment	QT_c and QT criteria removed as no ECG's are taken during the study
Rationale: Administrative: correction title attachment 3	
Attachment 3	'Severity' added to title to reflect that it is the Clinical Global Impression Questionnaire-Severity (CGI-S) that is used in this study.

Amendment INT-1 (2 Apr 2015)

This amendment is considered to be nonsubstantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union, in that it does not significantly impact the safety or physical/mental integrity of subjects, nor the scientific value of the study.

The overall reason for the amendment: The overall reason for the amendment is to update the physical description of study drug to be consistent with the IB version 9 addendum 1.

Applicable Section(s)	Description of Change(s)
Rationale: IB edition 9 addendum 1 contained updated description of the needle shield for the prefilled syringe (PFS)-Ultrasafe; the info in this protocol is updated so it is consistent.	
14.1. Physical Description of Study Drug	Specified that the needle shield on the PFS (assembled into UltraSafe needle guard) does contain a derivative of natural rubber latex, which may cause allergic reactions in individuals sensitive to latex.
Rationale: Correct an inconsistency in the protocol related to the criterion about improvement of ≥20% on $HDRS_{17}$ total score from the screening to baseline visit.	
4.1. Inclusion Criteria; 4.2. Exclusion Criteria	Clarified that improvement on $HDRS_{17}$ total score from screening to baseline should be less than 20% for a subject to be eligible.
Rationale: To decrease the burden on the subject, certain screening assessments will only be performed once the subject has been confirmed to be eligible for all other screening criteria.	
Synopsis – overview of study design; Time & Events schedule; 3.1 Overview of study design; 3.2 Study design rationale; 4. Subject population; 9.1.2. Screening phase	Split the screening in 2 visits: at the second visit only ²-ray and SAFER interview will be done, if subject has been confirmed eligible for all other screening criteria assessed at the first screening visit.

SYNOPSIS

A Double-Blind, Placebo-Controlled, Multicenter Study of Sirukumab as Adjunctive Treatment to a MonoAminergic antidepressant in Adults with Major Depressive Disorder

Sirukumab (also known as CNTO 136) is a human immunoglobulin G1κ (IgG1κ) monoclonal antibody (mAb) with a molecular weight of approximately 150,000 daltons. Sirukumab binds to and neutralizes human IL-6 and subsequently attenuates IL-6 signaling and the biological effects of IL-6. Sirukumab is being developed for the treatment of disorders of the immune system, including rheumatoid arthritis, and is being studied in neuropsychiatric conditions with an established immune component, such as depression.

OBJECTIVES AND HYPOTHESIS

Primary Objective

The primary objective of this study is to evaluate the efficacy of sirukumab as adjunctive treatment to antidepressant therapy (monoaminergic antidepressant) where sirukumab (administered as a 50mg subcutaneous (SC) injection at Day 1, Day 28 and Day 56 during the 12- week double-blind treatment period) is compared to adjunctive placebo based on the change from baseline to 12-week endpoint in depressive symptoms as measured by the total score on the Hamilton Depression Rating Scale ($HDRS_{17}$), in subjects diagnosed with Major Depressive Disorder (MDD) who have had a suboptimal response to the current standard oral antidepressant therapy and have a screening and baseline high sensitivity C-Reactive Protein (hsCRP) ≥0.300 mg/dL (International System of Units (SI) 3.00 mg/L) (approximately 142 subjects).

Secondary Objectives

- To evaluate the overall safety and tolerability of adjunctive sirukumab compared to adjunctive placebo in subjects with MDD.
- To evaluate the impact of adjunctive sirukumab compared to adjunctive placebo on anhedonia as measured by the change from study baseline to 12-week endpoint on the Snaith Hamilton Pleasure Scale (SHAPS) in subjects with MDD and screening hsCRP ⩾0.300 mg/dL.
- To evaluate the impact of treatment with adjunctive sirukumab compared to adjunctive placebo on global severity of symptoms of MDD, as measured by the change in the Clinical Global Impression - Severity (CGI-S) scale from study baseline to 12-week endpoint in subjects with MDD and screening hsCRP ⩾0.300 mg/dL.
- To evaluate the impact of treatment with adjunctive sirukumab compared to adjunctive placebo on remission and response rates at 12-week end point, defined as a $HDRS_{17}$ total score ≤7 or a ≥ 50% improvement in $HDRS_{17}$ total score from baseline, respectively in subjects with MDD and screening hsCRP ⩾0.300 mg/dL.
- To evaluate the impact of treatment with adjunctive sirukumab compared to adjunctive placebo on subject-reported severity of symptoms of MDD, as measured by the change in the Patient Health Questionnaire (PHQ-9) from study baseline to 1- week endpoint and to 12-week endpoint in subjects with MDD and screening hsCRP ⩾0.300 mg/dL.

- To evaluate the impact of treatment with adjunctive sirukumab compared to adjunctive placebo on fatigue, as measured by the change from study baseline to 1-week, 4-week, 8-week and 12-week endpoint in the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT Fatigue) scale in subjects with MDD and screening hsCRP ⩾0.300 mg/dL.

- To evaluate the efficacy measured by change in the $HDRS_{17}$ scores following adjunctive sirukumab compared to adjunctive placebo in the Treatment Resistant Depression (TRD) versus non-TRD subjects. TRD is defined as having being treated with ≥ 2 trials of antidepressants of adequate dose and duration (according to the Massachusetts General Hospital Antidepressant Treatment History Questionnaire (MGH-ATRQ)) during the current episode.

- To evaluate pharmacokinetics and immunogenicity of sirukumab in subjects with MDD.

- To evaluate the impact of treatment with adjunctive sirukumab in subjects with screening hsCRP≥0.300 mg/dL as compared to in those with screening hsCRP<0.300 mg/dL based on changes from baseline to Week 12 in $HDRS_{17}$ total score.

- To assess the efficacy of sirukumab compared to placebo as adjunctive therapy to an antidepressant in subjects with MDD with screening hsCRP levels <0.300 mg/dL versus those with screening hsCRP levels ≥ 0.300 mg/dL in improving response of depressive symptoms, defined as the proportion of subjects having a ≥50% improvement in $HDRS_{17}$ total score from baseline to the end of Week 12.

- To assess the efficacy of sirukumab compared to placebo as adjunctive therapy to an antidepressant in subjects with MDD with screening hsCRP levels <0.300 mg/dL versus those with screening hsCRP levels ≥ 0.300 mg/dL in achieving remission of depressive symptoms, defined as the proportion of subjects having a $HDRS_{17}$ total score ≤7 at the end of Week 12.

- To evaluate whether hsCRP levels correlate with clinical efficacy as measured by the change from baseline to Week 12 in $HDRS_{17}$ total score.

Exploratory Objectives

- To explore the efficacy of adjunctive sirukumab compared to adjunctive placebo, based on the change from baseline to 12-week endpoint in the Inventory of Depressive Symptomatology – Clinician Rated 30 Item Scale (IDS-C30) in subjects with MDD and screening hsCRP ⩾0.300 mg/dL.
- To explore immune-system related biomarkers (hsCRP, cytokines, chemokines), as well as other mood disorder related biomarkers (growth factors, hypothalamic–pituitary–adrenal (HPA) axis markers, metabolic markers) and to explore the potential correlation between these biomarkers and the clinical response, non-response or safety parameters of sirukumab.
- To explore genetic and epigenetic variation that may be related to clinical response, non-response, or safety parameters of sirukumab.
- To explore the effect of sirukumab on the pharmacokinetics of monoaminergic antidepressants.

- To explore the relationship between the severity of childhood trauma as assessed through the Childhood Trauma Questionnaire and the change in $HDRS_{17}$ scores following adjunctive sirukumab or placebo.

Hypothesis

The primary hypothesis of this study is that sirukumab will determine significant improvement in depressive symptoms from baseline compared to placebo when administered as an adjunctive treatment to a monoaminergic antidepressant in the treatment of patients with MDD who have shown a suboptimal response to standard oral antidepressant therapy and have a screening and baseline hsCRP ≥ 0.300 mg/dL (SI 3.00 mg/L), demonstrated by improvement in depressive symptoms from baseline to 12-week endpoint in the Hamilton Depression Rating Scale ($HDRS_{17}$) total score.

OVERVIEW OF STUDY DESIGN

This is a multicenter, double-blind, placebo-controlled study in male and female subjects, 21 to 64 years of age inclusive, with MDD who have had a suboptimal response to standard oral antidepressant therapy; have failed no more than 3 antidepressant treatments in the current major depressive episode; approximately 192 subjects will be enrolled.
Determination of suboptimal response to the current standard oral antidepressant therapy will be made retrospectively using the structured MGH-ATRQ. Determination of the number of failed antidepressant treatments in the current episode will be made retrospectively using medical or pharmacy records and documented on the MGH-ATRQ. Serum concentration of hsCRP will be measured from a venous blood sample at screening.

The study will consist of 3 phases: a screening phase of up to 4 weeks, consisting of 2 visits, a 12 week double-blind treatment phase, and a 14 week posttreatment follow-up phase. The total duration of subject participation will be approximately 26 weeks.

Screening Phase:

Subjects with a Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) diagnosis of MDD, confirmed by the MINI International Neuropsychiatric Inventory (MINI), who are currently being treated with a monoaminergic antidepressant and have failed no more than 3 antidepressants (of adequate dose and duration) in the current major depressive episode will be eligible for screening. Screening will include informed consent, evaluation for eligibility in the study, medical history, physical and psychiatric evaluations, venous blood sampling for hsCRP assay and standard labs. Determination of suboptimal response to the current standard oral antidepressant therapy will be made retrospectively using the structured MGH-ATRQ. Determination of failure of antidepressant treatments in the current episode will be made retrospectively using medical or pharmacy records and documented on the MGH-ATRQ. Subjects with partial improvement (<50%) according to the MGH-ATRQ and moderate to severe depression ($HDRS_{17}$ total score ≥18 at screening, as measured by a remote independent rater) will be eligible for inclusion. Subjects must be currently receiving no more than 2 of the following antidepressants for at least 6 weeks duration at screening with at least one antidepressant being at an adequate therapeutic dose, as determined by the MGH-ATRQ: bupropion, fluoxetine, citalopram, escitalopram, sertraline, paroxetine, venlafaxine,

desvenlafaxine, mirtazapine, fluvoxamine, agomelatine, imipramine, nortriptyline, amitriptyline, duloxetine, vilazodone, vortioxetine and levomilnacipram.
The screening phase will consist of 2 visits; the procedures scheduled during the first screening visit may be divided over two days, according to operational and/or site/country-specific needs; in case the first screening visit is conducted over two days, the following assessments must be performed on the same day: C-SSRS, IDS-C30 and $HDRS_{17}$.

The second visit will only be performed once all in- and exclusion criteria have been confirmed, except for the SAFER interview and chest X-ray (if applicable). These will only be performed at the second screening visit. If some in and/or exclusion criteria still have to be confirmed at the time of this second screening visit, this will be discussed prior to this second screening visit with the JRD responsible safety physician on a case by case basis.

Double blind treatment phase:

Subjects who continue to meet inclusion and exclusion criteria at the baseline visit will be eligible for randomization. At the baseline visit, subjects must have a $HDRS_{17}$ total score ≥18, as measured by a remote independent rater, and must not demonstrate an improvement of >25 % on their HDRS17 total score from the screening to baseline visit. Randomization will be stratified by country and screening hsCRP level: 0.00 to <0.300 mg/dL (SI 0.00 to <3.00 mg/L), ≥0.300 to <0.500 mg/dL (SI ≥3.00 to <5.00 mg/L), ≥0.500 to <0.800 mg/dL (SI ≥5.00 to <8.00 mg/L), and ≥0.800 mg/dL (SI ≥8.00 mg/L). Subjects will receive either adjunctive placebo or adjunctive sirukumab in a 1:1 ratio.

Refer to the Time and Events Schedule for a list of study evaluations that will be performed during the double-blind treatment phase.

Posttreatment Follow-Up:

Subjects will have two follow-up safety visits, 8 and 14 weeks after last SC injection, to assess clinical condition, monitor safety and adverse events and record concomitant medications. Subjects with unresolved adverse events at Week 22 will be continued to be monitored as clinically appropriate to ensure subjects' safety.

SUBJECT POPULATION

In total, approximately 192 subjects will be enrolled in this study, with approximately 96 subjects randomized per treatment group. The sample size may increase up to 228 if the interim analysis suggests the need to do so in order to ensure adequate statistical power to test the primary hypothesis.

The target study population is male and female subjects with MDD who have had a suboptimal response to standard oral antidepressant therapy; have failed no more than 3 antidepressant treatments in the current major depressive episode; approximately 142 subjects with screening

hsCRP ≥0.300 mg/dL (SI 3.00 mg/L) and approximately 50 subjects with screening hsCRP<0.300 mg/dL (SI 3.00 mg/L) will be enrolled.

Subjects will be enrolled after reading the subject information sheet and signing the informed consent form (ICF) indicating that they understand the purpose of the study and procedures required for the study and are willing to participate in the study and comply with the study procedures.

DOSAGE AND ADMINISTRATION

Subjects who meet the study criteria of a $HDRS_{17}$ total score ≥ 18 at the baseline visit will be randomly assigned in a 1:1 ratio to receive adjunctive treatment with SC injection of placebo or sirukumab 50 mg, while continuing on their baseline oral monoaminergic antidepressant(s). The matching placebo injection will consist of an identical volume of placebo solution, administered SC at the same time points. All subjects will receive 3 injections in total, one injection each at Day 1, Day 28 and Day 56.

If an injection is missed, every effort should be made to have the missed injection administered within 4 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 JRD responsible safety physician.

The study agent will be administered SC at the site by a health care professional.

EFFICACY EVALUATIONS/ENDPOINTS

Primary Efficacy Evaluation/Criteria

The primary efficacy endpoint for this study will be the improvement in depressive symptoms, as measured by the change in the $HDRS_{17}$ total score from baseline to 12-week endpoint (see section Efficacy Analyses). The primary comparisons will be between the adjunctive sirukumab group and the adjunctive placebo group in subjects hsCRP ⩾0.300 mg/dL at screening and baseline.

Hamilton Depression Rating Scale ($HDRS_{17}$)

The $HDRS_{17}$ is a clinician-administered rating scale designed to assess the severity of symptoms in subjects diagnosed with depression (Hamilton M 1960) with a score range of 0 to 52. It is the most widely used symptom severity measure for depression. Each of the 17 items is rated by the clinician on either a 3- or a 5-point scale. The $HDRS_{17}$ has an inter-rater reliability correlation of r = .90 and the internal consistency of the measure is reported to be high with a coefficient alpha of 0.88. Criterion-related validity for this measure is high (Knesevich J et al., 1977). The original HDRS17 scale lacks instructions for administration and clear anchor points for the assignment of severity ratings. For this reason, the structured interview guide version of the $HDRS_{17}$ (the Structured Interview Guide for the Hamilton Depression Scale [SIGH-D]) will be used in the current study to facilitate and standardize gathering clinical information from the subject.

An example of the $HDRS_{17}$ is provided in Attachment 7.

Secondary Efficacy Evaluations/Criteria

Secondary efficacy endpoints will include the change from baseline to 12-week endpoint between the adjunctive sirukumab group and the adjunctive placebo group in the SHAPS total score, CGI-S, PHQ-9 and FACIT as well as the distribution of remitters and responders in subjects with screening hsCRP ≥ 3.00 mg/L (the number and percentage of subjects in remission as measured by a $HDRS_{17}$ total score ≤ 7 or responders defined as ≥ 50% improvement on the $HDRS_{17}$ from baseline to 12 week endpoint). The same secondary efficacy endpoints will be compared between subjects with screening hsCRP ≥3.00 mg/L and subjects with hsCRP <3.00 mg/L

Clinical Global Impression - Severity (CGI-S)

The CGI-S will provide an overall clinician-determined summary measure that takes into account all available information, including knowledge of the subject's history, psychosocial circumstances, symptoms, behavior, and the impact of the symptoms on the subject's ability to function (Guy 1976). The CGI evaluates the severity of psychopathology from 1 to 7.

An example of the CGI-S is provided in Attachment 3.

Patient Health Questionnaire (PHQ-9)

The PHQ-9 will be used as a subject-reported measure of depressive symptomatology (Spitzer 1999). The PHQ-9 is a 9-item scale, where each item is rated on a 4-point scale (0=Not at all, 1=Several Days, 2=More than half the days, and 3=Nearly every day), with a total score range of 0 to 27. The recall period is 2 weeks.

An example of the PHQ-9 is provided in Attachment 9.

Snaith–Hamilton Pleasure Scale (SHAPS)

Anhedonia, the inability to experience pleasure, is a major endophenotype of depression. The Snaith–Hamilton Pleasure Scale (SHAPS) is a self-reported, short, 14-item instrument to measure anhedonia, which has been shown to be valid and reliable in normal and clinical samples (Snaith et al, 1995). Each of the 14 items has a set of four response categories: Definitely Agree (= 1), Agree (= 2), Disagree (= 3), and Definitely Disagree (= 4). A higher total score indicates higher levels of state anhedonia.

An example of the SHAPS is provided in Attachment 10.

Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT Fatigue)

The FACIT-Fatigue is a questionnaire that assesses self-reported tiredness, weakness, and difficulty conducting usual activities due to fatigue. The total FACIT-Fatigue score ranges from 0 to 52, with a higher score indicating less fatigue (Webster et al., 1999).

An example of the FACIT is provided in Attachment 11.

Exploratory Efficacy Evaluations/Criteria

Exploratory efficacy evaluations will include the change from baseline to 12-week endpoint in the IDS-C30 total score in subjects with MDD and screening hsCRP ⩾0.300 mg/dL, evaluation of the association between change from baseline of the $HDRS_{17}$, baseline and post-treatment biomarker measurements (including hsCRP)**,** the effect of sirukumab on the pharmacokinetics of monoaminergic antidepressants, evaluation of the relationship between the severity of childhood trauma as assessed through the CTQ and the change in $HDRS_{17}$ scores following adjunctive sirukumab or placebo and assessment of genes/genotypes.

Inventory of Depressive Symptomatology – Clinician Rated 30 (IDS-C30)

The clinician-rated IDS is a 30-item, depression-specific symptom severity rating scale (Rush et al., 1986). The IDS is designed to measure the specific signs and symptoms of depression, including melancholic, atypical and anxious features. Scores range from 0 to 84 with higher scores representing greater severity of depressive symptoms. The inter-rater reliability and internal consistency coefficients are high (Rush et al., 1996). The IDS-C and the IDS-self report have reasonable construct validity, and a concurrent validity index above 0.90, correlating well with the $HDRS_{17}$ and the Beck Depressive Inventory (Rush et al., 1996).

An example of the IDS-C30 is provided in Attachment 8.

Childhood Trauma Questionnaire (CTQ)

The CTQ was developed as a screening tool for histories of abuse and neglect. The self-report includes a 28-item test that measures 5 types of maltreatment – emotional, physical, and sexual abuse, and emotional and physical neglect (Bernstein et al., 1998). A 5-point Likert scale is used for the responses which range from Never True to Very Often True.

An example of the CTQ is provided in Attachment 12.

PHARMACOKINETIC EVALUATIONS

Venous blood samples will be collected for determination of serum sirukumab concentrations at the time points specified in the Time and Event Schedule. Additionally, to assess the effect of sirukumab on the pharmacokinetics of monoaminergic antidepressants, blood samples will be collected for the determination of monoaminergic antidepressant concentrations before and after sirukumab treatment.

Serum sirukumab concentrations will be summarized by visit. Monoaminergic antidepressants concentration data will be summarized.

IMMUNOGENICITY EVALUATIONS

Antibodies generated in response to sirukumab have the potential to accelerate the clearance of the drug and hence affect efficacy and safety. To evaluate the immunogenicity of sirukumab in subjects with MDD, serum samples for the detection of antibodies to sirukumab will be collected according to the Time and Events Schedule. The incidence and titers of antibodies to sirukumab will be summarized.

BIOMARKER EVALUATIONS

During the study, blood and saliva will be collected at the time points indicated in the Time and Events schedule for the assessment of biomarkers related to the immune system activity, hypothalamus pituitary adrenal (HPA) axis activation, neurotrophic factors and metabolic factors to allow for exploratory immunophenotyping and for an exploratory pharmacodynamics evaluation.

PHARMACOGENOMIC (DNA) EVALUATIONS

Pharmacogenomic blood samples will be collected to allow for the identification of genetic and/or epigenetic factors that may influence the pharmacokinetics, pharmacodynamics, efficacy, safety, or tolerability of sirukumab in a sample of subjects with MDD.

SAFETY EVALUATIONS

Safety will be monitored by the evaluation of adverse events, clinical laboratory test results, vital signs measurements, body weight, physical examination findings, allergic and injection site reactions to SC injections, early detection of active tuberculosis and hepatobiliary abnormalities. The Columbia Suicide Severity Rating Scale (C-SSRS) will be administered to monitor suicidal ideation and behavior.

STATISTICAL METHODS

Sample Size Determination

The expected sample size of 142 subjects for those with screening hsCRP≥0.300 mg/dL was determined based on the assumption of an effect size of at least 0.5 for the $HDRS_{17}$ (difference in mean change from baseline to Week 12 endpoint between the sirukumab and placebo groups of 4 units with SD=8). This is considered to be a clinically relevant difference in a population with suboptimal response to standard oral antidepressant therapy. Power is set at 90.0%, with a 1-sided alpha of 0.125 and a 12-week drop-out rate of 25%. It was also assumed that 10% of the

randomized subjects would be excluded from the primary efficacy analysis due to having hsCRP ≥0.300 mg/dL (SI 3.00 mg/L) at screening but not baseline. The number of treatment resistant subjects will be monitored on an on-going basis to ensure enough sample size for a secondary efficacy analysis in the TRD population. If an insufficient number of TRD subjects is being enrolled in the study, the sponsor will encourage the sites to enroll more TRD subjects. Note that the study is not statistically powered for comparing effect sizes between treatment groups in the TRD population.

Sample size determination for the additional stratum (screening hsCRP < 0.300 mg/dL (SI 3.00 mg/L):

Assuming a difference for the mean change from baseline to the week 12 primary endpoint of 4 between the hsCRP ≥0.300 mg/dL (SI 3.00 mg/L) stratum and the hsCRP < 0.300 mg/dL (SI 3.00 mg/L) stratum, and a SD of 8, a 1-sided alpha of 0.125, and a week 12 drop-out rate of 25%, a sample size of 71 subjects in the active treatment group (142 total) in the hsCRP ≥0.300 mg/dL (SI 3.00 mg/L) stratum and 25 subjects in the active treatment group (50 total) in the hsCRP < 0.300 mg/dL (SI 3.00 mg/L) stratum would provide 75% power to detect a difference between the two strata.

Interim Analysis

An interim analysis will be conducted to monitor safety data, assess futility, sample size re-estimation, and hsCRP enrichment criteria. The interim analysis is planned when 40-50% of the planned number of subjects who are eligible to be included in the primary efficacy analysis complete the week 12 assessment. Both Frequentist and Bayesian approaches will be applied for the interim analysis. Detailed approaches will be described in the interim statistical analysis plan and the Interim Analysis Committee (IAC) charter.

The interim analysis results will be used to assess the study for futility and as such the study may be terminated early if the probability of success of the study is calculated to be very low. In addition, based on the results of hsCRP-response relationship, the study may continue with the enriched population using a selected hsCRP level. The decision rule for futility at the interim analysis will be detailed in the interim SAP and the IAC charter.

In addition, the sample size for the study may be increased up to N=228 if the interim data suggest this is necessary to ensure robust conclusions.

Analyses for primary efficacy

Analyses for primary efficacy will be done when all subjects have completed the 12-week double-blind treatment phase. Detailed statistical approaches are summarized below and will be described in more detail in the statistical analysis plan. The results will be used to assess the potential efficacy of sirukumab in the treatment of MDD and to make strategic internal decisions regarding the development of the compound. This will be the final analyses for the primary efficacy. The results will not impact the further conduct of the trial.

Efficacy Analyses

Three analyses sets will be defined for efficacy analyses: the modified intent-to-treat 1 (mITT1), the modified intent-to-treat 2 (mITT2), and the modified intent-to-treat 3 (mITT3) analyses sets. The mITT1 analysis set is defined as all randomized subjects with hsCRP ≥0.300 mg/dL at

screening and baseline who receive at least 1 dose of study drug and have both the baseline and at least one postbaseline $HDRS_{17}$ total score measured within the double-blind treatment period. The mITT2 analysis set is defined as all randomized subjects (regardless of screening hsCRP level) who receive at least 1 dose of study drug and have both the baseline and at least one postbaseline $HDRS_{17}$ total score measured within the double blind treatment period. The mITT3 analysis set is defined as all randomized subjects with hsCRP≥ 0.300 mg/dL at screening who receive at least 1 dose of study drug and have both the baseline and at least one postbaseline $HDRS_{17}$ total score measured within the double blind treatment period.

The primary efficacy analyses will be based on the mITT1 analysis set. The sirukumab treatment group will be compared with the placebo group using the primary efficacy endpoint, change from baseline in $HDRS_{17}$ total score, with the comparison performed by means of a mixed-effects model using repeated measures (MMRM), with time, treatment (placebo, sirukumab), country, hsCRP stratification levels [i.e., ≥3.00 to <5.00 mg/L (≥0.300 to <0.500 mg/dL), ≥5.00 to <8.00 mg/L (≥0.500 to <0.800 mg/dL), and ≥8.00 mg/L (≥0.800 mg/dL)], and time-by-treatment interaction as factors, baseline $HDRS_{17}$ total score as a continuous covariate, and a random subject effect. An unstructured variance-covariance matrix will be used. The comparison of sirukumab versus placebo will be performed using the appropriate contrast. Subgroup analysis will be carried out for the primary efficacy endpoint based on TRD versus non-TRD status.

Analyses of secondary efficacy endpoints will be based on the mITT2 analysis set. The change from baseline to 12-week endpoint for the secondary continuous efficacy endpoints will be analyzed in the same way as for the HDRS17 total score.

The hsCRP ≥0.300 mg/dL (SI 3.00 mg/L) stratum will be compared with the hsCRP < 0.300 mg/dL (SI 3.00 mg/L) stratum using the primary efficacy endpoint, i.e., change from baseline to Week 12 in HDRS17 total score. A mixed effects model using repeated measures (MMRM), with time, hsCRP stratum (hsCRP ≥0.300 mg/dL (SI 3.00 mg/L), hsCRP < 0.300 mg/dL (SI 3.00 mg/L), treatment, country, and time-by-hsCRP stratum interaction as factors, baseline HDRS17 total score as a continuous covariate, and a random subject effect will be employed. An unstructured variance-covariance matrix will be used. The comparison of hsCRP ≥0.300 mg/dL (SI 3.00 mg/L) versus hsCRP < 0.300 mg/dL (SI 3.00 mg/L) will be performed using the appropriate contrast. Note that subjects whose CRP drops from ≥ 0.300 mg/dL (SI 3.00 mg/L) at screening to <0.300 mg/dL (SI 3.00 mg/L) at baseline will be included in the 4th stratum hsCRP (< 0.300 mg/dL (SI 3.00 mg/L) group) for the analyses.

In addition to evaluating hsCRP as a categorical variable (hsCRP<0.300mg/dL; hsCRP ⩾0.300 to <0.500 mg/dL; hsCRP ⩾0.500 to <0.800 mg/dL and hsCRP ⩾0.800 mg/dL), hsCRP will be analyzed as a continuous variable and correlated with the primary efficacy endpoint (change from baseline to Week 12 in HDRS17 total score) using Pearson and Spearman methods.

Sensitivity analyses of the primary endpoint will also be performed; these will be detailed further in the Statistical Analysis Plan. These will include analysis based on the mITT3 analysis set (that is, the mITT1 analysis set plus those subjects excluded for having a screening hsCRP ≥0.300 mg/dL (SI 3.00 mg/L) but hsCRP <0.300 mg/dL (SI 3.00 mg/L) at baseline). These will also include an analysis of covariance (ANCOVA) model using the last observation carried forward (LOCF) imputation method, with factors for treatment, country, and hsCRP

stratification levels, and baseline HDRS17 total score as a covariate. Other sensitivity analyses may also be performed to investigate the robustness of treatment estimates to the observed pattern of, and/or reason for, early withdrawals. Descriptive statistics for values and changes from baseline will be provided for all efficacy measures, including individual items for selected scales, subscales, and total score, at each time point of the double-blind treatment phase.

Sensitivity analyses of the secondary endpoints will also be performed; these will be detailed further in the Statistical Analysis Plan. These will include analysis based on the mITT1 and mITT3.

Details of the exploratory analyses will be provided in the SAP.

Safety analyses

All safety analyses will be performed based on the safety analysis set, which will include all randomized subjects who receive at least 1 dose of study drug. Adverse events will be coded using the current version of MedDRA and tabulated by system organ class and preferred term. Adverse events will also be tabulated by severity and relationship to study drug and will be presented by treatment group. Serious adverse events and treatment-limiting adverse events will be summarized separately.

Clinical laboratory test results, vital sign values, body weight and changes from baseline will be tabulated over time by treatment group, using descriptive statistics. Any treatment-emergent abnormalities will be presented. A listing of subjects with markedly abnormal results will also be provided. Subjects with changes from screening in physical examination findings from normal to abnormal will be listed.

The suicidality data collected from the C-SSRS using aggregate endpoints of suicidal behavior and suicidal ideation separately will be summarized descriptively at each scheduled visit by treatment group. Further details will be presented in the SAP.

TIME AND EVENTS SCHEDULE

Phase	Screening	Double-Blind Treatment[a]					Early withdrawal[b,s]	Posttreatment[a,b] (Follow up 1)	Posttreatment[a,b] (Follow up 2)
Visit	**1**	**2**	**3**	**4**	**5**	**6**		**7**	**8**
Week (end of)	**-**	**-**	**1**	**4**	**8**	**12**		**16**	**22**
Day	**-28 to -1**	**1**	**7**	**28**	**56**	**84**		**112**	**154**
Study Procedures									
Screening/Administrative									
Informed consent	X								
Inclusion/exclusion criteria	X	X							
Medical history and demographics	X								
Prestudy therapy MGH-ATRQ[c]	X								
SAFER	X[e]								
Preplanned surgery/procedure(s)	X								
MINI	X								
Study Drug Administration									
Randomization		X							
SC administration of sirukumab or placebo[f]		X		X	X				
Post-administration injection-site evaluation		X		X	X				
Post-administration allergic reaction evaluation		X		X	X				
Drug accountability		X		X	X				
Safety Assessments									
Physical examination	X	X				X	X		
C-SSRS	X[d]	X	X	X	X	X	X	X	X
Vital signs[g]	X	X		X		X	X	X	X
Body weight[h]	X	X				X	X		X
Height	X								
Clinical laboratory assessments[i]	X	X		X	X	X	X		X
Serology	X								
Lipid panel (fasting)		X			X	X	X		X
TB test (QuantiFERON®-TB Gold Test)	X								

Phase	Screening	Double-Blind Treatment[a]					Early withdrawal[b,s]	Posttreatment[a,b] (Follow up 1)	Posttreatment[a,b] (Follow up 2)
Visit	**1**	**2**	**3**	**4**	**5**	**6**		**7**	**8**
Week (end of)	**-**	**-**	**1**	**4**	**8**	**12**		**16**	**22**
Day	**-28 to -1**	**1**	**7**	**28**	**56**	**84**		**112**	**154**
Chest x-ray[j]	X[e]								
TB evaluation		X	X	X	X	X			
12-lead ECG	X								
Urine drug screen	X[k]	X							
Alcohol breath test	X	X							
Pregnancy test [l]	X	X		X	X		X	X	
Clinician-administered assessments									
IDS-C30	X[d]	X	X	X	X	X	X	X	X
$HDRS_{17}$ – performed by remote independent rater	X[d]	X	X	X	X	X	X		
CGI-S		X	X	X	X	X	X	X	X
Patient-reported assessments									
CTQ		X							
PHQ-9		X	X	X	X	X	X	X	X
SHAPS		X	X	X	X	X	X	X	X
FACIT Fatigue		X	X	X	X	X	X	X	X
Pharmacokinetics and immunogenicity									
Blood sample for sirukumab concentration[m]		X	X	X	X	X	X	X	X
Blood sample for antibodies to sirukumab[m]		X		X	X	X	X		X
Blood sample for monoaminergic antidepressants[n]		X	X			X		X	X
Biomarkers									
hsCRP measurement[o]	X	X	X			X			X
Blood sample for biomarkers[o]		X	X			X			X
Blood sample for DNA[p]		X	X			X			X
Saliva sample for cortisol[q]		X	X			X			X

Phase	Screening	Double-Blind Treatment[a]					Early withdrawal[b,s]	Posttreatment[a,b] (Follow up 1)	Posttreatment[a,b] (Follow up 2)
Visit	1	2	3	4	5	6		7	8
Week (end of)	-	-	1	4	8	12		16	22
Day	-28 to -1	1	7	28	56	84		112	154
Ongoing Subject Review									
Adherence to baseline oral antidepressants		X	X	X	X	X	X	X	X
Concomitant therapy [r]	*Continuous*								
Adverse events [r]	*Continuous*								

Footnotes:

a. Visits 2 and 3 should be conducted within +/-3 days of the scheduled day; all following visits should be conducted within +/-7 days of the scheduled day.

b. If a subject discontinues treatment before the end of the double-blind treatment phase or withdraws from the study, early withdrawal and post-treatment assessments should be obtained. Follow-up visit will take place 8 and 14 weeks after last dose intake.

c. Prestudy therapy will include all medications taken within 3 months before screening.

d. In case the first screening visit is conducted over two days, the following assessments must be performed on the same day: C-SSRS, IDS-C30 and $HDRS_{17}$.

e. To be done once all other screening assessments have been done and subject has been confirmed eligible according those assessments.

f. All assessments should be done prior to SC administration of sirukumab or placebo, except for post-administration injection-site and allergic reaction evaluation and drug accountability.

g. Supine blood pressure (after being in supine position for at least 5 minutes), pulse, and oral temperature.

h. Body weight will be measured with subjects lightly clothed.

i. Serum chemistry (including thyroid-stimulating hormone and follicle-stimulating hormone, if applicable [at screening only]), hematology and urinalysis. At week 4 no urinalysis, only serum chemistry and hematology.

j. Chest x-ray taken up to 3 months prior to Day 1 may be used to qualify at screening.

k. Refer to study exclusion criteria for circumstances in which a repeat test during screening is permitted.

l. Performed for all women of childbearing potential. Serum pregnancy test performed at screening and urine pregnancy test at other time points. For visits with study agent administration pregnancy test must be performed before the administration of the study agent. If the urine pregnancy test is positive, a serum β-hcg test will be performed. Investigators may perform additional pregnancy testing at their discretion as clinically needed.

m. Venous blood samples will be collected for the analyses of serum sirukumab concentrations and antibodies to sirukumab. Each serum sample will be split into 3 aliquots (1 aliquot for serum sirukumab concentration, 1 aliquot for antibodies to sirukumab, and 1 aliquot as a back-up). For visits with study agent administration (ie, Day 1, 28 and 56), blood samples MUST be collected BEFORE the administration of the study agent.

n. Venous blood samples for analysis of plasma monoaminergic antidepressants concentrations will be collected on Day 1 and 7 before sirukumab administration and on Day 84, 112 and 154. Samples collected after Day 1 must be collected at the same time as samples on Day 1 (+/- 1 hour).

o. Venous blood samples will be collected for biomarkers analysis. hsCRP measurement at screening will be used to assess eligibility. At visits at which an injection is scheduled, blood samples will be collected prior to dosing. Samples should be collected in the morning between 8 and 10 AM and under fasted conditions (for at least 8 hours), if feasible.

p. Venous blood samples will be collected for genetic research in this study.

[q.] Saliva samples will be collected by the subject the day before their visit just before bed and again at waking. Saliva samples should be collected with a site-provided standard collection device.

[r.] Concomitant therapies and adverse events must be recorded throughout the study beginning with signing of the informed consent to the final follow up visit (Visit 8).

[s.] Early withdrawal visit evaluations will be performed in subjects who prematurely discontinue study treatment (see Section 10.2, Discontinuation of Study Treatment) and in subjects who withdraw consent from the study (see Section 10.3, Withdrawal from the Study). The Early Withdrawal visit evaluation should be performed as soon as possible after the last dose of study drug is taken.

ABBREVIATIONS

ACR	American College of Rheumatology
ADHD	Attention deficit hyperactivity disorder
ADR	Adverse drug reaction
AE	Adverse event
ALT	alanine aminotransferase
ANC	Absolute neutrophil count
ANCOVA	Analysis of Covariance
AST	Aspartate aminotransferase
$AUC_{inf.}$	area under the concentration versus time curve extrapolated to infinity
BCG	Bacille Calmette-Guérin
CGI-S	Clinical Global Impression – Severity
CL	Clearance
CLE	Cutaneous Lupus Erythematosus
C_{max}	Maximum observed serum concentration
CRF	case report form
CRP	C-reactive protein
CSSR-S	Columbia Suicide Severity Rating Scale
CTQ	Childhood Trauma Questionnaire
DCF	data clarification form
DSM-5	Diagnostic and Statistical Manual of Mental Disorders (5th edition)
ECG	Electrocardiogram
eCRF	Electronic case report form
eDC	electronic data capture
FACIT	Functional Assessment of Chronic Illness Therapy
FSH	Follicle stimulating hormone
FT4	Free thyroxine
GAD	Generalized Anxiety Disorder
GCP	Good Clinical Practice
HBsAg	hepatitis B surface antigen
HDL	high-density protein
HDRS	Hamilton Depression Rating Scale
HIV	human immunodeficiency virus
HPA	hypothalamic–pituitary–adrenal
hsCRP	high sensitivity C-Reactive Protein
IAC	Interim Analysis Committee
ICF	informed consent form
ICH	International Conference on Harmonisation
IDS-C30	Inventory of Depressive Symptomatology – Clinician Rated 30 Item Scale
IEC	Independent Ethics Committee
IgG	Immunoglobulin G
IL-6	Interleukin 6
IRB	Institutional Review Board
IV	intravenous
IWRS	interactive web response system
LDL	low-density protein
LOCF	last observation carried forward
LPS	lipopolysaccharide
mAb	monoclonal antibody
MDD	Major Depressive Disorder
MedDRA	Medical Dictionary for Regulatory Activities
MGH-ATRQ	Massachusetts General Hospital Antidepressant Treatment History Questionnaire
MINI	MINI International Neuropsychiatric Inventory
mITT	Modified Intent-to-Treat
MTX	Methotrexate
NCI-CTCAE	National cancer Institute Common Terminology Criteria for Adverse Events

NOAEL	No observed adverse effect level
NSAID	nonsteroidal anti-inflammatory drug
PA	posterior-anterior
PSF	pre-filled syringe
PHQ-9	Patient Health Questionnaire
PK	Pharmacokinetic
PPD	purified protein derivative
PQC	Product Quality Complaint
PRN	Pro re nata / as needed
PRO	patient-reported outcome(s)
q2w	every 2 weeks
q4w	every 4 weeks
RA	rheumatoid arthritis
SAA	serum amyloid A
SAP	Statistical Analysis Plan
SC	subcutaneous
SHAPS	Snaith Hamilton Pleasure Scale
SI	International System of Units
SIGH-D	Structured Interview Guide for the Hamilton Depression Scale
SLE	Systemic Lupus Erythematosus
SUSAR	Suspected Unexpected Serious Adverse Reaction
$T_{1/2}$	Half-life
TB	time corresponding to the maximum observed serum concentration (single dose), or the first time
T_{max}	to reach the Cmax (multiple dose)
TNFα	Tumor Necrosis Factor alpha
TRD	Treatment Resistant Depression
TSH	Thyroid stimulating hormone
ULN	upper limit of normal
V_z	volume of distribution based on terminal phase
WBC	white blood cell

1. INTRODUCTION

Sirukumab (also known as CNTO 136) is a human immunoglobulin G1κ (IgG1κ) monoclonal antibody (mAb) that binds to human IL-6 with high affinity and specificity.

Low grade systemic inflammation, characterized by mild elevations in peripheral cytokine levels and other chemokines, has been demonstrated in depressed mood states (Maes 1999; Dowlati et al., 2010; Hiles et al., 2012; Howren et al., 2009). Interleukin-6 (IL-6) is a cytokine known for its pleiotropic and proinflammatory functions which has been shown in two recent meta-analyses to be elevated in clinical depression (Dowlati et al., 2010; Hiles et al., 2012).

Major Depressive Disorder (MDD) is well known to be a heterogeneous illness, and the approximately one-third of depressed patients who are deemed to be treatment resistant may have distinct mechanisms underlying their depression, including systemic inflammation, resulting in reduced responsiveness to traditional monoamine treatment approaches. In fact, IL-6 levels correlate with depression severity in patients who do not respond to conventional antidepressant treatments (Lanquillon et al., 2000), suggesting that a subset of depressed patients with treatment resistance may have an immune-mediated component to their illness which is evident in the periphery.

Recent nonclinical data have demonstrated that rodents predisposed to develop a depressed phenotype in response to stress exhibit pre-existing evidence of immune dysregulation, including greater secretion of IL-6 in response to ex vivo lipopolysaccharide (LPS) stimulation (Hodes et al., 2014). LPS challenge in humans is also associated with an acute increase in inflammatory cytokines, including Tumor Necrosis Factor alpha (TNF-α) and IL-6, which correlates with increased anxiety and depression levels following LPS challenge (Reichenberg et al., 2003). Similarly, monocytes from depressed subjects show increased IL-6 production after incubation with LPS compared to control subjects (Lisi et al., 2013). Interestingly, a recent study in teachers suffering from chronic work stress showed that those teachers with the highest effort-reward imbalance display higher IL-6 production after ex-vivo LPS stimulation, suggesting an increased inflammatory potential similar to that demonstrated in rodents (Bellingrath et al., 2013). In addition, in the same study dexamethasone had a lower capacity to suppress IL-6 production in vitro. This is not surprising in that clinical depression has long been associated with abnormalities of the hypothalamic-pituitary-adrenal (HPA) axis. Interestingly, IL-6 has significant neuroendocrine effects, including being a strong activator of the HPA axis. In turn, cortisol inhibits IL-6 secretion, restraining the inflammatory response during and after stress. Chronic stress has been shown to induce glucocorticoid resistance, which may enable a relatively unchecked inflammatory state. In fact, the normal phasic relationship between cortisol and IL-6 has been shown to be disrupted in depression, potentially contributing to chronic inflammation (Alesci et al., 2005).

These nonclinical and clinical data suggest that a genetic predisposition to heightened inflammatory response may be exacerbated by exposure to stress, and may be associated with a greater risk for developing depression-like behaviors in animals and depressive disorders in

humans. Neutralizing IL-6 is therefore an attractive target for antidepressant treatments. This study will focus on investigating the efficacy of the anti-IL-6 monoclonal antibody (mAb), sirukumab, for the treatment of depression.

Although the most commonly prescribed antidepressant classes, the monoaminergic antidepressants, have been shown to exhibit some minor anti-inflammatory effects (Miller et al., 2009), there is a significant subset of depressed patients who experience minimal response to these treatments. According to the findings from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, response to the antidepressant treatment citalopram was less than 50%, with less than one-third of patients achieving remission (Trivedi et al., 2006). Recent studies suggest that this subset of patients, who do not respond to conventional antidepressant treatments, have elevated immune markers. For example, this association was demonstrated in a study of depressed patients treated with the tricyclic antidepressant, amitriptyline. Compared to healthy control subjects, baseline production of IL-6 was significantly lower in depressed patients responding to amitriptyline treatment, whereas IL-6 was significantly higher in treatment nonresponders. These data suggest that IL-6 levels or other inflammation-related biomarkers might dichotomize patients into subsequent responders and nonresponders prior to the initiation of treatment with traditional, monamine-based antidepressant treatments (Lanquillon et al, 2000).

Recent data also support the idea that failure to normalize elevations in peripheral IL-6 may characterize subjects who do not respond to conventional antidepressants: a study in 50 subjects with MDD showed that after 12 weeks of treatment with antidepressants, treatment-responders showed decreased IL-6 compared to baseline, while subjects who continued to fulfill MDD criteria did not (Dahl et al., 2014). Overall, these data suggest that elevation of peripheral cytokines, and IL-6 in particular, might characterize a subset of subjects less prone to respond to conventional antidepressants and who show persistence of IL-6 elevation after ineffective treatment.

It remains unknown as to whether monotherapy treatments targeting specific aspects of the immune response will be effective in treating patients with suboptimal response to standard oral antidepressant therapy, or whether patients may respond best to an anti-inflammatory treatment given adjunctive to a background monoamine-based antidepressant. In general, adjunctive treatment approaches are preferred by clinicians, as even minimal effects of a baseline monoaminergic antidepressant may be augmented with an adjunctive treatment (Nelson et al., 2012, 2014), and may relieve depressive symptoms sooner versus switching to another monotherapy treatment (Al-Harbi 2012). Therefore, in this proof-of-concept study, the anti-IL-6 mAb sirukumab will be given adjunctively to a monoaminergic antidepressant in MDD subjects who have shown a suboptimal response to standard oral antidepressant therapy.

Additionally, it is hypothesized that subjects with Treatment Resistant Depression (TRD) and relatively high levels of peripheral pro-inflammatory markers will be mechanistically most likely to respond to anti-inflammatory adjunctive treatment (Raison and Miller, 2013). Specifically, it is anticipated that subjects with a biomarker profile indicative of upregulated IL-6 signaling at screening will be most likely to respond to sirukumab. To this end, the subject population

eligible for primary efficacy analysis will be enriched for higher levels of inflammation by requiring a high sensitivity C-reactive protein (hsCRP) level ≥ 0.300 mg/dL (International System of Units (SI) 3.00 mg/L) at screening and at baseline. C- reactive protein (CRP) is an acute phase protein whose hepatic synthesis is induced by IL-6 and rapidly attenuated following sirukumab infusion (Data on file, Janssen Phase 2 Rheumatoid Arthritis (RA) data). High levels of plasma CRP have been strongly associated with risk for depression (Wium-Andersen et al., 2013; Khandaker et al., 2014) and the assay for hsCRP is sensitive, reliable and practical in a multicenter study setting. The eligibility criterion of hsCRP ≥0.300 mg/dL (SI 3.00 mg/L) for subjects eligible for the primary analysis is specified on the basis of the available literature and Janssen data (data on file, Janssen) which show that a level of hsCRP ≥0.300 mg/dL (SI 3.00 mg/L) is consistent with a population of TRD subjects, as well as practical considerations regarding recruitment. Additionally, subjects will be stratified at randomization by country and 4 screening hsCRP levels: 0.00 to <0.300 mg/dL (0.000 to <3.00 mg/L), ≥0.300 to <0.500 mg/dL (≥3.00 to <5.00 mg/L), ≥0.500 to <0.800 mg/dL (≥5.00 to <8.00 mg/L), and ≥0.800 mg/dL (≥800 mg/L). By stratifying subjects on the basis of screening hsCRP values, and measuring change in inflammatory biomarkers throughout treatment, it will be possible to explore whether depressed subjects with more pronounced inflammation at screening are more responsive to treatment with sirukumab. Based on results from a planned interim analysis, the study may continue with an enriched population using a selected hsCRP level, if there is evidence from the first set of data that response is strongly correlated with hsCRP or the effect size of sirukumab is greater in subjects with higher hsCRP at screening

Thus the current study will be conducted to assess the efficacy, safety and tolerability of sirukumab versus placebo, administered adjunctively to a baseline monoaminergic antidepressant, in subjects with MDD who satisfy the additional eligibility criteria for screening hsCRP. During the 12-week double-blind treatment phase the subjects will receive a 50 mg dose of sirukumab or placebo SC at Day 1, Day 28 and Day 56. An interim analysis will be conducted when 40-50% of planned number of subjects who are eligible to be included in the primary efficacy analysis complete the week 12 assessment. The results will be used to monitor safety data, assess the study for futility, sample size re-estimation and adaption of eligibility criteria. More details will be provided in the interim SAP.

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

1.1. Background

1.1.1. Nonclinical Studies

1.1.1.1. Pharmacologic Profile

Sirukumab (also known as CNTO 136) is a human immunoglobulin G1κ (IgG1κ) monoclonal antibody (mAb) with a molecular weight of approximately 150,000 daltons. Sirukumab binds to

human IL-6 with high affinity and specificity. The high affinity binding of sirukumab to IL-6 (K_D = 0.175 pM) prevents the association of IL-6 with the IL-6R, thereby blocking receptor signaling and biological activities attributed to IL-6 both in vitro and in vivo. In vitro bioassays show that sirukumab neutralizes both cis- and trans-signaling of human IL-6 (mediated via cell surface IL-6R and soluble IL-6R, respectively) in a concentration-dependent manner. Sirukumab also blocks human IL-6-induced expression of the acute phase proteins haptoglobin and serum amyloid A (SAA) in mice; this effect is sirukumab-specific and dose-dependent. An anti-murine IL-6 mAb, analogous to sirukumab, was shown to attenuate the severity of disease in mouse model of collagen-induced arthritis. Thus, an IL 6-neutralizing antibody such as sirukumab may be an effective treatment in subjects with human autoimmune diseases such as RA.

1.1.1.2. Toxicology

Sirukumab is able to neutralize the IL-6 dependent proliferation of murine hybridoma cell line (7TD1) cells that were stimulated by conditioned supernatants from peripheral blood mononuclear cells (PBMC) of human and cynomolgus monkeys to a similar degree. Therefore, the cynomolgus monkey was selected as a pharmacologically relevant species for the nonclinical safety evaluation of sirukumab.

The nonclinical toxicology studies that have been conducted to support the sirukumab clinical studies include a 3 month multidose toxicity study and a 6-month multidose toxicity study conducted in cynomolgus monkeys, which included both IV and SC routes of administration and an investigation of the effects of sirukumab on embryo-fetal development in cynomolgus monkeys by weekly IV administration. In the 6-month study, histopathological findings consisted of mononuclear cell infiltrates and small foci of acute or healed necrosis in the heart of 5 monkeys (4 sirukumab-treated and 1 control). These findings were of minimal to mild intensity, are commonly observed in cynomolgus monkeys, and occurred with similar incidence across all treatment groups including the control group. These findings were not considered to be sirukumab treatment related. One male in the high dose group had multiple cardiac abnormalities consisting of myofiber disarray and fibrosis. This finding is likely a familial type of cardiomyopathy and therefore also not sirukumab treatment related.

The completed toxicology studies in cynomolgus monkeys demonstrated that sirukumab appeared to be well tolerated at multiple doses of up to 50 mg/kg, with the exception of the embryo-fetal developmental toxicity study. The results from the embryo-fetal developmental toxicity study demonstrated that the abortion/embryo-fetal death ratio was increased in the high dose 50 mg/kg group (35.7% at 50 mg/kg/week versus 20% in the control group). This increase in abortion/embryo-fetal death ratio was possibly related to sirukumab. In this study, the no observed adverse effect level (NOAEL) in dams and fetuses was 10 mg/kg weekly.

1.1.2 Clinical Studies

As of 23 Oct 2014, the following clinical studies were completed or in progress:

Sirukumab was studied in the first-in-human, placebo-controlled, Phase 1 study (C0136T01), which was designed to evaluate the safety and PK of a single IV administration of sirukumab in healthy subjects. Trial duration was 9 months. Safety data from the C0136T01 study showed that sirukumab was generally well tolerated in 34 healthy subjects who received single IV infusions of sirukumab. There was no dose-relatedtrend across the dose groups. There were no clusters of adverse events (AEs). No anaphylaxis, severe allergic reactions, or delayed hypersensitivity reactions were observed. No subjects discontinued study agent due to AEs. Most AEs were of mild intensity and generally self-limiting in nature. One serious adverse event (SAE) was reported in a patient in the placebo group; no SAEs were reported in the sirukumab groups. There were no clinically important differences in hematology, clinical chemistry, vital signs, or ECG measurements among the dose groups. In the sirukumab 1 mg/kg, 3 mg/kg, and 6 mg/kg male treatment groups, 1 subject each had markedly abnormal decreases in post-treatment neutrophil counts, with the lowest values in the range of 0.90 to 0.93 x 10^9/L in absolute neutrophil count (ANC).

CNTO136NAP1001 was a Phase 1, randomized, parallel-group, placebo-controlled, open to dose-level and double-blinded active/placebo single-center study to evaluate the PK and safety of sirukumab following a single SC administration to healthy male Japanese and Caucasian subjects. Trial duration was 7 months. Caucasian subjects reported more injection site reactions of erythema (37.5% vs. 12.0%) and upper respiratory tract infections (12.5% vs. 4.0%) than Japanese subjects. Absolute neutrophil counts decreased similarly in Japanese and Caucasian subjects treated with sirukumab, without evidence of dose dependency. Seven sirukumab-treated subjects had decreases to toxicity grade 2 ANC; 3 of the subjects returned to normal ANC and the other subjects were improving or showed stable values. No other relevant differences or changes from baseline were observed in any of the safety parameters.

CNTO136NAP1003: This is a Phase 1, randomized, open-label, parallel-design trial to assess absolute bioavailability and single-dose pharmacokinetics (PK) following SC administration of sirukumab delivered by a PFS fitted with Ultrasafe Passive™ delivery system or an Autoinjector in healthy male subjects. The trial is still ongoing.

CNTO136ARA1001: This is a Phase 1, open-label, multicenter, drug-drug interaction 12-week trial designed to evaluate the effect of a single SC dose of sirukumab on midazolam (cytochrome P450 [CYP]3A4), warfarin (CYP2C9), omeprazole (CYP2C19), and caffeine (CYP1A2), on the PK in subjects who have a diagnosis of RA and a screening C-reactive protein level of >8.00 mg/L (>0.8 mg/dL). The trial is ongoing.

C0136T03 was a Phase 1, 2-part, multicenter/multinational, randomized, double-blind, placebo-controlled study of sirukumab to evaluate the safety and PK of intravenously administered, multiple ascending doses of 1, 4, and 10 mg/kg in subjects with CLE and of 10 mg/kg in subjects with SLE. The single death reported during the study was due to a car accident and not related to the administration of sirukumab. No dose-limiting SAEs were observed in this study. Six SAEs in 3 subjects were reported in Part A and 3 SAEs in 3 subjects were reported in Part B. Serious infections reported were pneumonia, in a subject with SLE and treatment-emergent neutropenia, which was considered to be related to sirukumab

administration, and a bacterial infection of an iatrogenic wound, which was considered not related to sirukumab administration. Other infections were nonserious and most were mild upper respiratory tract infections. Subjects who received sirukumab showed immediate stable and sustained decreases compared with baseline in white blood cell count (WBC), ANC, and platelets at all individual dose levels, while subjects in the placebo group showed no change in results for all 3 parameters. The decreases were not dose dependent. There was little to no clear temporal association between low neutrophil counts and the occurrence of infections. Two subjects in the Part B SLE cohort were discontinued from administration because of low ANC and platelet counts, but no immediate apparent clinical symptoms were associated with these low values. Compared with the placebo subjects, sirukumab-treated CLE subjects in the 1 and 4 mg/kg groups reported a relatively higher number of skin-related AEs that were considered reasonably related to sirukumab, whereas the 10 mg/kg group did not report any reasonably related skin events. Laboratory results for fasting lipids showed minor elevations of total cholesterol in the cohorts that received sirukumab. In subjects with CLE or SLE in all sirukumab treatment groups, complement C3 and C4 showed immediate, and for C4 almost maximal, decreases. All other safety parameters did not show a signal, clinically significant trend over time or change from baseline, or a difference between subjects who received sirukumab and those who received placebo. On clinical evaluation, none of the abnormal QTc intervals or any abnormal morphology was associated with clinically relevant pathology. No dose relationship was observed for AEs in Part A or Part B. In Part A, autoantibodies (antinuclear antibody [ANA] and anti-dsDNA) showed no changes in either sirukumab or placebo subjects. In Part B, changes in autoantibodies (ANA and anti-ds-DNA) showed lower titers for sirukumab subjects, where placebo subjects showed no change or increase of titers. None of the other autoantibodies showed any change from baseline.

C1377T04 was a Phase 2, 2-part, multicenter, randomized, double-blind, parallel-group, placebo-controlled, proof-of-concept, and dose-finding study designed to evaluate the efficacy and safety of multiple doses of sirukumab administered subcutaneously in subjects with active RA despite methotrexate (MTX). Part A was the proof-of-concept portion of the study, comparing sirukumab 100 mg SC or placebo injection every 2 weeks (q2w). Part B was the dose-finding portion of the study. Subjects received study agent administrations for 24 weeks. Dose regimens in Part B included sirukumab 25 mg SC every 4 weeks (q4w), 50 mg q4w, 100 mg q4w, and 100 mg q2w. Subjects enrolled in Part B were distinct from those enrolled in Part A.

CNTO136LUN2001 was a Phase 2, multicenter, randomized, double-blind, placebo-controlled, proof-of-concept study to evaluate the efficacy and safety of sirukumab administered intravenously in subjects with active lupus nephritis. As of 23 Oct 2014 all subjects (25) have been randomized and the study has been completed.

CNTO136ARA3001, is a 68-weeks Phase 3 study to evaluate the efficacy and safety of sirukumab administered SC, in Japanese subjects with active RA unresponsive to MTX or Sulfasalazine. As of 23 Oct 2014, all subjects (122) were randomized and the study is ongoing.

CNTO136ARA3002, is a 120-weeks Phase 3 study to evaluate the efficacy and safety of sirukumab administered SC, in subjects with active RA despite disease-modifying antirheumatic drug (DMARD) therapy. As of 23 Oct 2014, 1111 of 1650 planned subjects had been randomized and the study is ongoing.

CNTO136ARA3003, is a Phase 3 study to evaluate the efficacy and safety of sirukumab administered SC, in subjects with active RA despite anti-TNFα therapy. As of 23 Oct 2014, 528 of 840 planned subjects had been randomized and the study is ongoing.

CNTO136ARA3004, is a Phase 3 study to evaluate the long-term safety and efficacy of CNTO136 (sirukumab) in subjects with RA who completed treatment in the CNTO136ARA3002 (SIRROUND-D) and CNTO136ARA3003 (SIRROUND-T) studies. As of 23 Oct 2014, 173 of 2490 planned subjects had been randomized and the study is ongoing.

CNTO136ARA3005: This is a Phase 3, multicenter, randomized, double-blind, parallel-group trial of sirukumab administered SC as monotherapy compared with adalimumab monotherapy in subjects with active RA. As of 23 Oct 2014, 13 of 510 planned subjects had been randomized and the study is ongoing.

Cumulatively, the following adverse drug reactions (ADR) have been identified for sirukumab: neutropenia, thrombocytopenia, lipids increased (total cholesterol, low-density lipoprotein [LDL], high density lipoprotein [HDL], and triglycerides), alanine aminotransferase increased, aspartate aminotransferase increased, injection site reaction (including erythema, pain, pruritis, and/or swelling), serious hypersensitivity reaction (including anaphylaxis), cellulitis, pneumonia, sepsis and gastrointestinal perforation (see Section 1.1.2.2.2Safety).

1.1.2.1 Human Pharmacokinetics and Immunogenicity

The PK of sirukumab has been evaluated in healthy subjects following both IV (C0136T01) and SC (CNTO136NAP1001) administrations. Following a single dose of either IV (0.3 to 10 mg/kg) or SC (25, 50, or 100 mg) administration, the systemic exposure of sirukumab (C_{max} and AUC_{inf}) increased in an approximately dose proportional manner. Mean values of total systemic clearance (CL) ranged from 3.8 to 6.1 mL/day/kg; and mean values of volume of distribution during terminal phase (Vz) ranged from 121.3 to 247.6 mL/kg. Following a single SC administration of sirukumab, median t_{max} ranged from 3 to 5 days; mean $T_{1/2}$ values were 15 to 18 days. No apparent sex-related differences in PK were observed. Sirukumab PK was generally comparable between Japanese and Caucasian healthy subjects.

The PK of sirukumab was also evaluated in subjects with RA in Phase 2 study C1377T04. Overall, the PK of sirukumab after SC administration in subjects with RA is consistent with that observed in healthy subjects. Refer to latest version of the Investigator's Brochure for a summary of PK parameters.

The effect of sirukumab on the pharmacokinetics of CYP enzyme substrates midazolam (CYP3A4), omeprazole (CYP2C19), S-warfarin (CYP2C9), and caffeine (CYP1A2) has been evaluated in subjects with active RA (CNTO136ARA1001). Twelve subjects received oral administrations of CYP probe cocktails consisting of 0.03 mg/kg midazolam, 10 mg warfarin, 20 mg omeprazole, and 100 mg caffeine at 1 week before and at 1, 3, and 6 weeks after a single subcutaneous dose of 300 mg sirukumab. AUCinf for midazolam, omeprazole, and S-warfarin were reduced by 29.9%–35.2%, 37.4%–44.8%, and 18.0%–19.1%, respectively, after sirukumab administration. Caffeine AUCinf was increased by 19.6%–34.2% after sirukumab administration. The effect of sirukumab on CYP activities was sustained for at least 6 weeks following sirukumab administration. These results suggest that sirukumab may restore IL-6-mediated suppression of CYP3A4, CYP2C9, and CYP2C19 activities in RA subjects.

Immunogenicity has been evaluated in 4 clinical studies: C0136T01, CNTO136NAP1001, C0136T03, and C1377T04. None of the subjects with evaluable serum samples tested positive for antibodies to sirukumab in C0136T01 (0/31), CNTO136NAP1001 (0/43), and C0136T03 (0/32). In C1377T04, 2 (1.2%) of 173 subjects tested positive for antibodies to sirukumab through Week 38.

1.1.2.2 Efficacy/Safety Studies

1.1.2.2.1 Efficacy

In Part A and Part B of C0136T03, C-reactive protein (CRP) levels were suppressed in subjects with CLE and SLE, in a manner similar to that observed for high-sensitivity CRP in the first-in-humans study C0136T01. Baseline CRP levels in the CLE and SLE subjects were normal to mildly elevated and after the first dose of sirukumab, the median CRP levels dropped to below the lower limit of normal (LLN) in subjects who received sirukumab IV at 1, 4, or 10 mg/kg. Sustained suppression of CRP in sirukumab-treated subjects was observed through the last CRP measurement at Week 14, approximately 8 weeks after the last dose of sirukumab.

In Part B of the Phase 2 RA study C1377T04, sirukumab subcutaneous (SC) doses of 25, 50, and 100 mg all rapidly suppressed the CRP levels by a median of 79 to 87% within 5 days and > 90% within 8 days, and this level of CRP suppression was maintained in each of the 4 sirukumab treatment groups for 6 to 14 weeks after the last sirukumab administration at Week 24. The change from baseline at Week 38 in CRP level suggested a dose-dependent effect on this acute phase marker, with the group that had received sirukumab 25 mg q4 weeks up to Week 24 rebounding most toward the baseline CRP levels.

In Part B, a greater proportion of subjects achieved the primary endpoint of ACR 50 response at Week 12 in each of the 4 sirukumab treatment groups (sirukumab 100 mg q2 weeks, 27%; 100 mg q4 weeks, 23%; 50 mg q4 weeks, 27%; 25 mg q4 weeks, 19%) compared with the placebo group (3.3%); subjects in the sirukumab 100 mg q2 weeks and 50 mg q4 weeks treatment groups achieved statistical significance ($p < 0.05$).

A post-hoc analysis of the SF-36 Mental Health and Vitality domain items from the C1377T04 study showed a beneficial effect of sirukumab on depressed mood at week 12, more pronounced

than in the placebo group and at least partly independent on the clinical benefit on the target disease. Patients with prevalent depressed mood and anhedonia receiving sirukumab but not placebo achieved significant improvements at week 12 in depressive symptoms (p=0.0006), and fatigue (p=0.0157). Significant improvements on depressed mood and anhedonia upon sirukumab treatment, but not placebo, were observed in both ACR50 responders (p=0.0024) and nonresponders (p=0.0014).

1.1.2.2.2 Safety

The sponsor's medical experts evaluated safety reports from clinical studies with sirukumab using the definition of adverse drug reactions (ADRs) from the International Conference on Harmonisation (ICH) guideline entitled Guideline for Good Clinical Practices, E6(R1). Reviews by the Sponsor of cumulative safety data from completed sirukumab studies in healthy subjects and subjects with RA and CLE/SLE resulted in the identification of the following adverse drug reactions: neutropenia, platelet count decreased, lipids increased (total cholesterol, low-density lipoprotein [LDL], high-density lipoprotein [HDL], and triglycerides), ALT increased, AST increased, injection site reaction (including erythema, pain, pruritus, and/or swelling), serious hypersensitivity reaction (including anaphylaxis), cellulitis, pneumonia, sepsis and gastrointestinal perforation (Table 1).

Overall, 252 healthy subjects and an estimated 3,015 subjects with lupus, LN, and RA have been enrolled in the sirukumab clinical program, of whom 2,419 subjects have received sirukumab (54 subjects with lupus/LN have received sirukumab and 2,365 subjects with RA have received sirukumab). Of these, 269 subjects were exposed to sirukumab in the Phase 1 trials, 203 subjects were exposed to sirukumab in the Phase 2 trials, and 1,947 subjects were exposed to sirukumab in the Phase 3 trials

A listing of adverse drug reactions (ADRs) determined for sirukumab based on a review of safety data through 27 April 2015 is provided in Table 1.

Table 1: Adverse Drug Reactions with Sirukumab (CNTO136)

Adverse Drug Reactions Coded by MedDRA (Version 17.1) Associated with Sirukumab		
MedDRA System Organ Class	**Frequency**	**Preferred term(s) Ordered by Seriousness**
Gastrointestinal Disorders		
	Uncommon:	Gastrointestinal Perforation
Infections and Infestations		
	Common:	Cellulitis Pneumonia
	Uncommon:	Sepsis
Immune System Disorders		
	Uncommon:	Serious hypersensitivity reaction (including anaphylaxis)
General disorders and administration site conditions		
	Very Common:	Injection site erythema
	Common:	Injection site pain Injection site pruritus Injection site swelling
Investigations		
	Very Common:	Alanine aminotransferase increased Aspartate aminotransferase increased Blood cholesterol increased Low density lipoprotein increased High density lipoprotein increased
	Common:	Triglycerides increased
Blood and lymphatic system disorders	Very Common:	Neutropenia Thrombocytopenia

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The preferred terms presented in this table are ordered by seriousness within each frequency grouping.
Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

Detailed description of safety and tolerability data is included in Section 4.4 (Safety and Tolerability) of the IB. Below a detailed description of the safety results only for the phase 2 study C1377T04 is provided.

C1377T04

Data from the Phase 2 RA study (C1377T04) in subjects who had an inadequate response to MTX suggest a safety profile in subjects with RA to be similar to that of other IL-6 pathway inhibitors. There was an increased incidence of infections and common occurrences of decreases in leukocytes and platelets, transient liver transaminase elevations, and increases in lipid parameters.

In Part A of the Phase 2 RA study, a single Serious Adverse Event (SAE) of staphylococcal cellulitis occurred in a subject treated with sirukumab 100 mg q2 weeks over the study. In the

initial 12-week, placebo controlled portion of the Phase 2 dose-ranging study (Part B), there were 7 subjects with SAEs. There was 1 malignancy: 1 subject reported fibrosarcoma of the right axillary and scapular regions after 4 weeks of participation, then withdrew from the study without providing any further details. The proportion of RA subjects with treatment-emergent SAEs was higher in the placebo group (13.3%) compared with the combined sirukumab treatment groups (2.5%) and any individual sirukumab treatment group. No dose-proportional relationship was observed between the sirukumab regimen and type or timing of SAE.

After Week 12, 10 additional SAEs were reported in Part B, including 1 death. The fatal case was a 59-year-female assigned to the placebo group, who per protocol crossed over to sirukumab 100 mg q2 weeks from Week 12 to 24. Approximately 6 weeks after the last study agent administration, she developed a severe headache, was diagnosed with a brain aneurysm and died during surgery.

Subjects in the treatment groups who received sirukumab had a greater number of infections compared with those in the placebo group (33.3% vs 13.3%). Most of the infections were upper respiratory tract infections. There were no opportunistic infections or tuberculosis (TB).

In Part A, from Weeks 0 to 12, the incidence of injection-site reactions was higher in subjects who received sirukumab 100 mg q2 weeks (35.3%) compared with subjects who received placebo (10.5%). In Part B, 15.7% of sirukumab-treated subjects reported at least 1 injection-site reaction compared with the 3.3% of placebo-treated subjects group (3.3%). The proportion of injections resulting in injection-site reactions was highest in the sirukumab 100 mg q2 weeks treatment group in both Parts A and B (15.4% [28/128] and 6.9% [50/726] of injections, respectively), whereas only 0.9% of Part A and 0.6% of Part B placebo injections resulted in injection-site reactions. All of the injection-site reactions were considered non-serious.

No hypersensitivity or anaphylactic reactions were reported.

Hematologic effects occurred within the first 4 weeks of treatment and were sustained through at least Week 24. In both Parts A and B, subjects in the sirukumab treatment groups (5.6% to 17.2%) had markedly abnormal[a], decreased neutrophil counts compared with no subjects with neutropenia in the placebo group.

One subject in Part A and 2 subjects in Part B had Grade 3 neutropenia (< 1.0 x 10^3/μL). Neither case of neutropenia was associated with infection. No clear, dose-proportional relationship was observed between the sirukumab regimen and neutropenia. In Part B, 11.6% of sirukumab treated subjects had absolute neutrophil count (ANC) < 1.5 x 10^3/μL. Markedly abnormal[b], decreased lymphocyte counts occurred in 3 (10.3%) of 29 subjects in the placebo group and 23 (15.8%) of 146 sirukumab-treated subject. In Part B, 1 subject had lymphopenia Grade 4 (< 0.5

[a] Decrease ≥ 33% and value < 1.5 x 10^3/μL

[b] Decrease ≥ 33% and value < 1.0 x 10^3/μL

x $10^3/\mu L$). Markedly abnormal[a] , decreased platelet counts occurred in 2 subjects (1.7%): 1 was Grade 2 (< 75 - 50 x $10^3/\mu L$) and one was Grade 4 (< 25 x $10^3/\mu L$). Neither subject had bleeding. The subject with Grade 4 thrombocytopenia continued dosing with sirukumab and had normal platelets thereafter. Neutrophil and platelet effects were resolving 14 weeks after the last dose.

National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) toxicity Grade 1 ALT (Upper Level of Normal (ULN) – 2.5 x ULN) values were observed very commonly (48.6%) in the sirukumab-treated subjects compared with 10.3% in the placebo group. Grade 3 ALT values (> 5 x ULN to 20 x ULN) were observed in 1 (6.3%) sirukumab-treated subject in Part A and 8 (5.5%) sirukumab-treated subjects in Part B compared with none in placebo subjects. No sirukumab dose relationship was observed. No subjects had both ALT elevation ≥ 3 x ULN and total bilirubin ≥ 2 x ULN. In a similar pattern but to a lesser degree, AST elevations were observed more often in sirukumab treatment groups. A single Grade 3 and no Grade 4 AST elevations occurred. Most of these liver transaminase abnormalities were transient, asymptomatic, and peaked within the first 8 weeks of treatment, and returned to normal upon further follow-up. One subject was discontinued from study agent because ALT was persistently elevated by local laboratory testing.

Total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides increased from baseline in the sirukumab treatment groups compared with the placebo group. There was no apparent relationship between sirukumab dose and change in total, LDL cholesterol, or HDL cholesterol. Lipid increases occurred by Week 2 and were sustained through Week 24.

Mean increases in HDL cholesterol at Week 24 were as follows: Sirukumab 100 mg q2 weeks, 9 mg/dL; 100 mg q4 weeks, 13 mg/dL; 50 mg q4 weeks, 10 mg/dL; 25 mg q4 weeks, 10 mg/dL.

Mean increases in LDL cholesterol at Week 24 were as follows: Sirukumab 100 mg q2 weeks, 13 mg/dL; 100 mg q4 weeks, 21 mg/dL; 50 mg q4 weeks, 23 mg/dL; 25 mg q4 weeks, 12 mg/dL.

At Week 24, in Part B, of the subjects with normal baseline LDL (≤ 130 mg/dL), an abnormal LDL (> 130 mg/dL) occurred in 54 (62.1%) of 87 subjects in the sirukumab groups combined compared with 4 (20.0%) of 20 subjects in the placebo group.

Laboratory data through Week 24 has shown a consistent pattern of hematologic parameter decreases, hepatic enzyme increases, and increases in lipid parameters. No dose response has been observed to date.

1.2. Overall Rationale for the Study

MDD is well known to be a heterogeneous illness, and the approximately one-third of depressed patients who are deemed to be treatment resistant may have distinct mechanisms underlying their

[a] Decrease ≥ 50% and value < 75 x $10^3/\mu L$

depression, including systemic inflammation, resulting in reduced responsiveness to traditional monoamine treatment approaches. In fact, IL-6 levels correlate with depression severity in patients who do not respond to conventional antidepressant treatment, suggesting that a subset of depressed patients with treatment resistance may have an immune-mediated component to their illness which is evident in the periphery (Dahl et al., 2014).

Neutralizing IL-6 is therefore an attractive and rational target for antidepressant treatments. This study will focus on investigating the efficacy of the anti-IL-6 mAb, sirukumab, for the treatment of depression. Analyses of the phase 2 sirukumab RA database both showed a beneficial effect on depressed mood, more pronounced than in the placebo group and at least partly independent on the benefit on the target disease, which provide further support to the peripheral route of administration as being potentially associated with antidepressant effects.

2. OBJECTIVES AND HYPOTHESIS

2.1. Objectives

Primary Objective

The primary objective of this study is to evaluate the efficacy of sirukumab as adjunctive treatment to monoaminergic antidepressant therapy where sirukumab (administered as a 50 mg SC injection at Day 1, Day 28 and Day 56 during the 12 week double-blind treatment period) is compared to adjunctive placebo based on the change from baseline to 12-week endpoint in depressive symptoms as measured by the total score on the Hamilton Depression Rating Scale ($HDRS_{17}$), in subjects diagnosed with MDD who have had a suboptimal response to the current standard oral antidepressant therapy and have a screening and baseline hsCRP ≥0.300 mg/dL (SI 3.00 mg/L).

Secondary Objectives

- To evaluate the overall safety and tolerability of adjunctive sirukumab compared to adjunctive placebo in subjects with MDD.
- To evaluate the impact of adjunctive sirukumab compared to adjunctive placebo on anhedonia as measured by the change from study baseline to 12-week endpoint on the Snaith Hamilton Pleasure Scale (SHAPS) in subjects with MDD and screening hsCRP ≥ 0.300 mg/dL.
- To evaluate the impact of treatment with adjunctive sirukumab compared to adjunctive placebo on global severity of symptoms of MDD, as measured by the change in the Clinical Global Impression - Severity (CGI-S) scale from study baseline to 12-week endpoint in subjects with MDD and screening hsCRP ⩾0.300 mg/dL.
- To evaluate the impact of treatment with adjunctive sirukumab compared to adjunctive placebo on remission and response rates at 12-week end point, defined as a $HDRS_{17}$ total

score ≤7 or a ≥ 50% improvement in $HDRS_{17}$ total score from baseline, respectively in subjects with MDD and screening hsCRP ⩾0.300 mg/dL.

- To evaluate the impact of treatment with adjunctive sirukumab compared to adjunctive placebo on subject-reported severity of symptoms of MDD, as measured by the change in the Patient Health Questionnaire (PHQ-9) from study baseline to 1- week endpoint and to 12-week endpoint in subjects with MDD and screening hsCRP ⩾0.300 mg/dL.

- To evaluate the impact of treatment with adjunctive sirukumab compared to adjunctive placebo on fatigue, as measured by the change from study baseline to 1-week, 4-week, 8-week and 12-week endpoint in the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT Fatigue) scale in subjects with MDD and screening hsCRP ≥0.300 mg/dL.

- To evaluate the efficacy measured by change in the $HDRS_{17}$ scores following adjunctive sirukumab compared to adjunctive placebo in the Treatment Resistant Depression (TRD) versus non-TRD subjects. TRD is defined as having being treated with ≥ 2 trials of antidepressants of adequate dose and duration [according to the Massachusetts General Hospital Antidepressant Treatment History Questionnaire (MGH-ATRQ)] during the current episode.

- To evaluate pharmacokinetics and immunogenicity of sirukumab in subjects with MDD.

- To evaluate the impact of treatment with adjunctive sirukumab in subjects with screening hsCRP≥0.300 mg/dL as compared to in those with screening hsCRP<0.300 mg/dL based on changes from baseline to Week 12 in $HDRS_{17}$ total score.

- To assess the efficacy of sirukumab compared to placebo as adjunctive therapy to an antidepressant in subjects with MDD with screening hsCRP levels <0.300 mg/dL versus those with screening hsCRP levels ≥ 0.300 mg/dL in improving response of depressive symptoms, defined as the proportion of subjects having a ≥50% improvement in $HDRS_{17}$ total score from baseline to the end of Week 12.

- To assess the efficacy of sirukumab compared to placebo as adjunctive therapy to an antidepressant in subjects with MDD with screening hsCRP levels <0.300 mg/dL versus those with screening hsCRP levels ≥ 0.300 mg/dL in achieving remission of depressive symptoms, defined as the proportion of subjects having a $HDRS_{17}$ total score ≤7 at the end of Week 12.

- To evaluate whether hsCRP levels correlate with clinical efficacy as measured by the change from baseline to Week 12 in $HDRS_{17}$ total score.

Exploratory Objectives

- To evaluate the efficacy of adjunctive sirukumab compared to adjunctive placebo, based on the change from baseline to 12-week endpoint in the Inventory of Depressive Symptomatology – Clinician Rated 30 Item Scale (IDS-C30) in subjects with MDD and screening hsCRP ⩾0.300 mg/dL.

- To explore immune-system related biomarkers (hsCRP, cytokines, chemokines), as well as other mood disorder related biomarkers (growth factors, hypothalamic–pituitary–adrenal (HPA) axis markers, metabolic markers) and to explore the potential correlation between these biomarkers and the clinical response, non-response or safety parameters of sirukumab.

- To explore genetic and epigenetic variation that may be related to clinical response, non-response, or safety parameters of sirukumab.

- To evaluate the effect of sirukumab on the pharmacokinetics of monoaminergic antidepressants.

- To explore the relationship between the severity of childhood trauma as assessed through the Childhood Trauma Questionnaire and the change in $HDRS_{17}$ scores following adjunctive sirukumab or placebo.

2.2. Hypothesis

The primary hypothesis of this study is that sirukumab will determine significant improvement in depressive symptoms from baseline compared to placebo when administered as an adjunctive treatment to a monoaminergic antidepressant in the treatment of patients with MDD who have shown a suboptimal response to standard oral antidepressant therapy and have a screening and baseline hsCRP ≥ 0.300 mg/dL (SI 3.00 mg/L), demonstrated by improvement in depressive symptoms from baseline to 12-week endpoint in the Hamilton Depression Rating Scale ($HDRS_{17}$) total score.

3. STUDY DESIGN AND RATIONALE

3.1. Overview of Study Design

This is a randomized, double-blind placebo-controlled multicenter study. A target of approximately 192 subjects will be randomly assigned in this study with approximately 96 subjects planned per treatment group. The sample size may increase up to 228 if the interim analysis suggests so.

The target study population is male and female subjects with MDD who have had a suboptimal response to standard oral antidepressant therapy; have failed no more than 3 antidepressant treatments in the current major depressive episode; approximately 142 subjects with screening hsCRP ≥0.300 mg/dL (SI 3.00 mg/L) and approximately 50 subjects with screening hsCRP<0.300 mg/dL (SI 3.00 mg/L) will be enrolled.

Determination of suboptimal response to the current standard oral antidepressant therapy will be made retrospectively using the structured MGH-ATRQ. Determination of the number of failed antidepressant treatments in the current episode will be made retrospectively using medical or pharmacy records and documented on the MGH-ATRQ. Serum concentration of hsCRP will be measured from a venous blood sample at screening.

The study will consist of 3 phases: a screening phase of up to 4 weeks, consisting of 2 visits, a 12 week double-blind treatment phase, and a 14 week posttreatment follow-up phase. The total duration of subject participation will be approximately 26 weeks.

Screening Phase: Subjects with a Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) diagnosis of MDD, confirmed by the MINI International Neuropsychiatric Inventory (MINI), who are currently being treated with a monoaminergic antidepressant and have failed no more than 3 antidepressants (of adequate dose and duration) in the current major depressive episode will be eligible for screening. Screening will include informed consent, evaluation for eligibility in the study, medical history, physical and psychiatric evaluations, venous blood sampling for hsCRP assay and standard lab safety tests. Determination of suboptimal response to the current standard oral antidepressant therapy will be made retrospectively using the structured MGH-ATRQ. Determination of failure of antidepressant treatments in the current episode will be made retrospectively using medical or pharmacy records and documented on the MGH-ATRQ. Subjects with partial improvement (<50%) according to the MGH-ATRQ and moderate to severe depression ($HDRS_{17}$ total score ≥18 at screening, as measured by a remote independent rater) will be eligible for inclusion. Subjects must be currently receiving no more than 2 of the following antidepressants for at least 6 weeks duration at screening with at least one antidepressant being at an adequate therapeutic dose, as determined by the MGH-ATRQ: bupropion, fluoxetine, citalopram, escitalopram, sertraline, paroxetine, venlafaxine, desvenlafaxine, duloxetine, vilazodone, mirtazapine, agomelatine, fluvoxamine, amitriptyline, imipramine, nortriptyline, vortioxetine and levomilnacipram.
The screening phase will consist of 2 visits; the procedures scheduled during the first screening visit may be divided over two days, according to operational and/or site/country-specific needs. In case the first screening visit is conducted over two days, the following assessments must be performed on the same day: C-SSRS, IDS-C30 and $HDRS_{17}$.

The second visit will only be performed once all in- and exclusion criteria have been confirmed, except for the SAFER interview and chest X-ray (if applicable). These will only be performed at the second screening visit.

Double blind treatment phase: Subjects who continue to meet inclusion and exclusion criteria at the baseline visit will be eligible for randomization. At the baseline visit, subjects must have a $HDRS_{17}$ total score ≥18, as measured by a remote independent rater, and must not demonstrate an improvement of >25% on their $HDRS_{17}$ total score from the screening to baseline visit. Randomization will be stratified by country and screening hsCRP level: 0.00 to <0.300 mg/dL (0.00 to <3.00 mg/L), ≥0.300 to <0.500 mg/dL (≥3.00 to <5.00 mg/L), ≥0.500 to <0.800 mg/dL (≥5.00 to <8.00 mg/L), and ≥0.800 mg/dL (≥8.00 mg/L). Subjects will receive either adjunctive placebo or adjunctive sirukumab in a 1:1 ratio.

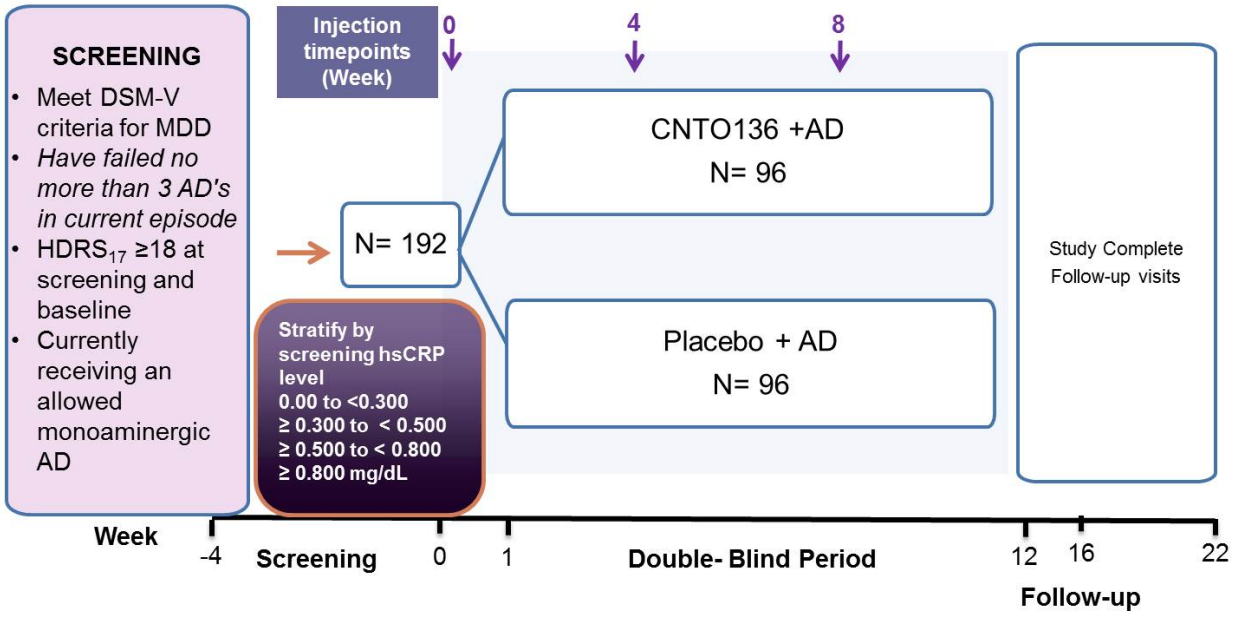
Refer to the Time and Events Schedule for a list of study evaluations that will be performed during the double-blind treatment phase.

Posttreatment Follow-Up: Subjects will have two follow-up safety visits, 8 and 14 weeks after last SC injection, to assess clinical condition, monitor safety and adverse events and record concomitant medications. Subjects with unresolved adverse events at Week 22 will be continued to be monitored as clinically appropriate to ensure subjects' safety.

Pharmacogenomic blood samples will be collected to allow the identification of genetic and/or epigenetic factors that may influence the pharmacokinetics, pharmacodynamics, efficacy, safety, or tolerability of sirukumab and to identify genetic and/or epigenetic factors associated with MDD.

A diagram of the study design is provided below in Figure 1.

Figure 1: Schematic Overview of the Study



Only subjects with screening and baseline CRP ≥ 3.00 mg/L will contribute to the primary analysis

3.2 Study Design Rationale

Based on the known efficacy and safety profile of sirukumab and the time by which these are observed, the 12-week double-blind treatment phase should allow sufficient time to fully evaluate the effect of sirukumab as an add-on therapy to a monoaminergic antidepressant in MDD patients who have shown a suboptimal response to standard oral antidepressant therapy, on the clinical endpoints. In the RA phase 2 study C0136T03, sirukumab showed greater efficacy than placebo at week 12; additionally, post-hoc analyses of depressive symptom change following sirukumab in subjects with RA, showed greater improvement in sirukumab-treated

subjects compared to placebo-treated subjects at week 12 (see Section 1.1.2.2.1 for additional details).

Patients will be stratified at randomization by country and 4 screening hsCRP levels: 0.00 to <0.300 mg/dL (SI 0.000 to <3.00 mg/L), ≥0.300 to <0.500 mg/dL (SI ≥3.00 to <500 mg/L), ≥0.500 to <0.800 mg/dL (SI ≥5.00 to <8.00 mg/L), and ≥0.800 mg/dL (SI ≥8.00 mg/L). The hsCRP values defining those strata were derived by tertiles analyses of CRP distribution in depressed subjects with CRP >3.00 mg/L participating in two recent JRD-sponsored phase 2 studies (data on file) and were consistent with CRP distribution reported in the literature (Woloshin et al., 2005). By stratifying patients on the basis of screening hsCRP values, and measuring change in inflammatory biomarkers throughout treatment, we will explore whether depressed patients with more pronounced inflammation at screening are more responsive to treatment with sirukumab, and whether treatment response is correlated with change in inflammatory processes, as reflected by changes in levels of inflammatory biomarkers. The 0.00 to <0.300 mg/dL (SI 0.00 to <3.00 mg/L) stratum has been added to achieve a better understanding of the relationship between hsCRP – and potentially other inflammatory biomarkers- and the clinical response.

A placebo control will be used to maintain the blind and to establish the frequency and magnitude of changes in clinical endpoints that may occur in the absence of active study treatment in subjects with suboptimal response to monoaminergic antidepressant. Randomization will be used to minimize bias in the assignment of subjects to treatment groups, to increase the likelihood that known and unknown subject attributes (eg, demographic and baseline characteristics) are evenly balanced across treatment groups, and to enhance the validity of statistical comparisons across treatment groups. Blinded treatment will be used to reduce potential bias during data collection and evaluation of clinical endpoints.

The duration of the study is considered adequate to test the potential efficacy of sirukumab. Not allowed antidepressant medication will not be discontinued for the sole purpose of entering the study; subjects will be carefully monitored for potential worsening of the depressive symptoms and suicidality and appropriate actions will be taken to ensure the safety of the subjects participating in the study. Clinical studies with similar study design show that both partial and non-responders had significant improvement, even in the placebo arm (Thase et al., 2008). All subjects will receive clinical care while in the trial.

The $HDRS_{17}$, IDS-C30, CGI-S and PHQ-9 are scales which capture depressive symptoms and severity and measure the magnitude of severity change following antidepressant interventions. The FACIT scale measures fatigue and will be used to investigate whether sirukumab decreases fatigue-related symptoms in subjects with depression, as elevation of inflammatory markers, including CRP, has been reported to be associated with greater fatigue severity.

The childhood trauma questionnaire will be used to investigate the potential association between the severity of childhood negative experiences and clinical change following sirukumab; preliminary evidence suggests that subjects with higher CTQ scores experience a greater level of depression and peripheral inflammation.

Length of Study Phases

All subjects will undergo a screening period of approximately 4 weeks, which will provide adequate time to assess their eligibility per inclusion/exclusion criteria for the study.

The duration of the screening period of approximately 4 weeks is chosen to ensure that subjects are experiencing suboptimal response to the current antidepressant treatment regimen and that elevation of hsCRP is stable across time and does not represent a transient increase related to medical conditions other than depression. The screening phase has been split in 2 visits, so the more burdensome assessments for the subjects are only performed once all other screening criteria have been met. The procedures scheduled during the first screening visit may be divided over two days, according to operational and/or site/country-specific needs. In case the first screening visit is conducted over two days, the following assessments must be performed on the same day: C-SSRS, IDS-C30 and $HDRS_{17}$.

The 12-week duration of the double-blind study is adequate to assess the potential efficacy of sirukumab in the treatment of MDD, as steady state is reached by approximately 12 weeks.

A posttreatment assessment visit 8 and 14 weeks after the last intake of study drug to determine the duration of the antidepressant effect and tolerability will be made to assess subject safety and mood symptoms A week 14 follow-up visit is deemed to be necessary to monitor potential risks of infections occurring after discontinuation of the study agent.

Study Population

The study population will consist of men and women, 21 to 64 years of age (inclusive), that meet the DSM-5 diagnosis of MDD, confirmed by the MINI, who are currently being treated with a monoaminergic antidepressant and have failed no more than 3 antidepressants (of adequate dose and duration) in the current major depressive episode. It is expected that this population will be representative for the targeted subject population for future clinical trials.

Dose selection

In a Phase 2 study in subjects with RA, all the doses tested (i.e., 100 mg q2w, 100 mg q4w, 50 mg q4w, and 25 mg q4w) showed a statistically significant reduction of serum CRP concentration compared to placebo which was maintained at least through week 24 (Smolen et al., 2014). The magnitude of CRP decrease in the sirukumab-treated subjects ranged from -81% to -91% compared to baseline and was not different between dose groups. As sirukumab is hypothesized to exert its potential clinical effect in depressed subjects with elevated inflammatory markers through a reduction in IL-6 and other cytokines, the aforementioned data suggest that the doses tested in RA might be in the therapeutic range for MDD. Moreover, in the phase 2 RA study subjects were required to have CRP ≥10.00 mg/L, which is a CRP level more than 3-fold higher than what is required in the present study, where the CRP level for primary analysis needs to be ≥0.300 mg/dL (SI ≥3.00 mg/L). This additional consideration implies that 50 mg q4w, a dose lower than the maximal dose tested in RA, might be sufficient in subjects with MDD to achieve suppression of the peripheral inflammatory component and there is no

reason to suggest that 100mg might provide added benefit. Thus the sirukumab dose of 50 mg q4w has been chosen for this proof of concept study in subjects with MDD.

The 25mg q4w dose has not been chosen here as it is a dose not tested in the RA phase 3 program. In case of unclear efficacy outcome in the present study it would be challenging to interpret ambiguous results as related to lack of compound efficacy in the depression indication or reflecting the use of a suboptimal dose of sirukumab. Further studies in depressed subjects might need to test the efficacy of lower and higher doses than 50mg q4w, including 25mg q4w and 100 mg q2w.

Pharmacokinetics and Immunogenicity

To assess the pharmacokinetics of sirukumab in subjects with MDD, venous blood samples will be collected for the measurement of serum sirukumab concentration according to the Time and Events Schedule.

Antibodies generated in response to sirukumab have the potential to accelerate the clearance of the drug and hence affect efficacy. To evaluate the immunogenicity of sirukumab in subjects with MDD, serum samples for the detection of antibodies to sirukumab will also be collected according to the Time and Events Schedule.

Inflammatory cytokines, including IL-6, are known to downregulate expression and activity of multiple CYP enzymes. Hypothetically, IL-6 inhibition in subjects with elevated inflammatory cytokines will restore CYP enzyme activities, and, in turn, increase the hepatic metabolism of drugs that are substrates for those enzymes. Since most of approved antidepressant medications are CYP substrates, effect of sirukumab on the pharmacokinetics of monoaminergic antidepressants will be evaluated. Venous blood samples will be collected for the assessment of plasma concentrations of monoaminergic antidepressants before and after sirukumab treatment as indicated in the Time and Events Schedule.

Safety assessments

The collection of adverse events and concomitant medications will start after the informed consent has been signed and will continue until the scheduled follow-up visit 14 weeks after last dose intake. Apart from this the following safety assessments will be done: physical examination (including temperature), body weight, vital signs, urine drug and pregnancy testing (female subjects only), clinical labs (hematology, chemistry panel, urinalysis, screening only: thyroid stimulating hormone (TSH) if applicable, follicle stimulating hormone (FSH) if applicable and serology) and allergic and injection site reactions to SC injections. In addition the Columbia Suicide Severity Rating Scale (C-SSRS) will be conducted at each study visit to monitor suicidal ideation and behavior. See Time and Events schedule below for more details.

Additional blood and urine samples may be taken (not exceeding the stated maximum blood volume) or vital signs and electrocardiograms (ECG's) recorded at the discretion of the investigators.

DNA and Biomarker Collection

It is recognized that genetic variation can be an important contributory factor to interindividual differences in drug distribution and response and can also serve as a marker for disease susceptibility and prognosis. Pharmacogenomic research may help to explain interindividual variability in clinical outcomes and may help to identify population subgroups that respond differently to a drug. The goal of the pharmacogenomic component is to collect DNA to allow the identification of genetic factors that may influence the pharmacokinetics, pharmacodynamics, efficacy, safety, or tolerability of sirukumab and to identify genetic factors associated with MDD. Specifically, genetic and epigenetic changes in genes known to be in pathways relevant to depression (HPA axis, inflammation, growth factors, monoamine transporters, ion channels, circadian rhythm) will be evaluated.

Biomarker samples will be collected to allow for exploratory immunophenotyping and for an exploratory pharmacodynamics evaluation.

DNA and biomarker samples may be used to help address emerging issues and to enable the development of safer, more effective, and ultimately individualized therapies.

4. SUBJECT POPULATION

Screening for eligible subjects will be performed within 28 days before administration of the study drug. Chest X-ray (if applicable) and SAFER interview will only be performed (in a second screening visit) once all other screening criteria have been confirmed. If some in and/or exclusion criteria still have to be confirmed at the time of this second screening visit, this will be discussed prior to this second screening visit with the JRD responsible safety physician on a case by case basis.

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.

4.1. Inclusion Criteria

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

1. Male or female between 21 and 64 years of age, inclusive

2. Criterion modified per Amendment INT-4

   2.1. Subjects must have a primary DSM-5 diagnosis of MDD

   a. Subjects with a diagnosis of comorbid Generalized Anxiety Disorder (GAD), Post-Traumatic Stress Disorder, Persistent Depressive Disorder, Attention Deficit Hyperactivity Disorder (ADHD), Social Anxiety Disorder, Panic Disorder with or without agoraphobia, or Nicotine Dependence may be included, if the investigator considers MDD to be the primary diagnosis.

3. Criterion modified per Amendment INT-4

   3.1. Subjects must have a $HDRS_{17}$ total score ≥18 at screening and predose at Day 1, as recorded by the remote independent rater and must not demonstrate an improvement of >25% on their $HDRS_{17}$ total score from the screening to baseline visit.

4. Criterion deleted per Amendment INT-4

   4.1. ~~Subjects must have a hsCRP ≥0.300 mg/dL (SI 3.00 mg/L) at screening.~~

5. Subject must be medically stable on the basis of physical examination, medical history, vital signs, clinical laboratory tests and 12-lead ECG performed at screening. If there are abnormalities, the subject may be included only if the investigator judges the abnormalities or deviations from normal to be not clinically significant. This determination must be recorded in the subject's source documents and initialed by the investigator.

6. Subjects with hypothyroidism who are on stable treatment for 3 months prior to screening are required to have TSH and free thyroxine (FT4) obtained. If the TSH value is out of range, but FT4 is normal, such cases should be discussed directly with the JRD responsible safety physician before the subject is enrolled. If the FT4 value is out of range, the subject is not eligible.

7. The subject's major depressive episode and treatment response must be deemed "valid" using the SAFER criteria interview (which includes the $HDRS_{17}$, a review of the MGH-ATRQ performed at screening, and the SAFER Criteria Inventory) administered by the remote independent rater.

8. Subjects must have had an inadequate response to at least 1 antidepressant in the current episode of depression, as measured by the MGH-ATRQ. Inadequate response is defined as partial improvement (<50%) according to the MGH-ATRQ and moderate to severe depression ($HDRS_{17}$ total score ≥18 at screening, as measured by a remote independent rater). The MGH-ATRQ and prior medication history will be used to determine antidepressant treatment response in prior episode(s).

9. Criterion modified per Amendment INT-4

   9.1. Subject must be currently receiving no more than 2 of the following antidepressants for at least 6 weeks duration at screening, with at least one being at an adequate therapeutic dose, as determined by the MGH-ATRQ and verified by medical or pharmacy records and should remain on a stable dose throughout the study: bupropion, fluoxetine, citalopram, escitalopram, sertraline, paroxetine, venlafaxine, desvenlafaxine, duloxetine, vilazodone, vortioxetine, mirtazapine, fluvoxamine, agomelatine, nortriptyline, imipramine, amitriptyline and levomilnacipram.

10. Women, sexually active or otherwise capable of pregnancy, must practice a method of birth control, including abstinence, intrauterine device, double barrier method (eg, condoms, diaphragm, or cervical cap with spermicidal foam, cream or gel) consistent with local regulations regarding the use of birth control methods for subjects participating in clinical trials. If using hormonal contraceptives, including oral contraceptives, injections and patches, a secondary method of contraception must be used. Contraception must be used for the duration of their participation in the study, and for 4 months after the last study agent administration. 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.

Note: If childbearing potential of a subject changes after start of the study (e.g., a woman who is not heterosexually active becomes active) a woman must begin a highly effective method of birth control, as described above. Not of childbearing potential: postmenopausal (>45 years of age with amenorrhea for at least 12 months or any age with amenorrhea for at least 6 months and a serum follicle stimulating hormone (FSH) level >40 IU/mL); permanently sterilized (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy); or otherwise be incapable of pregnancy.

11. A woman of childbearing potential must have a negative serum (β-human chorionic gonadotropin [β-hCG]) at screening and a negative urine pregnancy test prior to randomization on Day 1.

12. Men, if sexually active with women capable of pregnancy, are to use an effective method of birth control and to not donate sperm during the study and for 4 months after receiving the last dose of study agent. The exception to this restriction is if the subject or his female partner is sterilized; this situation does not require birth control.

13. Subject must be willing and able to adhere to the prohibitions and restrictions specified in this protocol.

14. Subject must be able to read, understand and complete study questionnaires.

15. Subjects will be included according to the following TB screening criteria:

    a. Have no history of latent or active TB prior to screening unless currently receiving treatment for latent TB for at least one month and showing no worsening in clinical status and there is no evidence of active TB. An exception is made for subjects who have a history of latent TB (defined for the purposes of this study as having had a positive result from either the tuberculin skin test (Attachment 2) or the QuantiFERON®-TB Gold test (Attachment 1) prior to screening) and documentation of having completed an adequate treatment regimen for latent TB within 3 years prior to the first administration of study agent under this protocol. These subjects do not need to be retested with the QuantiFERON-TB Gold test (or PPD) during screening. Adequate treatment for latent TB is defined according to local country guidelines for immunocompromised subjects. If

no local guidelines for immunocompromised subjects exist, US guidelines must be followed. It is the responsibility of the investigator to verify the adequacy of previous anti-TB treatment and provide appropriate documentation.

b. Have no signs or symptoms suggestive of active TB upon medical history and/or physical examination.
c. Have had no recent close contact with a person with active TB or, if there has been such contact, will be referred to a physician specializing in TB to undergo additional evaluation and, if warranted, receive appropriate treatment for latent TB prior to the first administration of study agent.
d. Within 6 weeks prior to the first administration of study agent, have a negative QuantiFERON-TB Gold test result or have a newly identified positive QuantiFERON-TB Gold test result in which active TB has been ruled out and for which appropriate treatment for latent TB has been initiated prior to the first administration of study agent. A negative tuberculin skin test or a newly identified positive tuberculin skin test result in which active TB has been ruled out and for which appropriate treatment for latent TB has been initiated prior to the first administration of study agent is additionally required if the QuantiFERON-TB Gold test is not approved/registered in that country. An exception is made for subjects who have a history of latent TB (a positive result from either the tuberculin skin test or the QuantiFERON-TB Gold test prior to screening) and documentation of having completed an adequate treatment regimen for latent TB within 3 years prior to the first administration of study agent. These subjects do not need to be retested with the QuantiFERON-TB Gold test (or PPD) during screening. Subjects with repeatedly indeterminate QuantiFERON-TB Gold test results from 2 samples tested in screening are ineligible (Section 9.1.2.).
e. Have a chest radiograph (both posterior-anterior and lateral views), taken within 12 weeks prior to the first administration of study agent and read by a qualified radiologist, with no evidence of current, active TB or old, inactive TB.

16. Each subject must sign an informed consent form (ICF) indicating that he or she understands the purpose of and procedures required for the study and is willing to participate in the study.

NOTE:

- 50 subjects must have a hsCRP < 0.300 mg/dL (SI <3.00 mg/L) at screening. Once 50 subjects with a hsCRP level <0.300 mg/dL (SI <3.00 mg/L) have been enrolled, all further subjects to be randomized must have hsCRP levels ≥0.300 mg/d (SI ≥3.00 mg/L); sites will be notified by the study team when 50 subjects with hsCRP <0.300 mg/dL (SI <3.00 mg/L) have been randomized and enrollment is completed in this stratum. Subjects with <0.300 mg/dL (SI <3.00 mg/L) hsCRP in active screening once the enrollment in the hsCRP <0.300 mg/dL (SI <3.00 mg/L) will be completed, will be considered screening failures.

- Retesting of an abnormal laboratory value, at the discretion of the Investigator, that may lead to exclusion will be allowed only once during the screening phase. Retesting will

take place during an unscheduled visit in the screening phase. After completion of the hsCRP < 0.300 mg/dL cohort, retesting for hsCRP will be allowed, but only for subjects who have hsCRP ≥ 0.250 mg/dL (SI ≥2.50 mg/L) and < 0.300 mg/dL (SI <3.00 mg/L) at screening. Retesting for hsCRP is only allowed once.

4.2. Exclusion Criteria

Any potential subject who meets any of the following criteria will be excluded from participating in the study.

1. Criterion modified per Amendment INT-4
   1.1. Any other current Axis I psychiatric condition, including, but not limited to, MDD with current psychotic features, bipolar disorder (including lifetime diagnosis), obsessive-compulsive disorder, borderline personality disorder, eating disorder (eg, bulimia, anorexia nervosa), or schizophrenia (lifetime). The MINI will be used to screen for comorbid psychiatric diagnoses. As noted above, subjects with a diagnosis of comorbid GAD, Post-Traumatic Stress Disorder, Persistent Depressive Disorder, ADHD, Social Anxiety Disorder, Panic Disorder with or without agoraphobia or Nicotine/Caffeine Dependence may be included, if the investigator considers MDD to be the primary diagnosis.
   Note: treatment with psychostimulants is not allowed

2. Age of onset of depression after 55 years of age.

3. A history of alcohol or substance use disorder (abuse/dependence) within 6 months prior to screening (nicotine and caffeine dependence are not exclusionary).

4. A current or recent (within the past year) history of clinically significant suicidal ideation (corresponding to a score of ≥ 3 for ideation) or any suicidal behavior within the past year, as validated on the C-SSRS at screening or baseline. Subjects with a prior suicide attempt of any sort, or history of prior serious suicidal ideation/plan should be carefully screened for current suicidal ideation and only included at the discretion of the investigator.

5. More than 3 failed antidepressant treatments (of adequate dose and duration) in the current episode of depression (verified by the MGH-ATRQ).

6. Criterion modified per Amendment INT-4

   6.1. Length of current major depressive episode > 60 months.

7. Criterion modified per Amendment INT-4

   7.1. Subjects who demonstrate improvement of >25% on the $HDRS_{17}$ between the screening and baseline visit.

8. Lifetime history of treatment with a monoclonal antibody (biologic) for any reason.

9. Organic brain disease or dementia.

10. Known or suspected mental retardation.

11. Subjects who have been treated with electroconvulsive therapy in the current episode or who have been treated with deep brain stimulation (lifetime) or who have been treated with repetitive transcranial magnetic stimulation within 4 weeks prior to baseline visit.

12. Any clinically relevant medical condition that could potentially alter the absorption, metabolism, or excretion of the study medication, such as liver disease or renal disease.

13. Relevant history of any significant immunologic disease including, but not limited to, Crohns Disease, Ulcerative Colitis, Rheumatoid Arthritis, Plaque Psoriasis, Psoriatic Arthritis, Lupus.

14. Relevant history of any significant and/or unstable cardiovascular, respiratory, neurological (including seizures - uncomplicated childhood febrile seizures with no sequelae are not exclusionary) or significant cerebrovascular, renal, hepatic, dermatologic, hematologic, gastrointestinal or endocrine diseases. Hospitalization for a cardiovascular event (myocardial infarction, unstable angina, stroke, transient ischemic attack) within 3 months prior to the first administration of study agent is exclusionary.

    - subjects with non-insulin dependent diabetes mellitus who are adequately controlled (not on insulin) may participate in the study.

15. Have any known malignancy or has a history of malignancy within the previous 5 years (with the exception of a nonmelanoma skin cancer that has been treated with no evidence of recurrence for at least 3 months before the first study agent administration or cervical intraepithelial neoplasia with surgical cure).

16. Female subjects who are pregnant or breastfeeding.

17. Screening laboratory test result as follows:

    a. Hemoglobin <10 g/dL (SI: <85 g/L) or < 5.3 mmol/L

    b. White blood cells (WBC) $<3.5 \times 10^3$ cells/µL (SI: $<3.5 \times 10^9$ cells/L)

    c. Neutrophils $<1.95 \times 10^3$ cells/µL (SI: $<1.95 \times 10^9$ cells/L)

    d. Platelets $<140 \times 10^3$ cells/µL (SI: $<140 \times 10^9$ cells/L)

    e. Serum ALT or AST >1.5 times the ULN for the central laboratory conducting the test

    f. Total bilirubin >ULN

    g. Serum creatinine ≥2.0 mg/dL (SI: ≥177 µmol/L)

18. Subject has had a severe infection (including, but not limited to hepatitis, pneumonia, sepsis, or pyelonephritis); or has been hospitalized for an infection; or has been treated with intravenous antibiotics for an infection, within 2 months prior to the first administration of study agent.

19. History of chronic or recurrent infectious disease or ongoing infection including, but not limited to, chronic renal infection, chronic chest infection, recurrent urinary tract infection (eg, recurrent pyelonephritis, chronic non-remitting cystitis), or open, draining skin wound or an ulcer.

20. Nontuberculous mycobacterial infection or opportunistic infection (eg, cytomegalovirus, pneumocystosis, aspergillosis) within 6 months prior to screening.

21. Chest radiograph within 3 months prior to the first administration of study agent that shows an abnormality suggestive of a malignancy or current active infection, including TB.

22. Criterion modified per Amendment INT-4

    22.1. Subjects with uncontrolled hypertension – hypertension must be controlled for at least 3 months prior to screening; the dosage of any antihypertensive medication must have been stable for the past 3 months. Subjects with a supine systolic blood pressure >150 mmHg, a supine diastolic blood pressure >95 mmHg, or a pulse >100 bpm at screening or baseline will be excluded.

23. Is infected with HIV (positive serology for HIV antibody), hepatitis B [positive serology for hepatitis B surface antigen (HBsAg)] or hepatitis C (positive serology for hepatitis C virus antibody). If seropositive, consultation with a physician with expertise in the treatment of HIV or hepatitis B and C virus infection is recommended.

24. Criterion modified per Amendment INT-4

    24.1. Positive urine drug screen for opiates, cocaine, barbiturates, methadone, marijuana and amphetamine/methamphetamine or positive alcohol screen at screening. In the case of a subject having a positive drug screen for marijuana, barbiturates or opioids, a one-time repeat urine drug screen may be performed at the discretion of the investigator, provided the subject is willing to abstain from marijuana and other prohibited substances during the study.

25. Clinically significant abnormal physical examination, vital signs or 12-lead ECG at screening. Minor deviations in ECG, which are not considered to be of clinical significance to the investigator, are acceptable. Clinically significant abnormal observations in ECG at screening are defined as:

a. A confirmed screening visit QTcB or QTcF, males or females, interval ≥470 ms), or >480 ms if bundle branch block and prolongation of the QTc interval are present; or a history of untreated second- or third-degree heart block.

26. Diagnosis of congestive heart failure Class III or IV.

27. History of known demyelinating diseases such as multiple sclerosis or optic neuritis.

28. History of gastrointestinal perforation or currently has active diverticulitis.

29. Has received, or is expected to receive, any live virus or bacterial vaccination within 3 months before the first administration of study agent, during the study, or within 4 months after the last administration of study agent. Have had a Bacille Calmette-Guérin (BCG) vaccination within 12 months of screening.

30. Use of monoamine oxidase inhibitors within 4 weeks before screening.

31. Criterion modified per Amendment INT-4

31.1 Use of benzodiazepines in dose in excess of 2mg/day equivalent of lorazepam (see section 'prohibited medications' below for equivalents)

32. Use of mood stabilizers (e.g. anticonvulsants and/or lithium) or antipsychotics within 2 weeks before screening.

33. Criterion modified per Amendment INT-4
33.1. Daily use of aspirin, ibuprofen, Cox-2 inhibitors, NSAIDs or other anti-inflammatory drugs or combination treatments for headache or pain which contains those products within 2 weeks prior to screening (acetaminophen/paracetamol permitted) and unwilling to use acetaminophen/paracetamol only during study participation.

Note:
- PRN use of following NSAIDs is allowed: Ibuprofen up to 1600 mg/day; Diclofenac up to 75 mg/day; Aspirin up to 1500 mg/day. NSAIDs must be discontinued 3 days before the in-clinic visits for biomarkers measurements.
- Prophylactic use of low dose aspirin prescribed for cardiovascular or cerebrovascular disease is allowed.

34. Current use of immunomodulators (eg azathioprine, tacrolimussulfasalazine)

35. Has received immunosuppressant agents, as follows:

a. Has a history of cyclophosphamide or cytotoxic agent use.

b. Has received cyclosporine A, azathioprine, tacrolimus, mycophenolate mofetil, oral or parenteral gold, hydroxychloroquine and methotrexate within 4 weeks of the first study agent administration.

36. Subjects with previous exposure to sirukumab.

37. Known allergies, hypersensitivity, or intolerance to sirukumab or its excipients.

38. History of severe allergic reaction to monoclonal antibodies or to murine, chimeric, or human proteins or their excipients.

39. Major surgery, (eg, requiring general anesthesia) within 8 weeks before screening, or has not fully recovered from surgery, or has planned major surgery during the time the subject is expected to participate in the study.

Note: subjects with planned surgical procedures to be conducted under local anesthesia may participate.

40. Exposure to an experimental drug or experimental medical device within 90 days before screening.

41. Criterion modified per Amendment INT-4

    41.1. Involuntarily committed to psychiatric hospitalization in the current episode.

42. Donation of 1 or more units (approximately 450 mL) of blood or acute loss of an equivalent amount of blood within 90 days prior to study drug administration.

43. Any condition that, in the opinion of the investigator, would compromise the well-being of the subject or the study or that could prevent, limit or confound the protocol-specified assessments.

44. Employees of the investigator or study center, persons with direct involvement in the proposed study or other studies under the direction of that investigator or study center, or family members of the employees or the investigator.

NOTE: Investigators should ensure that all study enrollment criteria have been met at screening. If a subject's status changes (including laboratory results or receipt of additional medical records) after screening but before the first dose of study drug is given such that he or she no longer meets all eligibility criteria, then the subject should be excluded from participation in the study.

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. Subjects should abstain from using illegal drugs within 3 days prior to Day 1 and at any time during the study. Alcohol consumption should be limited to maximum 3 alcoholic beverages during the week prior to Day 1 and maximum 3 alcoholic beverages weekly throughout study.

2. If a woman is 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 dose of 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 (see inclusion criteria #10). 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.

3. 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 #12).

4. For a list of prohibited medications, please see Prestudy and Concomitant Medication.

5. 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. TREATMENT ALLOCATION AND BLINDING

Treatment Allocation

Procedures for Randomization and Stratification

Central randomization will be implemented in this study. Subjects will be randomly assigned to 1 of 2 treatment groups based on a computer-generated randomization schedule prepared before the study by or under the supervision of the sponsor. The randomization will be balanced by using randomly permuted blocks and will be stratified by country and 4 screening hsCRP levels: 0.00 to <0.300 mg/dL (SI 0.00 to <3.00 mg/L), ≥0.300 to <0.500 mg/dL (SI ≥3.00 to <5.00 mg/L), ≥0.500 to <0.800 mg/dL (SI ≥5.00 to <8.00 mg/L), and ≥0.800 mg/dL (SI ≥8.00 mg/L). The interactive web response system (IWRS) will assign a unique treatment code, which will dictate the treatment assignment and matching study drug kit for the subject. The requestor must use his or her own user identification and personal identification number when contacting the IWRS, and will then give the relevant subject details to uniquely identify the subject.

Blinding

To maintain the study blind, the study drug container will have a label containing the study name, study drug number and reference number. The label will not identify the study drug in the container. However, if it is necessary for a subject's safety, the study blind may be broken and the identity of the study drug ascertained. The study drugs will be identical in appearance and will be packaged in identical containers.

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.

The investigator will not be provided with randomization codes. The codes will be maintained within the IWRS, which has the functionality to allow the investigator to break the blind for an individual subject.

Data that may potentially unblind the treatment assignment (ie, cholesterol, LDL, HDL, triglycerides and hsCRP) will be handled with special care to ensure that the integrity of the blind is maintained and the potential for bias is minimized. This can include making special provisions, such as segregating the data in question from view by the investigators, clinical team, or others as appropriate until the time of database lock and unblinding. Sponsor staff, investigators, site staff, subjects, and remote independent rater will all be blinded to the treatment assignment, as well as hsCRP, cholesterol, LDL, HDL and triglyceride values during the trial. The remote independent rater will be blinded to any adverse events (AEs) reported by subjects; subjects will be instructed not to discuss AEs with the rater.

Under normal circumstances, the blind should not be broken until all subjects have completed the study and the database is finalized. Otherwise, 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 in an emergency determine the identity of the treatment by contacting the IWRS. It is recommended that the investigator contact the sponsor or its designee if possible to discuss the particular situation, before breaking the blind. 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 case report form (CRF) and in the source document. The documentation received from the IWRS indicating the code break must be retained with the subject's source documents in a secure manner.

Subjects who have had their treatment assignment unblinded should continue to return for scheduled evaluations.

In general, randomization codes will be disclosed fully only if the study is completed and the clinical database is closed. At the interim efficacy analysis, the randomization codes and, if required, the translation of randomization codes into treatment and control groups will be disclosed to those authorized and only for those subjects included in the interim analysis. The details about disclosure of randomization codes and treatment assignment at the interim efficacy analysis will be provided in the Interim Analysis Committee (IAC) charter. In addition, prespecified Clinical Pharmacology representatives may be unblinded prior to the clinical database lock for the purpose of performing PK and immunogenicity analyses.

At the time of the first database lock for the primary efficacy analyses, randomization codes will be disclosed fully. Unblinding after completion of the 12-week double-blind treatment phase will not impact the integrity of the study data, as only follow-up visits will be performed after the unblinding and those visits will not include the primary outcome measures of the study.

6. DOSAGE AND ADMINISTRATION

Subjects will be randomly assigned in a 1:1 ratio to receive adjunctive treatment with a SC injection of sirukumab 50 mg or placebo, while continuing on their baseline oral monoaminergic antidepressant(s). The matching placebo injection will consist of an identical volume of placebo solution, administered SC every 4 weeks. All subjects will receive 3 injections in total, one injection each at Day 1, Day 28 and Day 56. The study agent will be administered SC in the outer area of the upper arms.

The study agent will be administered subcutaneously at the site by a healthcare professional who administers study agent through Week 8.

If an injection is missed every effort should be made to have the missed injection administered within 4 days after the scheduled study visit for that injection.

In case it is not possible to administer an injection on time, the injection will be considered as missed for that visit, and the site personnel should discuss the issue with the JRD responsible safety physician.

Time and date of dose administration will be recorded in the CRF.

7. TREATMENT COMPLIANCE

Study agent administered at the site will be administered SC by an appropriately licensed and authorized health care professional. Study personnel will maintain a log of all study agent administrations. Study agent supplies for each subject will be inventoried and accounted for. All ongoing therapies administered at the time of screening must be recorded.

8. PRESTUDY AND CONCOMITANT THERAPY

Prestudy oral antidepressant therapies, monoamine oxidase inhibitors, benzodiazepines and mood stabilizers, antipsychotics, immunosuppressants, immunomodulators, aspirin, ibuprofen, Cox-2 inhibitors, NSAIDs or other anti-inflammatory medication administered before first dose of study drug must be recorded at screening.

Concomitant therapies must be recorded throughout the study beginning with start of the first dose of study drug until last follow-up visit.

All therapies (prescription or over-the-counter medications, including vaccines, vitamins, herbal supplements; non-pharmacologic therapies such as electrical stimulation, acupuncture, special diets, exercise regimens) different from the study drug must be recorded in the CRF. Recorded information will include a description of the type of the drug, treatment period, dosing regimen, route of administration, and its indication.

Subject's baseline oral antidepressants (bupropion, fluoxetine, citalopram, escitalopram, sertraline, venlafaxine, desvenlafaxine, mirtazapine, fluvoxamine, agomelatine, amitriptyline

imipramine, nortriptyline, vilazodone, vortioxetine and levomilnacipram) will be taken as prescribed (without dose change) throughout the screening and double-blind phase of the study. Adherence to subject's baseline oral antidepressants will be checked at each visit to the site.

Subjects must agree not to use any of the following medications with psychotropic properties, including but not limited to:

– Psychiatric medications, including mood stabilizers, antipsychotics, psychostimulants and antidepressants other than their baseline monoaminergic antidepressant(s) (e.g., monoamine-oxidase inhibitors (MAOIs) and milnacipram are prohibited).

– Benzodiazepines in excess of the equivalent of 2 mg of lorazepam per day. A subject may continue to take a benzodiazepine only if the subject has been taking a fixed daily dose of a benzodiazepine for at least 2 weeks prior to screening. As required (PRN) use of benzodiazepines is not allowed.

Benzodiazepine Equivalent Dosages:

Benzodiazepine	Oral Dose (mg)
Lorazepam	2
Clonazepam	1
Clorazepate	30
Diazepam	10
Temazepam	20
Alprazolam	1

Phenazepam is also allowed in dosages up to 1.5 mg daily.

Allowable sleep medications include: zolpidem, zaleplon, zoplicone, eszopliclone, diphenhydramine, and ramelteon. Continuous fixed dose or PRN use of sleep medications is allowed. Subjects with PRN use of sleep medications shall be advised not to take any sleep medications the day prior to the clinical visits and/or the remote ratings interview procedures (i.e., $HDRS_{17}$ and SAFER interview). Other sleep aids such as chloral hydrate and sedating antipsychotics are prohibited.

A dosage of trazodone not exceeding 150 mg/day given as a sleep aid or for sexual dysfunction is allowed.

Other prohibited medications include:

- S-adenosyl methionine (SAMe), St. John's wort, ephedra, ginkgo, ginseng, or kava kava

- Opiates
- Anticonvulsants
- Antipsychotics (typical and atypical)
- Cox-2 inhibitors, chronic use of NSAIDs or other anti-inflammatory drugs or combination treatments for headache or pain which contains those products (acetaminophen/paracetamol allowed, dose as recommended by the site staff, but not to exceed 3 g/day)

  Note: PRN use of following NSAIDs is allowed: Ibuprofen up to 1600 mg/day; Diclofenac up to 75 mg/day; Aspirin up to 1500 mg/day. NSAIDs must be discontinued 3 days before the in-clinic visits for biomarkers measurements.
- Immunomodulators
- Immunosuppressants

Subjects receiving psychotherapy can continue receiving psychotherapy provided this therapy has been stable in terms of frequency for the last 3 months prior to screening and will remain unchanged throughout study treatment.

Cognitive behavioral therapy for ADHD is allowed.

The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

Drugs Metabolized by Cytochrome P450

Inflammatory cytokines, including IL-6, are known to downregulate activity and expression of multiple CYP450 enzymes. Hypothetically, IL-6 inhibition in a subject 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 subjects 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). Substrates with a narrow therapeutic range include alfentanil, astemizole, cisapride, dihydroergotamine, ergotamine, fentanyl, quinidine, terfenadine.

9. STUDY EVALUATIONS

9.1. Study Procedures

9.1.1. Overview

The Time and Events Schedule summarizes the frequency and timing of efficacy, pharmacokinetic, immunogenicity, biomarker, pharmacogenomic, and safety measurements applicable to this study.

All visit-specific Patient-Reported Outcomes (PRO) assessments should be conducted/completed before any tests, procedures, or other consultations for that visit to prevent influencing subject 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.

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.

For each subject, approximately 350 mL of blood will be drawn. The maximum amount of blood drawn from each subject in this study will not exceed 450 mL. Detailed blood volumes per blood sample will be provided in the lab manual.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

9.1.2. Screening Phase

Within 4 weeks prior to Day 1, potential subjects will be screened to determine their eligibility for study participation.

Prior to conducting any study procedure, the investigator (or designated study personnel) will review and explain the written ICF to each subject. No study procedures can be performed until after the subject signs the ICF.

The screening visit will include obtaining informed consent, assessment of inclusion and exclusion criteria, medical history and demographics, physical examination, psychiatric and safety evaluations and venous blood sampling for hsCRP assay and standard labs as described in the Time and Events Schedule.

The procedures scheduled during the first screening visit may be divided over two days, according to operational and/or site/country-specific needs. In case the first screening visit is conducted over two days, the following assessments must be performed on the same day: C-SSRS, IDS-C30 and $HDRS_{17}$.

$HDRS_{17}$ and SAFER will be done by an independent rater during the screening visit. The SAFER interview will only be performed (at a second screening visit) once subjects have been confirmed eligible for all other screening criteria.

Adverse events will be collected starting after the ICF has been signed until the final study procedure at the final visit.

Subjects with a DSM-5 diagnosis of MDD, confirmed by the MINI, who are currently being treated with a monoaminergic antidepressant and have failed no more than 3 antidepressants (of adequate dose and duration) in the current major depressive episode will be eligible for screening. Determination of suboptimal response to the current standard oral antidepressant therapy will be made retrospectively using the structured MGH-ATRQ. Determination of failure of antidepressant treatments in the current episode will be made retrospectively using medical or pharmacy records and documented on the MGH-ATRQ. Subjects with partial improvement (<50%) according to the MGH-ATRQ and moderate to severe depression ($HDRS_{17}$ total score ≥18 at screening, as measured by a remote independent rater) will be eligible for inclusion. Subjects must be currently receiving no more than 2 of the following antidepressants for at least 6 weeks duration at screening with at least one antidepressant being at an adequate therapeutic dose, as determined by the MGH-ATRQ: bupropion, fluoxetine, citalopram, escitalopram, sertraline, paroxetine, venlafaxine, desvenlafaxine, duloxetine, vilazodone, vortioxetine fluvoxamine, mirtazapine, agomelatine, nortiptyline, imipramine, amitriptyline and levomilnacipram. hsCRP levels used for stratification during the randomization process are determined at screening. Once 50 subjects with a hsCRP level <0.300 mg/dL have been enrolled, all further subjects to be randomized must have hsCRP levels ≥0.300 mg/dL; sites will be notified by the study team when 50 subjects with hsCRP <0.300 mg/dL have been randomized and enrollment is completed in this arm.

A chest radiograph (lateral and posterior-anterior view unless local guidelines recommend only single view) will be performed at screening to ensure that the subject does not have any abnormality suggestive of a malignancy or current active infection, including TB. This chest radiograph will only be performed (at a second screening visit) once subjects have been confirmed eligible for all other screening criteria. Chest x-rays taken up to 3 months prior to Day 1 may also be used.

Subjects must undergo testing for TB (Attachment 1 and Attachment 2) and their medical history assessment must include specific questions about a history of TB or known occupational, or other personal exposure to individuals with active TB. The subject should be asked about past testing for TB, including chest radiograph results and responses to tuberculin skin or other TB testing.

Subjects with a negative QuantiFERON-TB Gold test result (and a negative tuberculin skin test result in countries in which the QuantiFERON-TB Gold test is not approved/registered) are eligible to continue with prerandomization procedures. Subjects with a newly identified positive QuantiFERON-TB Gold test (or tuberculin skin test) result must undergo an evaluation to rule out active TB and initiate appropriate treatment for latent TB prior to first dose. An exception is

made for subjects who have a history of latent TB (defined for the purposes of this study as having had a positive result from either the tuberculin skin test (Attachment 2) or the QuantiFERON TB Gold test (Attachment 1) prior to screening) and documentation of having completed an adequate treatment regimen for latent TB within 3 years prior to the first administration of study agent under this protocol. These subjects do not need to be retested with the QuantiFERON-TB Gold test (or PPD) during screening. Appropriate treatment for latent TB is defined according to local country guidelines for immunocompromised subjects. If no local country guidelines for immunocompromised subjects exist, US guidelines must be followed or the subject must be excluded from the study. It is the responsibility of the investigator to verify the adequacy of previous anti-TB treatment and provide appropriate documentation.

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.

Subject must not use a disallowed therapy (prior or concomitant), within 1 week (or longer, if specified) before the planned first dose of study drug. Refer to Section 8, Pre-trial and Concomitant Therapy for a list of prohibited therapies.

Subject-completed assessments should be completed before any clinical tests are taken or clinician-administered assessments associated with the study visit are conducted.

9.1.3. Double-Blind Treatment Phase

Subjects who continue to meet inclusion and exclusion criteria at the baseline visit will be eligible for randomization. At the baseline visit, subjects must have a $HDRS_{17}$ total score ≥18, as measured by a remote independent rater, and must not demonstrate an improvement of >25 % on their $HDRS_{17}$ total score from the screening to baseline visit. Randomization will be stratified by country and screening hsCRP level: 0.00 to <0.300 mg/dL (SI 0.00 to <3.00 mg/L), ≥0.300 to <0.500 mg/dL (SI ≥3.00 to <5.00 mg/L), ≥0.500 to <0.800 mg/dL (SI ≥5.00 to <8.00 mg/L), and ≥0.800 mg/dL (SI ≥8.00 mg/L). Subjects will receive either adjunctive placebo or adjunctive sirukumab in a 1:1 ratio.

During the treatment phase, efficacy, safety, tolerability, immunogenicity, PK, biomarker, and pharmacogenomic evaluations will be performed as per the Time and Events Schedule.

On days when blood samples for lab safety or biomarkers are collected, subjects should come to the site fasted, whenever feasible.

Study drug will be administered on Day 1, Day 28 and Day 56. Refer to Section 6 (Dosage and Administration) for further details.

During the double blind treatment phase, at visits in which the subject-completed and clinician-administered assessments, clinical tests and blood samples are scheduled at the same time point, the following sequence will be used:

1. Subject-completed assessments
2. Clinician-administered assessments
3. Clinical tests
4. Blood samples

The sequence of clinician-administered assessments will be:

1. IDS-C30
2. CGI-S
3. C-SSRS

$HDRS_{17}$ will be done by an independent rater.

If a subject discontinues treatment before the end of the double-blind treatment phase, early withdrawal assessments should be obtained as soon as possible.

9.1.4. Posttreatment Phase (Follow-Up)

Subjects will have follow-up assessments performed according to the Time and Events Schedule.

In the event a subject discontinues study agent injections, but does not terminate study participation, the first safety and efficacy follow-up visit should occur 8 weeks after the date of discontinuation of the study agent. The second safety and efficacy follow-up visit should occur 14 weeks after the date of discontinuation of the study agent. The visit window for follow-up assessments is ± 7 days.

Any clinically significant abnormalities persisting at the end of the study will be followed by the investigator until resolution or until a clinically stable endpoint is reached.

9.2. Efficacy

9.2.1. Evaluations

Every effort should be made to ensure that all clinician administered assessments are completed by the same individual who made the initial baseline determinations.

Hamilton Depression Rating Scale ($HDRS_{17}$)

The $HDRS_{17}$ is a clinician-administered rating scale designed to assess the severity of symptoms in subjects diagnosed with depression (Hamilton M 1960) with a score range of 0 to 52. It is the most widely used symptom severity measure for depression. Each of the 17 items is rated by the clinician on either a 3- or a 5-point scale. The $HDRS_{17}$ has an inter-rater reliability correlation of r = .90 and the internal consistency of the measure is reported to be high with a coefficient alpha of 0.88. Criterion-related validity for this measure is high (Knesevich J et al., 1977).

The original HDRS17 scale lacks instructions for administration and clear anchor points for the assignment of severity ratings. For this reason, the structured interview guide version of the HDRS17 (the Structured Interview Guide for the Hamilton Depression Scale [SIGH-D]) will be used in the current study to facilitate and standardize gathering clinical information from the subject.

An example of the $HDRS_{17}$ is provided in Attachment 7.

CGI-S

The CGI-S will provide an overall clinician-determined summary measure that takes into account all available information, including knowledge of the subject's history, psychosocial circumstances, symptoms, behavior, and the impact of the symptoms on the subject's ability to function (Guy 1976). The CGI evaluates the severity of psychopathology from 1 to 7.
An example of the CGI-S is provided in Attachment 3.

Patient Health Questionnaire (PHQ-9)

The PHQ-9 will be used as a subject-reported measure of depressive symptomatology (Spitzer 1999). The PHQ-9 is a 9-item scale, where each item is rated on a 4-point scale (0=Not at all, 1=Several Days, 2=More than half the days, and 3=Nearly every day), with a total score range of 0 to 27. The recall period is 2 weeks.
An example of the PHQ-9 is provided in Attachment 9.

Snaith–Hamilton Pleasure Scale (SHAPS)

Anhedonia, the inability to experience pleasure, is a core symptom of depression. The Snaith–Hamilton Pleasure Scale (SHAPS) is a short, 14-item instrument to measure anhedonia, which has been shown to be valid and reliable in normal and clinical samples (Snaith et al, 1995). Each of the 14 items has a set of four response categories: Definitely Agree (= 1), Agree (= 2), Disagree (= 3), and Definitely Disagree (= 4). A higher total score indicates higher levels of state anhedonia.
An example of the SHAPS is provided in Attachment 10.

Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT Fatigue)

The FACIT-Fatigue is a questionnaire that assesses self-reported tiredness, weakness, and difficulty conducting usual activities due to fatigue. The total FACIT-Fatigue score ranges from 0 to 52, with a higher score indicating less fatigue (Webster et al., 1999).
An example of the FACIT is provided in Attachment 11.

Exploratory evaluation:

Inventory of Depressive Symptomatology – Clinician Rated 30 (IDS-C30)

The clinician-rated IDS is a 30-item, depression-specific symptom severity rating scale (Rush et al., 1986). The IDS is designed to measure the specific signs and symptoms of depression, including melancholic, atypical and anxious features. Scores range from 0 to 84 with higher

scores representing greater severity of depressive symptoms. The inter-rater reliability and internal consistency coefficients are high (Rush et al., 1996). The IDS-C and the IDS-self report have reasonable construct validity, and a concurrent validity index above 0.90, correlating well with the $HDRS_{17}$ and the Beck Depressive Inventory (Rush et al., 1996).
An example of the IDS-C30 is provided in Attachment 8.

Childhood Trauma Questionnaire (CTQ)

The CTQ was developed as a screening tool for histories of abuse and neglect (Bernstein et al. 1998). The self-report includes a 28-item test that measures 5 types of maltreatment – emotional, physical, and sexual abuse, and emotional and physical neglect. A 5-point Likert scale is used for the responses which range from Never True to Very Often True.
An example of the CTQ is provided in Attachment 12.

9.2.2. Endpoints

Primary Endpoint

Efficacy will be based on the change from baseline to 12-week endpoint for the $HDRS_{17}$ total score for the adjunctive sirukumab treatment group compared with the adjunctive placebo treatment group in subjects with hsCRP ≥0.300 mg/dL (SI ≥3.00 mg/L) at screening and baseline.

Secondary Endpoints

Secondary efficacy endpoints will include the change from baseline to 12-week endpoint between the adjunctive sirukumab group and the adjunctive placebo group in the SHAPS total score, CGI-S, PHQ-9 and FACIT as well as the distribution of remitters and responders in subjects with screening hsCRP ≥ 0.300 mg/dL (SI ≥3.00 mg/L) (the number and percentage of subjects in remission as measured by a $HDRS_{17}$ total score ≤ 7 or responders defined as ≥ 50% improvement on the $HDRS_{17}$ from baseline to 12 week endpoint). The same secondary efficacy endpoints will be compared between subjects with screening hsCRP≥0.300 mg/dL (SI ≥3.00 mg/L) and subjects with hsCRP<0.300 mg/dL (SI <3.00 mg/L).

Exploratory Endpoints

Exploratory efficacy evaluations will include the change from baseline to 12-week endpoint in the IDS-C30 total score, evaluation of the association between change from baseline of the $HDRS_{17}$, baseline and post-treatment biomarker measurements (including hsCRP), the effect of sirukumab on the pharmacokinetics of monoaminergic antidepressants, evaluation of the relationship between the severity of childhood trauma as assessed through the CTQ and the change in $HDRS_{17}$ scores following adjunctive sirukumab or placebo and assessment of genes/genotypes.

9.3. Pharmacokinetics and Immunogenicity

9.3.1. Evaluations

Venous blood samples will be collected for measurement of serum sirukumab concentrations and immunogenicity of sirukumab (antibodies to sirukumab). Samples collected for analyses of sirukumab serum concentration and antibodies to sirukumab may additionally be used to evaluate safety or efficacy aspects that address concerns arising during or after the study period, for further characterization of immunogenicity or for the evaluation of relevant biomarkers. Additionally, venous blood samples will be collected for measurement of plasma concentrations of monoaminergic antidepressants. Genetic analyses will not be performed on these serum samples. Subject confidentiality will be maintained.

9.3.2. Pharmacokinetics

9.3.2.1. Sample Collection and Handling

Venous blood samples for measurement of serum sirukumab concentrations and antibodies to sirukumab will be collected at the time points shown in the Time and Events Schedule. Subjects who terminate from study participation should have final visit samples collected at the time of termination. At visits where serum concentration and antibodies to sirukumab will be evaluated, termination. At visits where serum concentration and antibodies to sirukumab will be evaluated, 1 blood draw can be used. Each serum sample will be divided into 3 aliquots (1 each for pharmacokinetics, antibodies to study drug, and a back-up). Samples must be collected before study drug administration at visits when study drug administration is scheduled. The exact dates and times of blood sample collection must be recorded in the laboratory requisition form.

Additionally, venous blood samples for measurement of plasma concentrations of monoaminergic antidepressants will be collected at the time points shown in the Time and Events Schedule. Samples collected after Day 1 must be collected at the same time as samples on Day 1 (+/- 1 hour). On days when samples for concentrations of monoaminergic antidepressants are collected, date and time of the last 3 intakes of the monoaminergic antidepressants will be recorded in the CRF. If a monoaminergic antidepressant has less than 20 subjects taking it, samples for that antidepressant will not be analyzed since the small sample size may not provide useful data to evaluate the effect of sirukumab on the pharmacokinetics of monoaminergic antidepressants.

Additional information about the collection, handling, and shipment of biological samples can be found in the laboratory manual.

9.3.2.2. Analytical Procedures

Serum samples will be analyzed to determine concentrations of sirukumab using a validated, immunoassay method by or under the supervision of the sponsor.

Plasma samples will be analyzed to determine the concentrations of monoaminergic antidepressants using validated, specific and sensitive (eg, liquid chromatography mass spectrometry/mass spectrometry [LC-MS/MS]) methods by or under supervision of the sponsor.

9.3.3. Immunogenicity Assessments (Antibodies to sirukumab)

Antibodies to sirukumab will be detected using a validated immunoassay method in serum samples collected from all subjects. 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 further characterize the immunogenicity of sirukumab.

9.4. Biomarkers

During the study, blood and saliva will be collected for the assessment of biomarkers at the time points indicated in the Time and Events schedule. The biomarker blood samples will be collected between 08:00 and 10:00 am as indicated in the T&E schedule. Subjects should be fasting for at least 8 hours prior to blood draw (if feasible). Subjects should also refrain from strenuous exercise in 24 hours before blood collection (if feasible). Subjects should not consume any food or drink other than water (including use of toothpaste or mouthwash) for at least 60 min prior to saliva collections (if feasible).

In blood, biomarkers related to the immune system activity, HPA axis activation, neurotrophic factors and metabolic factors will be investigated to allow for exploratory immunophenotyping and for an exploratory pharmacodynamics evaluation.

Biomarkers may be added or deleted based on scientific information or technical innovations under the condition that the total volume of blood collected will not increase.

Date and time of blood and saliva collection should be recorded on the laboratory requisition form.

Further information regarding handling, shipment, and labeling of biological samples will be provided in a separate lab manual.

Subject data

To evaluate the biomarker results, the following information needs to be documented on each day of collection of blood samples for biomarker analysis.

- Diet (extremes during the previous week)
- In women of childbearing potential: average duration of menstrual cycle in days and last date of menses to determine follicular phase
- Any sickness or allergy in the previous 2 weeks

The biomarker data obtained from this study may also be included in an ongoing cross-study analysis to investigate the relationship between depression severity and phenotypes and biomarkers.

9.5. Pharmacogenomic (DNA) Evaluations

DNA samples will be collected at the time points indicated in the Time and Events Schedule for the assessment of genetic and epigenetic changes in genes known to be in pathways relevant to depression (HPA axis, inflammation, growth factors, monoamine transporters, ion channels, circadian rhythm).

Additional analyses may be conducted if it is hypothesized that this may help resolve issues with the clinical data.

DNA samples will be used for research related to sirukumab or MDD. They may also be used to develop tests/assays related to sirukumab and MDD. Pharmacogenomic research may consist of the analysis of one or more candidate genes or of the analysis of genetic markers throughout the genome or analysis of the entire genome (as appropriate) in relation to sirukumab or MDD clinical endpoints.

9.6. Safety Evaluations

Details regarding the Data Monitoring Committee are provided in Section 11.11.

Any clinically relevant changes occurring during the study must be recorded on the Adverse Event section of the CRF.

Any clinically significant abnormalities persisting at the end of the study/early withdrawal will be followed by the investigator until resolution or until a clinically stable endpoint is reached.

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 11.12, Adverse Event Reporting.

Clinical Laboratory Tests

Blood samples for hsCRP, serum chemistry, serology and hematology and a random urine sample for urinalysis 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 adverse event section of the CRF.

The following tests will be performed by the central laboratory:

- hsCRP
- Hematology Panel

  -hemoglobin -platelet count
  -hematocrit

-red blood cell (RBC) count
-white blood cell (WBC) count with differential

- Serum Chemistry Panel

-sodium
-potassium
-chloride
-bicarbonate
-blood urea nitrogen (BUN)
-creatinine
-glucose
-aspartate aminotransferase (AST)
-alanine aminotransferase (ALT)
-total bilirubin, with fractionation if hyperbilirubinemia
-alkaline phosphatase
-calcium
-phosphate
-albumin
-total protein

- Lipid Panel (fasting)
  - Total cholesterol
  - Low-density lipoprotein (LDL)
  - High-density lipoprotein (HDL)
  - Triglycerides

- Urinalysis

Dipstick
-specific gravity
-pH
-glucose
-protein
-blood
-ketones
-bilirubin
-urobilinogen
-nitrite
-leukocyte esterase
[Sediment (if dipstick result is abnormal)]
-red blood cells
-white blood cells
-epithelial cells
-crystals
-casts
-bacteria

Specific gravity, pH, glucose, protein, blood, ketones, bilirubin, and urobilinogen will be determined using a dipstick. If dipstick result is abnormal, flow cytometry will be used to measure sediment. Red blood cells, white blood cells, epithelial cells, crystals, casts, and bacteria will be measured using flowcytometry. In case of discordance between the dipstick results and the flow cytometric results, the sediment will be examined microscopically.

- Serum Pregnancy Testing for women of childbearing potential only
- Serology (HIV antibody, hepatitis B surface antigen [HBsAg], and hepatitis C virus antibody)

- Urine Drug Screen: opiates, cocaine, barbiturates, methadone, marijuana and amphetamine/methamphetamine
- thyroid-stimulating hormone (if applicable)
- follicle-stimulating hormone (if applicable)

Electrocardiogram (ECG)

During the collection of ECG, subjects should be in a quiet setting without distractions (eg, television, cell phones). Subjects should rest in a supine position for at least 5 minutes before ECG collection and should refrain from talking or moving arms or legs. If blood sampling or vital signs measurement is scheduled for the same time point as ECG recording, the procedures should be performed in the following order: ECG, vital signs, blood draw.

Vital Signs (oral temperature, pulse/heart rate, blood pressure)

Blood pressure and pulse/heart rate measurements will be assessed after being in supine position for at least 5 minutes with a completely automated device. Manual techniques will be used only if an automated device is not available.

Blood pressure and pulse/heart rate measurements should be preceded by at least 5 minutes of rest in a quiet setting without distractions (eg, television, cell phones).

Physical Examination

The study investigator, or other authorized and appropriately qualified designee, will perform the physical examinations.

Height will be measured at screening only. Body weight will be measured as per the Time and Events Schedule.

Suicidal Risk

Subjects of all ages with major MDD or bipolar disorder may experience worsening of their depression, the emergence of suicidal ideation and behaviour (suicidality), and/or unusual changes in behaviour whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Certain subjects, such as those with a history of suicidal behaviour or thoughts, young adults, and those subjects exhibiting a significant degree of suicidal ideation before beginning treatment, may be at a greater risk of suicidal thoughts or suicide attempts during the course of a clinical trial.

All subjects being treated with sirukumab should be monitored appropriately and observed closely for clinical worsening, suicidality and unusual changes in behaviour, especially at the beginning and end of the course of treatment, or at the time of dose changes, either increases or decreases. The following symptoms have been reported in some subjects being treated with antidepressants for major depressive disorder as well as for other indications: anxiety, agitation, panic attacks, insomnia, irritability, hostility (aggressiveness), impulsivity, akathisia (psychomotor restlessness), hypomania, and mania. Although a causal link between the

emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality.

A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with an antidepressant alone may increase the likelihood of precipitating a mixed/manic episode in subjects at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with sirukumab, subjects should be adequately screened to determine if they are at risk for bipolar disorder. Screening should include a detailed psychiatric history.

Consideration should be given to discontinuing sirukumab in subjects whose depression is persistently worse or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the subject's presenting symptomatology.

Families and caregivers of subjects being treated with sirukumab should be alerted about the need to monitor subjects for the emergence of agitation, irritability, unusual changes in behaviour and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to the study investigator. Baseline assessment of suicidality and treatment emergent suicidality will be monitored during this trial using the C-SSRS.

Columbia Suicide Severity Rating Scale (C-SSRS)
The C-SSRS is a low-burden measure of the spectrum of suicidal ideation. It can also be used during treatment to monitor for clinical worsening. C-SSRS will be administered each visit to monitor suicidal ideation and behavior. An example of the C-SSRS is provided in Attachment 5 and Attachment 6.

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. If mild or moderate allergic reaction is observed, acetaminophen 650 mg orally and diphenhydramine 25 mg orally or IV may be administered. If the reaction is not severe, subsequent injections at the appropriate treatment intervals may be undertaken with caution. Subjects with severe reactions following an injection such as bronchospasm with wheezing and/or dyspnea requiring ventilatory 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 at the site

for symptoms of an injection-site reaction. 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 extra pulmonary 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, a repeat tuberculin skin test 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. If the result is indeterminate, the test should be repeated. If recommended, treatment for latent TB must be initiated prior to 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.

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 (a kit put together by the central laboratory, containing all necessary tubes to do the require testing) 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)

See Section 10.2 for specific instructions regarding discontinuation of treatment guidelines and evaluation of hepatobiliary abnormalities.

Consultation with a specialist may be warranted. Temporary or permanent discontinuation of study agent may be required.

9.7. Sample Collection and Handling

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

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

Collection, handling, storage, and shipment of samples must be under the specified, and where applicable, controlled temperature conditions as indicated in the laboratory manual and instructions will be provided in the laboratory manual.

10. SUBJECT COMPLETION/WITHDRAWAL

10.1. Completion

Subjects must remain in the study until the last visit of the safety follow-up phase to be considered as having completed participation in the study. Subjects who completed the double-

blind phase, but did not complete the follow-up visits, will be considered completers for efficacy. Subjects who prematurely discontinue study treatment for any reason before completion of the double-blind phase will not be considered to have completed the study.

10.2. Discontinuation of Study 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.

A subject's study treatment should be discontinued if:

- The investigator believes that for safety reasons (eg, adverse event) it is in the best interest of the subject to discontinue study treatment
- The subject becomes pregnant
- 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.
- 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.
- 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).
- Tuberculosis (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
- Malignancy, excluding nonmelanoma skin cancer.
- Demyelination, either central or peripheral.
- Two confirmed consecutive absolute neutrophil counts of $< 0.5 \times 10^3/\mu$ (SI: $< 0.5 \times 10^9$ cells/L).
- Two confirmed consecutive platelet counts < 50,000/µL (SI: $< 50 \times 10^9$ cells/L).
- The initiation of protocol-prohibited medications (see Section 8).
- Acute diverticulitis requiring antibiotic treatment
- Gastrointestinal perforation
- Drug induced liver injury, including any one of the following (see Section 10.2):
    a. ALT or AST ≥5 x ULN but <8 x ULN and cannot be monitored weekly for ≥2 weeks.
    b. ALT or AST ≥8 x upper limit of normal (ULN)
    c. ALT or AST ≥5 x ULN for 2 or more weeks

d. ALT or AST ≥ 3 x ULN and total bilirubin ≥ 2 x ULN (>35% direct bilirubin) (or ALT or AST ≥3 x 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 ≥3 x ULN and total bilirubin ≥2 x 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 ≥3 x 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)
- All events that meet criteria as described below, **must also be reported as an SAE.**
    - ALT or AST ≥ 3 x ULN **and** total bilirubin ≥ 2 x ULN (> 35% direct bilirubin) or
    - ALT or AST ≥ 3 x ULN **and** INR > 1.5 (INR measurement is not required and the threshold value stated will not apply to subjects 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.
- 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, lactate dehydrogenase, and albumin.

- Fractionate bilirubin, if total bilirubin ≥ 2 x 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/paracetamol, 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 ≥ 3 x ULN and bilirubin ≥ 2 x 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, anti-smooth muscle antibodies (ASMA), 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, anti-mitochondrial antibody (AMA) should be tested.

  - If subject is < 50 years of age, ceruloplasmin should also be tested.

- If subject is sick enough to require hospitalization and 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 (e.g. CT, MRI, MRCP, ERCP, Doppler studies of hepatic vessels, etc., if indicated based on ultrasound findings or clinical situation)

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 meningoencephalitis, 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 follow-up.

If a subject discontinues study treatment before the end of the double-blind phase, end-of-treatment and posttreatment assessments should be obtained and scheduled assessments should be continued.

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 2.

Table 2: 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 **Error! Reference source not found.** Safety Evaluations below Hepatobiliary abnormalities.* May resume study agent when < 3x ULN**
Criteria for drug-induced liver injury (Section **Error! Reference source not found.**,)	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 **Error! Reference source not found.**)

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 **Error! Reference source not found.**)
* Retesting should be done by Central laboratory ** In case of more than 3 subsequent injections are missed, and the PI wishes to resume study agent, please contact the JRD responsible safety physician.	

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 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 drug assigned to the withdrawn

subject may not be assigned to another subject. Subjects who withdraw will not be replaced. If a subject withdraws from the study before the end of the double-blind treatment phase, end-of-treatment assessments should be obtained.

Withdrawal From the Use of Samples in Future Research

The subject may withdraw consent for use of samples for research (refer to Section 16.1.5, Long-Term Retention of Samples for Additional Future Research). In such a case, samples will be destroyed after they are no longer needed for the clinical study. Details of the sample retention for research are presented in the main ICF.

11. STATISTICAL METHODS

Statistical analysis will be done by the sponsor or under the authority of the sponsor. A general description of the statistical methods to be used to analyze the efficacy and safety data is outlined below. Specific details will be provided in the SAP.

This study will use an adaptive design to assess for futility, optimize the final sample size and review the hsCRP eligibility criterion based on interim data when 40-50% of the planned number of subjects who are eligible to be included in the primary efficacy analysis complete the week 12 assessment. Depending on the results of the interim analysis, the study may be stopped for futility or it may continue to enroll up to an appropriate sample size which is expected to be N=192, but may go up to N=228 if in the interim data suggests this is necessary. The hsCRP eligibility and/or stratification criteria may also be amended following the interim analysis. Details will be provided in the interim SAP.

11.1. Subject Information

Three analyses sets will be defined for efficacy analyses: the modified intent-to-treat 1 (mITT1), the modified intent-to-treat 2 (mITT2), and the modified intent-to-treat 3 (mITT3) analyses sets. The mITT1 analysis set is defined as all randomized subjects with hsCRP $\geq$ 0.300 mg/dL at screening and baseline who receive at least 1 dose of study drug and have both the baseline and at least one postbaseline $HDRS_{17}$ total score measured within the double-blind treatment period. The mITT2 analysis set is defined as all randomized subjects (regardless of screening hsCRP level) who receive at least 1 dose of study drug and have both the baseline and at least one postbaseline $HDRS_{17}$ total score measured within the double blind treatment period. The mITT3 analysis set is defined as all randomized subjects with hsCRP$\geq$ 0.300 mg/dL at screening who receive at least 1 dose of study drug and have both the baseline and at least one postbaseline $HDRS_{17}$ total score measured within the double blind treatment period.

All safety analyses will be performed based on the safety analysis set, which will include all randomized subjects who receive at least 1 dose of study drug.

11.2. Sample Size Determination

The expected sample size of 142 subjects with hsCRP $\geq$ 0.300 mg/dL (SI 3.00 mg/L) was determined based on the assumption of an effect size of at least 0.5 for the $HDRS_{17}$ (difference in mean change from baseline to week 12 endpoint between the sirukumab and placebo groups of 4 with SD=8). This is considered to be a clinically relevant difference in a population with

suboptimal response to standard oral antidepressant therapy. Power is set at 90.0%, with a 1-sided alpha of 0.125 and a 12-week drop-out rate of 25%. It was also assumed that 10% of the randomized subjects would be excluded from the primary efficacy analysis due to having hsCRP ≥0.300 mg/dL (SI 3.00 mg/L) at screening but not baseline. The number of treatment resistant subjects will be monitored on an on-going basis to ensure enough sample size for a secondary efficacy analysis in the TRD population. If an insufficient number of TRD subjects is being enrolled in the study, the sponsor will encourage the sites to enroll more TRD subjects. Note that the study is not statistically powered for comparing effect sizes between treatment groups in the TRD population. Sample size for subjects with hsCRP ≥0.300 mg/dL (SI 3.00 mg/L) may be increased up to 178 if the interim analysis results suggest so.

Sample size determination for the additional stratum (screening hsCRP < 0.300 mg/dL (SI 3.00 mg/L):

Assuming a difference for the mean change from baseline to the week 12 endpoint of 4 between the hsCRP ≥0.300 mg/dL (SI 3.00 mg/L) stratum and the hsCRP < 0.300 mg/dL (SI 3.00 mg/L) stratum, and a SD of 8, a 1-sided alpha of 0.125, and a week 12 drop-out rate of 25%, a sample size of 71 subjects in the active treatment group (142 total) in the hsCRP ≥0.300 mg/dL (SI 3.00 mg/L) stratum and 25 subjects in the active treatment group (50 total) in the hsCRP < 0.300 mg/dL (SI 3.00 mg/L) stratum would provide 75% power to detect a difference between the two strata.

11.3. Efficacy Analyses

The primary efficacy analyses will be based on the mITT1 analysis set. The sirukumab treatment group will be compared with the placebo group using the primary efficacy endpoint, change from baseline in $HDRS_{17}$ total score, with the comparison performed by means of a mixed-effects model using repeated measures (MMRM), with time, treatment (placebo, sirukumab), country, hsCRP stratification levels and time-by-treatment interaction as factors, baseline $HDRS_{17}$ total score as a continuous covariate, and a random subject effect. An unstructured variance-covariance matrix will be used. The comparison of sirukumab versus placebo will be performed using the appropriate contrast. Subgroup analysis will be carried out for the primary efficacy endpoint based on TRD versus non-TRD status.

Analyses of secondary efficacy endpoints will be based on the mITT2 analysis set. The change from baseline to 12-week endpoint for the secondary continuous efficacy endpoints will be analyzed in the same way as for the $HDRS_{17}$ total score.
For change from baseline in HDRS17 total score, the hsCRP ≥0.300 mg/dL (SI 3.00 mg/L) stratum will be compared to the hsCRP < 0.300 mg/dL (SI 3.00 mg/L) stratum, using MMRM, with time, hsCRP stratum (hsCRP ≥0.300 mg/dL (SI 3.00 mg/L), hsCRP < 0.300 mg/dL (SI 3.00 mg/L), treatment, country, and time-by-hsCRP stratum interaction as factors, baseline HDRS17 total score as a continuous covariate, and a random subject effect. An unstructured variance-covariance matrix will be used. The comparison of hsCRP ≥0.300 mg/dL (SI 3.00 mg/L) versus hsCRP < 0.300 mg/dL (SI 3.00 mg/L) will be performed using the appropriate contrast.

In addition to evaluating hsCRP as a categorical variable (hsCRP<0.300mg/dL; hsCRP ⩾0.300 to <0.500 mg/dL; hsCRP ⩾0.500 to <0.800 mg/dL and hsCRP ⩾0.800 mg/dL), hsCRP will be analyzed as a continuous variable and correlated with the primary efficacy endpoint (change from baseline to Week 12 in $HDRS_{17}$ total score) using Pearson and Spearman methods.

Sensitivity analyses of the primary endpoint will also be performed; these will be detailed further in the SAP. These will include analysis based on the mITT3 analysis set (that is, the mITT1 analysis set plus those subjects excluded for having a screening hsCRP ≥0.300 mg/dL (SI 3.00 mg/L) but hsCRP <0.300 mg/dL (SI 3.00 mg/L) at baseline). These will also include an analysis of covariance (ANCOVA) model using the last observation carried forward (LOCF) imputation method, with factors for treatment, country, hsCRP stratification levels, and baseline $HDRS_{17}$ total score as a covariate. Other sensitivity analyses may also be performed to investigate the robustness of treatment estimates to the observed pattern of, and/or reason for, early withdrawals.

Sensitivity analyses of the secondary endpoints will also be performed; these will be detailed further in the Statistical Analysis Plan. These will include analysis based on the mITT1 and mITT3.

Descriptive statistics for values and changes from baseline will be provided for all efficacy measures, including individual items for selected scales, subscales, and total score, at each time point of the double-blind treatment phase.

Details of the exploratory analyses will be provided in the SAP.

11.4. Pharmacokinetic Analyses

Serum sirukumab concentrations will be summarized over time. Descriptive statistics, including arithmetic mean, standard deviation (SD), median, interquartile range, minimum, and maximum will be calculated at each sampling time point. Monoaminergic antidepressants concentration data before and after sirukumab treatment, will also be summarized.

If feasible, a population PK analysis using nonlinear mixed effects modeling (NONMEM) may be conducted to characterize the disposition characteristics of sirukumab using the data in the current study or combined data with other studies. Details will be given in a population PK analysis plan, and results of the population PK analysis will be presented in a separate technical report.

Data will be listed for all subjects with available serum concentrations.

All concentrations below the lowest quantifiable concentration or missing data will be labeled as such in the concentration database. All subjects and samples excluded from the analysis will be clearly documented in the study report.

11.5. Immunogenicity

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

11.6. Pharmacokinetic/Pharmacodynamic Analyses

If data permit, the relationships between serum sirukumab concentration and efficacy or pharmacodynamic measures may be analyzed graphically.

11.7. Biomarker Analyses

Changes in biomarkers over time will be summarized by treatment group.

Associations between baseline levels and changes from baseline in selected biomarkers and clinical endpoints will be explored.

Exploratory analyses may be performed for additional biomarkers. Results may be presented in a separate Biomarkers report.

11.8. Pharmacogenomic Analyses

A composite genotype will be derived from the raw genotyping data for the analyzed genes, as appropriate.
The relationship between genetic subgroups and sirukumab PK endpoints and/or selected biomarkers and/or clinical endpoints may be examined through descriptive statistics or graphically, and association tests may be performed.

Results of the pharmacogenomic analysis will be summarized in a separate Pharmacogenomics report.

11.9. Safety Analyses

All safety analyses will be performed based on the safety analysis set, which will include all randomized subjects who receive at least 1 dose of study drug.

Adverse Events

The verbatim terms used in the CRF by investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent adverse events are adverse events with onset during the treatment phase or that are a consequence of a pre-existing condition that has worsened since baseline. All reported adverse events will be included in the analysis. For each adverse event, the percentage of subjects who experience at least 1 occurrence of the given event will be summarized by treatment group. In addition, comparisons between treatment groups will be provided if appropriate.

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

Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test. Reference ranges and markedly abnormal results (specified in the SAP) will be used in the summary of laboratory data. Descriptive statistics will be calculated for each laboratory analyte at baseline and for observed values and changes from baseline at each scheduled time point. Changes from baseline results] will be presented in pre- versus posttreatment cross-tabulations (with classes for below, within, and above normal ranges). A listing of subjects with any laboratory results outside the reference ranges will be provided. A listing of subjects with any markedly abnormal laboratory results will also be provided.

Vital Signs

Vital signs will be summarized by vital signs parameters (temperature, pulse/heart rate and blood pressure (systolic and diastolic, supine). Descriptive statistics will be calculated at baseline and for observed values and changes from baseline at each scheduled time point. Frequency tabulations of the abnormalities will be made.

Physical Examination

Descriptive statistics of changes from baseline will be summarized at each scheduled time point. Physical examination findings will be summarized at each scheduled time point. Descriptive statistics will be calculated at baseline and for observed values and changes from baseline at each scheduled time point. Frequency tabulations of the abnormalities will be made.

C-SSRS

The suicidality data collected from the C-SSRS using aggregate endpoints of suicidal behavior and suicidal ideation separately will be summarized descriptively at each scheduled visit by treatment group. Further details will be presented in the SAP.

11.10. Interim Analysis

An interim analysis will be conducted to monitor safety data, assess futility, sample size re-estimation, and hsCRP enrichment criteria. The interim analysis is planned when 40-50% of the planned number of subjects who are eligible to be included in the primary efficacy analysis complete the week 12 assessment. Both Frequentist and Bayesian approaches will be applied for the interim analysis. An internal IAC will be employed to review the unblinded efficacy and safety data at the interim analysis and to provide recommendations about the futility, sample size re-estimation, and hsCRP enrichment criteria. Detailed approaches will be described in the interim SAP and the IAC charter.

The interim analysis results will be used to assess the study for futility and as such the study may be terminated early if the probability of success of the study is calculated to be very low. In addition, based on the results of hsCRP-response relationship, the study may continue with the enriched population using a selected hsCRP level. The decision rule for futility at the interim analysis will be detailed in the interim SAP and the IAC charter.

In addition the sample size for the study may be increased up to N=228 if the interim data suggests this is necessary to ensure robust conclusions.

The interim analysis will be conducted such that the ongoing study integrity is maintained. Only the independent statistician and programmer responsible for providing the interim analysis results will be unblinded to the individual treatment group assignments. Individual and interim analysis results will not be shared with investigators, subjects or the sponsor staff who are involved in the conduct of the study before the final database lock.

Statistical procedures to be used, data to be analyzed, analysis method, p value adjustment will be provided in the interim SAP.

11.11. Interim Analysis Committee

An internal IAC will be established to monitor data on an ongoing basis to ensure the continuing safety of the subjects enrolled in this study and to meet efficacy objectives.

The IAC will consist of at least one medical expert in the relevant therapeutic area and at least one statistician.

To protect the integrity of the clinical study the IAC members (medical and statistical experts) will not be study team personnel or otherwise directly involved in the study conduct, data management, or statistical analysis for the study.

The objectives and scope of the IAC and the operational and logistical procedures to perform the IAC activities will be documented in the IAC charter prior to the review of any data by the IAC. Only blinded information, conclusions, or recommendations will be communicated by the IAC chairperson while the study is ongoing.

The committee will meet periodically to review interim safety data. At the time of interim analysis the IAC will meet once to review the unblinded efficacy and safety data to make recommendations regarding futility, sample size re-estimation, and the hsCRP enrichment criteria. The details will be provided in a separate IAC charter.

11.12. First Database Lock for the Primary Efficacy Analyses

Analyses for primary efficacy will be done when all subjects have completed the 12-week double-blind period. Detailed statistical approaches are summarized below and will be described in more detail in the statistical analysis plan. The results will be used to assess the potential efficacy of sirukumab in the treatment of MDD and to make strategic internal decisions regarding the development of the compound. The results will not impact the further conduct of the trial.

At the the first database lock for the primary efficacy analyses, randomization codes will be disclosed fully. Sponsor staff will be unblinded to the individual treatment group assignments, however primary efficacy analyses results will not be shared with investigators and subjects before the final database lock.

Unblinding after completion of the 12-week double-blind treatment phase will not impact the integrity of the study data, as only follow-up visits will be performed after the unblinding and those visits will not include the primary outcome measures of the study.

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 International Conference on Harmonisation [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 (refer to Section 12.3.1, All Adverse Events, for time of last adverse event recording).

Serious Adverse Event

A serious adverse event based on ICH and EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use 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 unlisted if the nature or severity is not consistent with the applicable product reference safety information. For sirukumab, the 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.

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 study drug that may require expedited reporting and/or safety evaluation include, but are not limited to:

- Overdose of a sponsor study drug
- Suspected abuse/misuse of a sponsor study drug
- Inadvertent or accidental exposure to a sponsor study drug
- Medication error involving a sponsor product (with or without subject/patient exposure to the sponsor study drug, eg, name confusion)

Special reporting situations should be recorded in the CRF. Any special reporting situation that meets the criteria of a serious adverse event should be recorded on the serious adverse event 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-related procedure (which may include contact for follow-up of safety). Serious adverse events, 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 serious adverse event will be reported as serious adverse events, regardless of whether they are protocol-specific assessments.

All adverse events, regardless of seriousness, severity, or presumed relationship to study drug, 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.

The sponsor assumes responsibility for appropriate reporting of adverse events to the regulatory authorities. The sponsor will also report to the investigator (and the head of the investigational institute where required) all suspected unexpected serious adverse reactions (SUSARs). The investigator (or sponsor where required) must report SUSARs to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB. A SUSAR will be reported to regulatory authorities unblinded. Participating investigators and IEC/IRB will receive a blinded SUSAR summary, unless otherwise specified.

For all studies with an outpatient phase, including open-label studies, the subject must be provided with a "wallet (study) card" and instructed to carry this card with them for the duration of the study indicating the following:

- Study number
- Statement, in the local language(s), that the subject is participating in a clinical study
- Investigator's name and 24-hour contact telephone number
- Local sponsor's name and 24-hour contact telephone number (for medical staff only)
- Site number
- Subject number
- Any other information that is required to do an emergency breaking of the blind

12.3.2. Serious Adverse Events

All serious adverse events occurring during the study must be reported to the appropriate sponsor contact person by study-site personnel within 24 hours of their knowledge of the event.

Information regarding serious adverse events will be transmitted to the sponsor using the Serious Adverse Event Form, which must be completed and signed by a physician from the study site, and transmitted to the sponsor within 24 hours. The initial and follow-up reports of a serious adverse event should be made by facsimile (fax).

All serious adverse events 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 drug 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)

Suspected transmission of an infectious agent by a medicinal product will be reported as a serious adverse event. Any event requiring hospitalization (or prolongation of hospitalization) that occurs during the course of a subject's participation in a study must be reported as a serious adverse event, except hospitalizations for the following:

- Hospitalizations not intended to treat an acute illness or adverse event (eg, social reasons such as pending placement in long-term care facility)
- Surgery or procedure planned before entry into the study (must be documented in the CRF). Note: Hospitalizations that were planned before the signing of the ICF, and where the underlying condition for which the hospitalization was planned has not worsened, will not be considered serious adverse events. Any adverse event that results in a prolongation of the originally planned hospitalization is to be reported as a new serious adverse event.
- For convenience the investigator may choose to hospitalize the subject for the duration of the treatment period.

The cause of death of a subject in a study within 4 months of the last dose of study drug, whether or not the event is expected or associated with the study drug, is considered a serious adverse event.

12.3.3. Pregnancy

All initial reports of pregnancy in female subjects or partners of male subjects must be reported to the sponsor by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered serious adverse events 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 drug on sperm is unknown, pregnancies in partners of male subjects included in the study will be reported by the study-site personnel 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.

12.4. Adverse Events of Special Interest

All initial reports of 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 described below **must be reported as an SAE**.

- ALT or AST ≥3 x ULN and bilirubin ≥2 x ULN (>35% direct) or
- ALT or AST ≥3 x ULN and INR >1.5 (INR measurement is not required and the threshold value stated will not apply to subjects receiving anticoagulants)

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

a. ALT or AST ≥8 x ULN

b. ALT or AST ≥5 x ULN for 2 or more weeks

c. ALT or AST ≥3 x ULN and total bilirubin ≥2 x ULN (> 35% direct bilirubin) (or ALT or AST ≥3 x ULN and INR >1.5, if INR measured; see above)

d. ALT or AST ≥3 x 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 ≥5 x ULN but <8 x 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. A PQC may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from 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 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 study-site personnel within 24 hours after being made aware of the event.

If the defect is combined with a serious adverse event, the study-site personnel must report the PQC to the sponsor according to the serious adverse event reporting timelines (refer to Section 12.3.2, Serious Adverse Events). 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 DRUG INFORMATION

14.1. Physical Description of Study Drug

The sirukumab drug product provided for this study is supplied in a 1 mL Pre-Filled Syringe (PFS) fitted with a passive safety needle guard (UltraSafe Passive™ Delivery System, Safety Syringes, Inc.) that is permanently assembled on the syringe. The sirukumab PFS is aseptically filled to 50 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, an elastomeric needle shield, and a fluoropolymer coated elastomeric plunger stopper. The needle shield on the PFS (assembled into UltraSafe needle guard) is made with a derivative of natural rubber latex, which may cause allergic reactions in individuals. For a list of excipients, refer to the Investigator's Brochure for sirukumab.

Placebo for sirukumab PFS provided for this study is supplied in a 1 mL PFS fitted with a passive safety needle guard (UltraSafe Passive™ Delivery System, Safety Syringes, Inc.) 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 gauge (G) ½ inch fixed needle, an elastomeric needle shield, and a fluoropolymer coated elastomeric plunger stopper. The needle shield on the PFS (assembled into UltraSafe needle guard) is made with a derivative of natural rubber latex, which may cause allergic reactions in individuals. For a list of excipients, refer to the Investigator's Brochure for sirukumab.

14.2. Packaging

The sirukumab PFS and placebo for 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.

14.3. Labeling

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

14.4. Preparation, Handling, and Storage

All sirukumab and sirukumab placebo study agent presentations should be stored in a secured refrigerator at 2ºC to 8ºC (36ºF to 46ºF). Sirukumab should not be frozen or shaken. During extended storage, protect from excessive exposure to light. Protection from light is not required during administration.

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.

Refer to the study site investigational product manual for additional guidance on study drug preparation, handling, administration and storage.

14.5. Drug Accountability

The study agents are to be prescribed only by the principal investigator or a qualified physician listed as a sub-investigator on required forms (eg, FDA Form 1572).

The investigator is responsible for ensuring that all study drug received at the site is inventoried and accounted for throughout the study. The study drug administered to the subject must be documented on the drug accountability form. All study drug will be stored and disposed of according to the sponsor's instructions. Study-site personnel must not combine contents of the study drug containers.

Study drug 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 drug must be available for verification by the sponsor's study site monitor during on-site monitoring visits. The return to the sponsor of unused study drug, or used returned study drug for destruction, will be documented on the drug return form. When the study site is an authorized destruction unit and study drug supplies are destroyed on-site, this must also be documented on the drug return form.

Potentially hazardous materials such as used ampules, needles, syringes and vials containing hazardous liquids, should be disposed of immediately in a safe manner and therefore will not be retained for drug accountability purposes.

Study drug should be dispensed under the supervision of the investigator or a qualified member of the study-site personnel, or by a hospital/clinic pharmacist. Study drug will be supplied only to subjects participating in the study. Returned study drug must not be dispensed again, even to the same subject. Study drug may not be relabeled or reassigned for use by other subjects. The investigator agrees neither to dispense the study drug 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 supplies:

- Investigator Brochure and any addenda
- Site Investigational Product Binder
- Central Laboratory Manual
- PRO Questionnaires
- IVRS/IWRS Manual
- Electronic Data Capture (eDC) Manual
- Sample ICF

16. ETHICAL ASPECTS

16.1. Study-Specific Design Considerations

Clinical Study in Treatment-Resistant Major Depression

Major depressive disorder is a common, severe, chronic and often life-threatening illness. It is now the leading cause of disability worldwide. There is a clear need to develop novel and improved therapeutics for major depression. Whilst at present the clinical efficacy of sirukumab as an adjunctive treatment for depression is unknown many studies suggest that a subgroup of subjects may be characterized by elevated levels of circulating IL-6. Moreover, these subjects may benefit relatively less from treatment with monoaminergic antidepressant drug therapy (see introduction). These subjects are hypothesized to have a higher chance to respond to active treatment. Sirukumab showed a beneficial effect on depressed mood in the phase 2 sirukumab RA studies and has been well tolerated and safe in these clinical studies.

Selection of Subjects

The primary aim of the study is to evaluate the efficacy of subcutaneously administered sirukumab for the treatment of MDD. Thus, the study cannot be completed in healthy subjects. Subjects selected in the study will have adequate capacity to give consent for participation in the study.

Justification for Using Placebo

Some have considered it unethical to do placebo-controlled studies in major depression due to the potential risk of irreversible harm (Rothman and Michels, 1994). In a meta-analysis (Khan et al., 2000) of drug studies conducted in major depression, it was reported that adult subjects did not have higher rates of suicide behaviors or attempts in the placebo group compared with those receiving an active antidepressant. These studies show annual suicide rates of 0.8% on the investigational drug, 0.7% on the active comparator, and 0.4% on placebo. The risk of

irreversible harm is not higher in the placebo arm compared to the active control arms. Some subjects may decide not to participate due to the potential for increased distress and dysfunction due to prolonged depression.

Therefore, the use of a placebo-controlled study remains the gold standard for assessment of efficacy of new compound to allow for scientifically meaningful results. Placebo-controlled studies in major depression have been argued to be ethically and scientifically justifiable (Adam et al., 2005; Temple et al., 2000).

In this study the subjects will continue existing and allowed anti-depressant medications. Not allowed antidepressant medication will not be discontinued for the sole purpose of entering the study; subjects will be carefully monitored for potential worsening of the depressive symptoms and suicidality and appropriate actions will be taken to ensure the safety of the subjects participating in the study. Clinical studies with similar study design show that both partial and non-responders had significant improvement, even in the placebo arm (Thase et al., 2008). All subjects will receive clinical care while in the trial.

Precautions to Ensure Subject Safety in the Study

Subjects may participate in the study only if they have adequate capacity to give consent and after fully understanding the potential risks and giving an informed consent. Determination of capacity will be made by the study investigator. Subjects may withdraw from the study at any time. The probability of receiving placebo and the concept of random assignment will be explained to the subject. Potential disadvantages and adverse events of participating in the study and alternative treatment options will be discussed.

The subjects will visit the study site monthly during the double-blind study period and their symptoms will be carefully monitored during each study visit. Safety evaluations will include evaluation of suicidal ideation/behavior at each clinic visit. At any point in the study the subject may withdraw consent or be removed from the study by the investigator if there are any clinical concerns.

A prospective assessment of suicidal ideation and behavior, the CSSR-S, will be conducted by the investigator/subinvestigator at every study visit. Subjects with a current or recent (within the past year) history of clinically significant suicidal ideation (corresponding to a score of ≥ 3 for ideation) or any suicidal behavior within the past year, as validated on the C-SSRS at screening or baseline will be excluded.

Subjects receiving sirukumab are more susceptible to infections. Therefore it will be thoroughly evaluated during screening that subjects currently do not have or recently have not had any severe or chronic or recurrent infections. In addition a week 14 follow-up visit will be done to monitor potential risks of infections occurring after discontinuation of the study agent.

Subjects receiving sirukumab might experience an increase in transaminase levels. Therefore subjects with serum ALT or AST >1.5 times the ULN at screening will be excluded. Specific

stopping criteria in case of drug induced liver injury are described in detail in Section 10.2 to ensure proper guidance and follow-up for subjects.

Compensation for any procedure will be fair per local standards and approved by the participating sites IEC/IRB in order to not offer any undue incentive to participate in the study.

Subjects who are unable to tolerate study drug during the double-blind treatment phase will be discontinued from the study. If the investigator judges it to be necessary to immediately stop study drug, he or she has the option to do so.

Only subjects who have not adequately responded to their antidepressant where a clinician would consider changing it for lack of response or poor tolerability in addition to meeting the severity criteria for the study will be enrolled.

Only highly qualified and experienced investigators will participate in the study.

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 adverse events of the study, and provide their consent voluntarily will be enrolled.

The study medication, sirukumab, will not be available after the study, however, following completion of the double-blind treatment phase, subjects can be treated according to standard of care.

The total blood volume to be collected is approximately 350 mL and will not exceed 450 mL, which is considered to be acceptable in comparison to a Red Cross blood donation.

16.1.1. Investigator Responsibilities

The investigator is responsible for ensuring that the study is performed in accordance with the protocol, current ICH guidelines on Good Clinical Practice (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 study data are credible.

16.1.2. 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 (as required by local regulations):

- 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
- 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, excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct), the 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.

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 (excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct)
- Revision(s) 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 study 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
- Notification if a new investigator is responsible for the study at the site
- Development Safety Update Report and 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 study 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 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.

16.1.3. Informed Consent

Each subject must give written consent according to local requirements after the nature of the study has been fully explained. The ICF(s) must be signed before performance of any study-related activity. The ICF(s) that is/are 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 study-site personnel 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 not to 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 personnel 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.

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 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.

Where local regulations require, a separate ICF may be used for the required DNA component of the study.

16.1.4. 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 subjects confidential.

The informed consent obtained from the subject includes explicit consent for the processing of personal data and for the investigator/institution to allow direct access to his or her original medical records (source data/documents) 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, pharmacodynamics, biomarker, PK and immunogenicity, research is not 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 or local regulations. 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.

16.1.5. Long-Term Retention of Samples for Additional Future Research

Samples collected in this study may be stored for up to 15 years (or according to local regulations) for additional research. Samples will only be used to understand sirukumab, to understand MDD, to understand differential drug responders, and to develop tests/assays related to sirukumab and MDD. The research may begin at any time during the study or the post-study storage period.

Stored samples will be coded throughout the sample storage and analysis process and will not be labeled with personal identifiers. Subjects may withdraw their consent for their samples to be stored for research (refer to Section 10.3, Withdrawal From the Study).

16.1.6. 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, Study-Specific Design Considerations.

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. 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. Required Prestudy Documentation

The following documents must be provided to the sponsor before shipment of study drug to the study site:

- Protocol and amendment(s), if any, signed and dated by the principal investigator
- A copy of the dated and signed (or sealed, where appropriate per local regulations), 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 (or sealed, where appropriate per local regulations) 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, from the IEC/IRB, a general statement may be substituted for this list. If an investigator or a member of the study-site personnel 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 principal investigator, 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 subinvestigators
- Documentation of subinvestigator 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 identification 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 on 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 signed informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all adverse events and follow-up of adverse events; concomitant medication; drug receipt/dispensing/return records; study drug administration information; and date of study completion and reason for early discontinuation of study drug or withdrawal from the study, if applicable.

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

At a minimum, the type and level of detail of source data available for a subject should be consistent with that commonly recorded at the study 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).

Subject- and investigator-completed scales and assessments designated by the sponsor will be recorded and will be considered source data.

The minimum source documentation requirements for Section 4.1, Inclusion Criteria and Section 4.2, Exclusion Criteria that specify a need for documented medical history are as follows:

- Referral letter from treating physician or
- Complete history of medical notes at the site
- Discharge summaries

Inclusion and exclusion criteria not requiring documented medical history must be verified at a minimum by subject interview or other protocol required assessment (eg, physical examination, laboratory assessment) and documented in the source documents.

17.5. Case Report Form Completion

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

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

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

All subjective measurements (eg questionnaires) will be completed by the same individual who made the initial baseline determinations whenever possible. The investigator must verify that all data entries in the CRFs are accurate and correct.

All CRF 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.

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

- Study 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).
- Study site manager can generate a query for resolution by the study-site personnel.

- Clinical data manager can generate a query for resolution by the study-site personnel.

17.5.1. 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.

17.6. 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 study-site personnel before the study, periodic monitoring visits by the sponsor, and direct transmission of clinical laboratory data from a central laboratory into the sponsor's data base. Written instructions will be provided for collection, handling, storage, and shipment of samples.

Guidelines for CRF completion will be provided and reviewed with study-site personnel before the start of the study.

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 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.

17.8. Monitoring

The sponsor will use a combination of monitoring techniques to monitor this study.

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 study site. The first post-initiation visit will be made as soon as possible after enrollment has begun. At these visits, the monitor will compare data entered into the CRFs with the hospital or clinic records (source documents); a sample may be reviewed. 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 study-site personnel and are accessible for verification by the sponsor study-site contact. If electronic records are maintained at the study site, the method of verification must be discussed with the study-site personnel.

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 study-site personnel. The sponsor expects that, during monitoring visits, the relevant study-site personnel 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.

In addition to on-site monitoring visits, remote contacts can occur. It is expected that during these remote contacts, study-site personnel will be available to provide an update on the progress of the study at the site.

Central monitoring will take place for data identified by the sponsor as requiring central review.

17.9. Study Completion/Termination

17.9.1. Study Completion

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

17.9.2. Study Termination

The sponsor reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-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 a study 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 subjects by the investigator
- Discontinuation of further study drug development

17.10. On-Site Audits

Representatives of the sponsor's clinical quality assurance department may visit the study 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 study-site personnel are responsible for being present and available for consultation during routinely scheduled study-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 he or she has 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, including pharmacogenomic or exploratory biomarker research 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 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 Clinical Study Report generated by the sponsor and will contain CRF data from all study sites that participated in the study and direct transmission of clinical laboratory data from a central laboratory into the sponsor's database. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the study will be used to determine a coordinating investigator. Results of pharmacogenomics or exploratory biomarker analyses performed after the Clinical Study Report has been issued will

be reported in a separate report and will not require a revision of the Clinical Study Report. Study subject identifiers will not be used in publication of 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.

Consistent with Good Publication Practices and International Committee of Medical Journal Editors guidelines, the sponsor shall have the right to publish such primary (multicenter) data and information without approval from the investigator. The investigator has the right to publish study site-specific data after the primary data are published. 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 study 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 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.

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Attachment 1: 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-γ 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.

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Attachment 2: 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.

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Attachment 3: Representative Example of the Clinical Global Impression Questionnaire-Severity (CGI-S) questions that will be used in this study

Severity of illness

Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?

0 = Not assessed
1 = Normal, not at all ill
2 = Borderline mentally ill
3 = Mildly ill
4 = Moderately ill
5 = Markedly ill
6 = Severely ill
7 = Among the most extremely ill patients

Reproduced from Guy W, editor. ECDEU Assessment Manual for Psychopharmacology. 1976. Rockville, MD, U.S. Department of Health, Education, and Welfare

Attachment 4: Representative Example of the Massachusetts General Hospital – Antidepressant Treatment Response Questionnaire questions that will be used in this study

(Non-Geriatric Population: 18 to 64 years of age)(Global)

Note: The minimum therapeutic dose for each antidepressant treatment in Section I is based on prescribing information, relevant literature, and consultation with expert clinicians.

Section I. Antidepressant Medications

Instructions:

1. Please **check (√)** the names of any medications that the patient has taken since the beginning of **THIS CURRENT EPISODE** of depression.
2. Please **check (√)** if the daily dosage of the medication was **equal to or greater than the minimum** therapeutic dose for at least 6 weeks.
3. Only for those taken at the minimum therapeutic dose for at least 6 weeks, indicate the amount (%) of improvement in depression that the patient reported when they felt it was working at its best.
4. If the subject initially experienced an improvement of ≥50% and then lost that response (tolerance/bradyphylaxis), that medication will not be counted towards a failed antidepressant trial.

Tricyclic Antidepressants

Generic Name	Taken during THIS current episode of depression(√)	Took at least this dose* *for at least 6 weeks*? (√)		Only for those taken at minimum therapeutic dose for at least 6 weeks: Based on subject's feedback, indicate the amount (%) of improvement in depression he/she reported when they feel it was working at its best. A. 75% to 100% B. 50% to <75% C. 26% to <50% D. ≤ 25%
doxepin		150mg/d		
clomipramine		150mg/d		
amoxapine		150mg/d		
amitriptyline		150mg/d		
maprotiline		150mg/d		
desipramine		150mg/d		
nortriptyline		75 mg/d		
doxepin		150mg/d		
trimipramine		150mg/d		
imipramine		150mg/d		
protriptyline		30mg/d		
pipofezine		150mg/d		
noxiptiline		100mg/d		

* If the dose is below the minimum dose required, a blood level that is within the therapeutic

(antidepressant) range is also acceptable.

Monoamine Oxidase Inhibitors (MAOIs)

Generic Name	Taken during THIS current episode? (√)	Took at least this dose *for at least 6 weeks?* (√)		Only for those taken at minimum therapeutic dose for at least 6 weeks: Based on subject's feedback, indicate the amount (%) of improvement in depression he/she reported when they feel it was working at its best. A. 75% to 100% B. 50% to <75% C. 26% to <50% D. ≤ 25%
isocarboxazid		30mg/d		
phenelzine		45mg/d		
tranylcypromine		30mg/d		
selegiline patch		6 mg/24 hrs		
moclobemide		300 mg/d		
pirlindole		200 mg/d		

Selective Serotonin Reuptake Inhibitors (SSRIs)

Generic Name	Taken during THIS current episode? (√)	Took at least this dose *at least 6 weeks?* (√)		Only for those taken at minimum therapeutic dose for at least 6 weeks: Based on subject's feedback, indicate the amount (%) of improvement in depression he/she reported when they feel it was working at its best. A. 75% to 100% B. 50% to <75% C. 26% to <50% D. ≤ 25%
fluvoxamine		50mg/d		
paroxetine		20/25mg/d		
fluoxetine		20 mg/d		
sertraline		50 mg/d		
citalopram		20mg/d		
escitalopram		10 mg/d		
vilazodone		40 mg/d		

vortioxetine		10 mg/d		

Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)

Generic Name	Taken during THIS current episode? (√)	Took at least this dose for *at least 6 weeks?* (√)		Only for those taken at minimum therapeutic dose for at least 6 weeks: Based on subject's feedback, indicate the amount (%) of improvement in depression he/she reported when they feel it was working at its best. A. 75% to 100% B. 50% to <75% C. 26% to <50% D. ≤ 25%
venlafaxine / venlafaxine XR		150 mg/d		
duloxetine		60mg/d		
desvenlafaxine		50mg/d		
milnacipran		100mg/d		
levomilnacipran		40mg/d		

Other Antidepressants

Generic Name	Taken during THIS current episode? (√)	Took at least this dose for at least 6 weeks? (√)		Only for those taken at minimum therapeutic dose for at least 6 weeks: Based on subject's feedback, indicate the amount (%) of improvement in depression he/she reported when they feel it was working at its best. A. 75% to 100% B. 50% to <75% C. 26% to <50% D. ≤ 25%
trazodone		300mg/d		
bupropion		300mg/d		
mirtazapine		15 mg/d		
mianserin		30 mg/d		
opipramol		150 mg/d		
netazadone		300 mg/d		
agomelatine		25 mg/d		
tianeptine		37.5 mg/d		
reboxetine		4 mg/d		

Section II. FDA-Approved Medications added to Augment /Boost Antidepressant Effect

Instructions:

1. Please **check** (√) the names of any medication you have taken to augment or boost the antidepressant effect during **THIS CURRENT EPISODE** of depression.
2. Please **check** (√) if the subject took at least this dose for at least 6 weeks in combination with an antidepressant treatment from Section I.
3. Please indicate the name of antidepressant treatment from Section I this drug was taken with to augment /boost its antidepressant effect.
4. Please indicate the amount (%) of improvement in depression that the patient reported when they felt this combination was working at its best.

Generic Name	Taken during THIS current episode? (√)	Took at least this dose for *at least* 6 weeks in combination with an antidepressant treatment from Section I**? (√)		Name of Antidepressant Treatment from Section I (see above) this drug was taken with	Only for those taken at minimum therapeutic dose for at least 6 weeks: Based on subject's feedback, indicate the amount (%) of improvement in depression he/she reported when they feel the combination was working at its best. A. 75% to 100% B. 50% to <75% C. 26% to <50% D. ≤ 25%
Aripiprazole		5 mg/d			
Quetiapine		200 mg/d			

**The antidepressant treatment from Section I must also have been taken at the minimum therapeutic dose during the 6 weeks that the medication was taken to augment/boost antidepressant effect.

Attachment 5: Representative Example of the Columbia Suicide Severity Rating Scale – Baseline questions that will be used in this study

SUICIDAL IDEATION

Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes," ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.

Lifetime: Time He/She Felt Most Suicidal

1. Wish to be Dead
Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up.
Have you wished you were dead or wished you could go to sleep and not wake up?
If yes, describe:
Yes ☐ No ☐

2. Non-Specific Active Suicidal Thoughts
General, non-specific thoughts of wanting to end one's life/commit suicide (e.g. *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan.
Have you actually had any thoughts of killing yourself?
If yes, describe:
Yes ☐ No ☐

3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g. thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it....and I would never go through with it".*
Have you been thinking about how you might do this?
If yes, describe:
Yes ☐ No ☐

4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan
Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them".*
Have you had these thoughts and had some intention of acting on them?
If yes, describe:
Yes ☐ No ☐

5. Active Suicidal Ideation with Specific Plan and Intent
Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out.
Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?
If yes, describe:
Yes ☐ No ☐

INTENSITY OF IDEATION

The following features should be rated with respect to the most severe type of ideation (i.e.,1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal.

Most Severe Ideation: ____ _____
Type # (1-5) *Description of Ideation*

Most Severe

Frequency
How many times have you had these thoughts?
(1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day
___

Duration
When you have the thoughts, how long do they last?
(1) Fleeting - few seconds or minutes
(2) Less than 1 hour/some of the time
(3) 1-4 hours/a lot of time
(4) 4-8 hours/most of day
(5) More than 8 hours/persistent or continuous
___

Controllability
Could /can you stop thinking about killing yourself or wanting to die if you want to?
(1) Easily able to control thoughts
(2) Can control thoughts with little difficulty
(3) Can control thoughts with some difficulty
(4) Can control thoughts with a lot of difficulty
(5) Unable to control thoughts
(0) Does not attempt to control thoughts
___

Deterrents
Are there things - anyone or anything (e.g. family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?
(1) Deterrents definitely stopped you from attempting suicide
(2) Deterrents probably stopped you
(3) Uncertain that deterrents stopped you
(4) Deterrents most likely did not stop you
(5) Deterrents definitely did not stop you
(0) Does not apply; wish to die only
___

Reasons for Ideation
What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?
(1) Completely to get attention, revenge or a reaction from others.
(2) Mostly to get attention, revenge or a reaction from others.
(3) Equally to get attention, revenge or a reaction from others and to end/stop the pain.
(4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling).
(5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling).
___

Version 7/19/08

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Lifetime**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act*. Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is *any* intent/desire to die associated with the act, then it can be considered an actual suicide attempt. *There does not have to be any injury or harm*, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g. gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. *Have you made a suicide attempt?* *Have you done anything to harm yourself?* *Have you done anything dangerous where you could have died?* *What did you do?* *Did you_____ as a way to end your life?* *Did you want to die (even a little) when you_____?* *Were you trying to end your life when you _____?* *Or did you think it was possible you could have died from_____?* *Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?* (Self-Injurious Behavior without suicidal intent) If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?**	Yes ☐ No ☐ Total # of Attempts _____ Yes ☐ No ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred)*. Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. *Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?* If yes, describe:	Yes ☐ No ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. *Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?* If yes, describe:	Yes ☐ No ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g. buying pills, purchasing a gun) or preparing for one's death by suicide (e.g. giving things away, writing a suicide note). *Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?* If yes, describe:	Yes ☐ No ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes ☐ No ☐

Answer for Actual Attempts Only	Most Recent Attempt Date:	Most Lethal Attempt Date:	Initial/First Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g. surface scratches). 1. Minor physical damage (e.g. lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g. conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g. comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g. comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____

Attachment 6: Representative Example of the Columbia Suicide Severity Rating Scale (Since Last Visit) questions that will be used in this study

SUICIDAL IDEATION	
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes," ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	Since Last Visit
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. *Have you wished you were dead or wished you could go to sleep and not wake up?* If yes, describe:	Yes ☐ No ☐
2. Non-Specific Active Suicidal Thoughts General, non-specific thoughts of wanting to end one's life/commit suicide (e.g. *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. *Have you actually had any thoughts of killing yourself?* If yes, describe:	Yes ☐ No ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g. thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it.....and I would never go through with it".* *Have you been thinking about how you might do this?* If yes, describe:	Yes ☐ No ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them".* *Have you had these thoughts and had some intention of acting on them?* If yes, describe:	Yes ☐ No ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. *Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?* If yes, describe:	Yes ☐ No ☐
INTENSITY OF IDEATION	
The following features should be rated with respect to the most severe type of ideation (i.e.,1-5 from above, with 1 being the least severe and 5 being the most severe). *Most Severe Ideation:* ____ _____ *Type # (1-5)* *Description of Ideation*	Most Severe
Frequency *How many times have you had these thoughts?* (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	___
Duration *When you have the thoughts, how long do they last?* (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	___
Controllability *Could /can you stop thinking about killing yourself or wanting to die if you want to?* (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	___
Deterrents *Are there things - anyone or anything (e.g. family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?* (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply; wish to die only	___
Reasons for Ideation *What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?* (1) Completely to get attention, revenge or a reaction from others. (2) Mostly to get attention, revenge or a reaction from others. (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain. (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling). (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling).	___
Version 7/19/08	

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	Since Last Visit
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is *any* intent/desire to die associated with the act, then it can be considered an actual suicide attempt. *There does not have to be any injury or harm*, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g. gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. *Have you made a suicide attempt?* *Have you done anything to harm yourself?* *Have you done anything dangerous where you could have died?* *What did you do?* *Did you_____ as a way to end your life?* *Did you want to die (even a little) when you_____?* *Were you trying to end your life when you _____?* *Or did you think it was possible you could have died from_____?* *Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?* (Self-Injurious Behavior without suicidal intent) If yes, describe:	Yes No ☐ ☐ Total # of Attempts _____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	Yes No ☐ ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. *Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?* If yes, describe:	Yes No ☐ ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. *Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?* If yes, describe:	Yes No ☐ ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g. buying pills, purchasing a gun) or preparing for one' s death by suicide (e.g. giving things away, writing a suicide note). *Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?* If yes, describe:	Yes No ☐ ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes No ☐ ☐
Completed Suicide:	Yes No ☐ ☐
Answer for Actual Attempts Only	Most Lethal Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g. surface scratches). 1. Minor physical damage (e.g. lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g. conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g. comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g. comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____

Attachment 7: Representative Example of the 17-Item Hamilton Depression Rating Scale ($HDRS_{17}$) questions that will be used in this study

For each item, write the correct number on the line next to the item. (Only one response per item)

1. **DEPRESSED MOOD** (Sadness, hopeless, helpless, worthless)

_____
0= Absent
1= These feeling states indicated only on questioning
2= These feeling states spontaneously reported verbally
3= Communicates feeling states non-verbally—i.e., through facial expression, posture, voice, and tendency to weep
4= Patient reports VIRTUALLY ONLY these feeling states in his spontaneous verbal and non-verbal communication

2. **FEELINGS OF GUILT**

_____
0= Absent
1= Self reproach, feels he has let people down
2= Ideas of guilt or rumination over past errors or sinful deeds
3= Present illness is a punishment. Delusions of guilt
4= Hears accusatory or denunciatory voices and/or experiences threatening visual hallucinations

3. **SUICIDE**

_____
0= Absent
1= Feels life is not worth living
2= Wishes he were dead or any thoughts of possible death to self
3= Suicidal ideas or gesture
4= Attempts at suicide (any serious attempt rates 4)

4. **INSOMNIA EARLY**

_____
0= No difficulty falling asleep
1= Complains of occasional difficulty falling asleep—i.e., more than 1/2 hour
2= Complains of nightly difficulty falling asleep

5. **INSOMNIA MIDDLE**

_____
0= No difficulty
1= Patient complains of being restless and disturbed during the night
2= Waking during the night—any getting out of bed rates 2 (except for purposes of voiding)

6. **INSOMNIA LATE**

_____
0= No difficulty
1= Waking in early hours of the morning but goes back to sleep
2= Unable to fall asleep again if he gets out of bed

7. **WORK AND ACTIVITIES**

_____
0= No difficulty
1= Thoughts and feelings of incapacity, fatigue or weakness related to activities; work or hobbies
2= Loss of interest in activity; hobbies or work—either directly reported by patient, or indirect in listlessness, indecision and vacillation (feels he has to push self to work or activities)
3= Decrease in actual time spent in activities or decrease in productivity
4= Stopped working because of present illness

8. RETARDATION: PSYCHOMOTOR (Slowness of thought and speech; impaired ability to concentrate; decreased motor activity)

_____
0= Normal speech and thought
1= Slight retardation at interview
2= Obvious retardation at interview
3= Interview difficult
4= Complete stupor

9. AGITATION

_____
0= None
1= Fidgetiness
2= Playing with hands, hair, etc.
3= Moving about, can't sit still
4= Hand wringing, nail biting, hair-pulling, biting of lips

10. ANXIETY (PSYCHOLOGICAL)

_____
0= No difficulty
1= Subjective tension and irritability
2= Worrying about minor matters
3= Apprehensive attitude apparent in face or speech
4= Fears expressed without questioning

11. ANXIETY SOMATIC: Physiological concomitants of anxiety, (i.e., effects of autonomic overactivity, "butterflies," indigestion, stomach cramps, belching, diarrhea, palpitations, hyperventilation, paresthesia, sweating, flushing, tremor, headache, urinary frequency). Avoid asking about possible medication side effects (i.e., dry mouth, constipation)

_____
0= Absent
1= Mild
2= Moderate
3= Severe
4= Incapacitating

12. SOMATIC SYMPTOMS (GASTROINTESTINAL)

_____
0= None
1= Loss of appetite but eating without encouragement from others. Food intake about normal
2= Difficulty eating without urging from others. Marked reduction of appetite and food intake

13. SOMATIC SYMPTOMS GENERAL

_____
0= None
1= Heaviness in limbs, back or head. Backaches, headache, muscle aches. Loss of energy and fatigability
2= Any clear-cut symptom rates 2

14. GENITAL SYMPTOMS (Symptoms such as: loss of libido; impaired sexual performance; menstrual disturbances)

_____
0= Absent
1= Mild
2= Severe

15. HYPOCHONDRIASIS

_____

0= Not present
1= Self-absorption (bodily)
2= Preoccupation with health
3= Frequent complaints, requests for help, etc.
4= Hypochondriacal delusions

16. LOSS OF WEIGHT

_____

A. When rating by history:
0= No weight loss
1= Probably weight loss associated with present illness
2= Definite (according to patient) weight loss
3= Not assessed

17. INSIGHT

_____

0= Acknowledges being depressed and ill
1= Acknowledges illness but attributes cause to bad food, climate, overwork, virus, need for rest, etc.
2= Denies being ill at all

Attachment 8: Representative Example of the Inventory of Depressive Symptomatology - Clinician (IDS-C30) questions that will be used in this study

NAME: _____ TODAY'S DATE: _____

Please circle one response to each item that best describes the patient for the last seven days.

1. Sleep Onset Insomnia:

   0 Never takes longer than 30 minutes to fall asleep.
   1 Takes at least 30 minutes to fall asleep, less than half the time.
   2 Takes at least 30 minutes to fall asleep, more than half the time.
   3 Takes more than 60 minutes to fall asleep, more than half the time.

2. Mid-Nocturnal Insomnia:

   0 Does not wake up at night.
   1 Restless, light sleep with few awakenings.
   2 Wakes up at least once a night, but goes back to sleep easily.
   3 Awakens more than once a night and stays awake for 20 minutes or more, more than half the time.

3. Early Morning Insomnia:

   0 Less than half the time, awakens no more than 30 minutes before necessary.
   1 More than half the time, awakens more than 30 minutes before need be.
   2 Awakens at least one hour before need be, more than half the time.
   3 Awakens at least two hours before need be, more than half the time.

4. Hypersomnia:

   0 Sleeps no longer than 7-8 hours/night, without naps.
   1 Sleeps no longer than 10 hours in a 24 hour period (include naps).
   2 Sleeps no longer than 12 hours in a 24 hour period (include naps).
   3 Sleeps longer than 12 hours in a 24 hour period (include naps).

5. Mood (Sad):

   0 Does not feel sad.
   1 Feels sad less than half the time.
   2 Feels sad more than half the time.
   3 Feels intensely sad virtually all of the time.

6. Mood (Irritable):

   0 Does not feel irritable.
   1 Feels irritable less than half the time.
   2 Feels irritable more than half the time.
   3 Feels extremely irritable virtually all of the time.

7. Mood (Anxious):

   0 Does not feel anxious or tense.
   1 Feels anxious/tense less than half the time.
   2 Feels anxious/tense more than half the time.
   3 Feels extremely anxious/tense virtually all of the time.

8. Reactivity of Mood:

   0 Mood brightens to normal level and lasts several hours when good events occur.
   1 Mood brightens but does not feel like normal self when good events occur.
   2 Mood brightens only somewhat with few selected, extremely desired events.
   3 Mood does not brighten at all, even when very good or desired events occur.

9. Mood Variation:

   0 Notes no regular relationship between mood and time of day.
   1 Mood often relates to time of day due to environmental circumstances.
   2 For most of week, mood appears more related to time of day than to events.
   3 Mood is clearly, predictably, better or worse at a fixed time each day.

   9A. Is mood typically worse in morning, afternoon, or night (circle one).

   9B. Is mood variation attributed to environment by the patient? (yes or no) (circle one).

10. Quality of Mood:

   0 Mood is virtually identical to feelings associated with bereavement or is undisturbed.
   1 Mood is largely like sadness in bereavement, although it may lack explanation, be associated with more anxiety, or be much more intense.
   2 Less than half the time, mood is qualitatively distinct from grief and therefore difficult to explain to others.
   3 Mood is qualitatively distinct from grief nearly all of the time.

Complete either 11 or 12 (not both)

11. Appetite (Decreased):

0 No change from usual appetite.
1 Eats somewhat less often and/or lesser amounts than usual.
2 Eats much less than usual and only with personal effort.
3 Eats rarely within a 24-hour period, and only with extreme personal effort or with persuasion by others.

12. Appetite (Increased):

0 No change from usual appetite.
1 More frequently feels a need to eat than usual.
2 Regularly eats more often and/or greater amounts than usual.
3 Feels driven to overeat at and between meals.

Complete either 13 or 14 (not both)

13. Weight (Decrease) Within The Last Two Weeks:

0 Has experienced no weight change.
1 Feels as if some slight weight loss occurred.
2 Has lost 2 pounds or more.
3 Has lost 5 pounds or more.

14. Weight (Increase) Within the Last Two Weeks:

0 Has experienced no weight change.
1 Feels as if some slight weight gain has occurred.
2 Has gained 2 pounds or more.
3 Has gained 5 pounds or more.

15. Concentration/Decision Making:

0 No change in usual capacity to concentrate and decide.
1 Occasionally feels indecisive or notes that attention often wanders.
2 Most of the time struggles to focus attention or make decisions.
3 Cannot concentrate well enough to read or cannot make even minor decisions.

16. Outlook (Self):

0 Sees self as equally worthwhile and deserving as others.
1 Is more self-blaming than usual.
2 Largely believes that he/she causes problems for others.
3 Ruminates over major and minor defects in self.

17. Outlook (Future):

0 Views future with usual optimism.
1 Occasionally has pessimistic outlook that can be dispelled by others or events.
2 Largely pessimistic for the near future.
3 Sees no hope for self/situation anytime in the future.

18. Suicidal Ideation:

0 Does not think of suicide or death.
1 Feels life is empty or is not worth living.
2 Thinks of suicide/death several times a week for several minutes.
3 Thinks of suicide/death several times a day in depth, or has made specific plans, or attempted suicide.

19. Involvement:

0 No change from usual level of interest in other people and activities.
1 Notices a reduction in former interests/ activities.
2 Finds only one or two former interests remain.
3 Has virtually no interest in formerly pursued activities.

20. Energy/Fatiguability:

0 No change in usual level of energy.
1 Tires more easily than usual.
2 Makes significant personal effort to initiate or maintain usual daily activities.
3 Unable to carry out most of usual daily activities due to lack of energy.

21. Pleasure/Enjoyment (exclude sexual activities):

0 Participates in and derives usual sense of enjoyment from pleasurable activities.
1 Does not feel usual enjoyment from pleasurable activities.
2 Rarely derives pleasure from any activities.
3 Is unable to register any sense of pleasure/ enjoyment from anything.

22. Sexual Interest:

0 Has usual interest in or derives usual pleasure from sex.
1 Has near usual interest in or derives some pleasure from sex.
2 Has little desire for or rarely derives pleasure from sex.
3 Has absolutely no interest in or derives no pleasure from sex.

23. Psychomotor Slowing:

    0 Normal speed of thinking, gesturing, and speaking.
    1 Patient notes slowed thinking, and voice modulation is reduced.
    2 Takes several seconds to respond to most questions; reports slowed thinking.
    3 Is largely unresponsive to most questions without strong encouragement.

24. Psychomotor Agitation:

    0 No increased speed or disorganization in thinking or gesturing.
    1 Fidgets, wrings hands and shifts positions often.
    2 Describes impulse to move about and displays motor restlessness.
    3 Unable to stay seated. Paces about with or without permission.

25. Somatic Complaints:

    0 States there is no feeling of limb heaviness or pains.
    1 Complains of headaches, abdominal, back or joint pains that are intermittent and not disabling.
    2 Complains that the above pains are present most of the time.
    3 Functional impairment results from the above pains.

26. Sympathetic Arousal:

    0 Reports no palpitations, tremors, blurred vision, tinnitus or increased sweating, dyspnea, hot and cold flashes, chest pain.
    1 The above are mild and only intermittently present.
    2 The above are moderate and present more than half the time.
    3 The above result in functional impairment.

27. Panic/Phobic Symptoms:

    0 Has neither panic episodes nor phobic symptoms.
    1 Has mild panic episodes or phobias that do not usually alter behavior or incapacitate.
    2 Has significant panic episodes or phobias that modify behavior but do not incapacitate.
    3 Has incapacitating panic episodes at least once a week or severe phobias that lead to complete and regular avoidance behavior.

28. Gastrointestinal:

    0 Has no change in usual bowel habits.
    1 Has intermittent constipation and/or diarrhea that is mild.
    2 Has diarrhea and/or constipation most of the time that does not impair functioning.
    3 Has intermittent presence of constipation and/or diarrhea that requires treatment or causes functional impairment.

29. Interpersonal Sensitivity:

    0 Has not felt easily rejected, slighted, criticized or hurt by others at all.
    1 Occasionally feels rejected, slighted, criticized or hurt by others.
    2 Often feels rejected, slighted, criticized or hurt by others, but with only slight effects on social/occupational functioning.
    3 Often feels rejected, slighted, criticized or hurt by others that results in impaired social/occupational functioning.

30. Leaden Paralysis/Physical Energy:

    0 Does not experience the physical sensation of feeling weighted down and without physical energy.
    1 Occasionally experiences periods of feeling physically weighted down and without physical energy, but without a negative effect on work, school, or activity level.
    2 Feels physically weighted down (without physical energy) more than half the time.
    3 Feels physically weighted down (without physical energy) most of the time, several hours per day, several days per week.

Attachment 9: Representative Example of the Patient Health Questionnaire questions that will be used in this study

Over the past 2 weeks, how often have you been bothered by any of the following problems?	Not At all	Several Days	More Than Half the Days	Nearly Every Day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed or hopeless	0	1	2	3
3. Trouble falling asleep, staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself - or that you're a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed. Or, the opposite - being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead or of hurting yourself in some way	0	1	2	3

Column Totals _____ + _____ + _____

Add Totals Together _____

Attachment 10: Representative Example of the Snaith Hamilton Pleasure Scale questions that will be used in this study

This questionnaire is designed to measure your ability to experience pleasure in the last few days. It is important to read each statement very carefully. Tick *one* of the boxes to indicate how much you agree or disagree with each statement.

1. **I have enjoyed my favourite television or radio program:** ❑ Strongly disagree ❑ Disagree ❑ Agree ❑ Strongly agree	5. **I have enjoyed a warm bath or refreshing shower:** ❑ Definitely agree ❑ Agree ❑ Disagree ❑ Strongly disagree
2. **I have enjoyed being with my family or close friends:** ❑ Definitely agree ❑ Agree ❑ Disagree ❑ Strongly disagree	6. **I have found pleasure in the scent of flowers or the smell of a fresh sea breeze or freshly baked bread:** ❑ Strongly disagree ❑ Disagree ❑ Agree ❑ Strongly agree
3. **I have found pleasure in my hobbies and pastimes:** ❑ Strongly disagree ❑ Disagree ❑ Agree ❑ Strongly agree	7. **I have enjoyed seeing other people's smiling faces:** ❑ Definitely agree ❑ Agree ❑ Disagree ❑ Strongly disagree
4. **I have been able to enjoy my favourite meal:** ❑ Definitely agree ❑ Agree ❑ Disagree ❑ Strongly disagree	8. **I have enjoyed looking nice when I have made an effort with my appearance:** ❑ Strongly disagree ❑ Disagree ❑ Agree ❑ Strongly agree

9. **I have enjoyed reading a book, magazine or newspaper:** ❑ Definitely agree ❑ Agree ❑ Disagree ❑ Strongly disagree	12. **I have been able to enjoy a beautiful landscape or view:** ❑ Definitely agree ❑ Agree ❑ Disagree ❑ Strongly disagree
10. **I have enjoyed a cup of tea or coffee or my favourite drink:** ❑ Strongly disagree ❑ Disagree ❑ Agree ❑ Strongly agree	13. **I have gotten pleasure from helping others:** ❑ Strongly disagree ❑ Disagree ❑ Agree ❑ Strongly agree
11. **I have found pleasure in small things, e.g. bright sunny day, a telephone call from a friend:** ❑ Strongly disagree ❑ Disagree ❑ Agree ❑ Strongly agree	14. **I have felt pleasure when I received praise from other people:** ❑ Definitely agree ❑ Agree ❑ Disagree ❑ Strongly disagree

Attachment 11: Representative Example of the Functional Assessment of Chronic Illness Therapy-Fatigue questionnaire questions that will be used in this study

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

	PHYSICAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	EMOTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
HI7	I feel fatigued	0	1	2	3	4
HI12	I feel weak all over	0	1	2	3	4
An1	I feel listless ("washed out")	0	1	2	3	4
An2	I feel tired	0	1	2	3	4
An3	I have trouble starting things because I am tired	0	1	2	3	4
An4	I have trouble finishing things because I am tired	0	1	2	3	4
An5	I have energy	0	1	2	3	4
An7	I am able to do my usual activities	0	1	2	3	4
An8	I need to sleep during the day	0	1	2	3	4
An12	I am too tired to eat	0	1	2	3	4
An14	I need help doing my usual activities	0	1	2	3	4
An15	I am frustrated by being too tired to do the things I want to do	0	1	2	3	4
An16	I have to limit my social activity because I am tired	0	1	2	3	4

Attachment 12: Representative Example of the Childhood Trauma Questionnaire questions that will be used in this study

Instructions: These questions ask about some of your experiences growing up as a child and a teenager. For each question, circle the number that best describes how you feel. Although some of these questions are of a personal nature, please try to answer as honestly as you can. Your answers will be kept confidential.

When I was growing up,…	**Never True**	**Rarely True**	**Sometimes True**	**Often True**	**Very Often True**
1. I didn't have enough to eat.	**1**	**2**	**3**	**4**	**5**
2. I knew there was someone to take care of me and protect me.	**1**	**2**	**3**	**4**	**5**
3. People in my family called me things like "stupid", "lazy", or "ugly".	**1**	**2**	**3**	**4**	**5**
4. My parents were too drunk or too high to take care of me.	**1**	**2**	**3**	**4**	**5**
5. There was someone in my family who helped me feel important or special.	**1**	**2**	**3**	**4**	**5**
6. I had to wear dirty clothes.	**1**	**2**	**3**	**4**	**5**
7. I felt loved.	**1**	**2**	**3**	**4**	**5**
8. I thought that my parents wished I had never been born.	**1**	**2**	**3**	**4**	**5**
9. I got hit so hard by someone in my family that I had to see a doctor or go to the hospital.	**1**	**2**	**3**	**4**	**5**
10. There was nothing I wanted to change about my family.	**1**	**2**	**3**	**4**	**5**
11. People in my family hit me so hard that it left bruises or marks.	**1**	**2**	**3**	**4**	**5**
12. I was punished with a belt, a board, a cord, or some hard object.	**1**	**2**	**3**	**4**	**5**
13. People in my family looked out for each other.	**1**	**2**	**3**	**4**	**5**
14. People in my family said hurtful or insulting things to me.	**1**	**2**	**3**	**4**	**5**
15. I believe that I was physically abused.	**1**	**2**	**3**	**4**	**5**
16. I had the perfect childhood.	**1**	**2**	**3**	**4**	**5**
17. I got hit or beaten so badly that it was noticed by someone like a teacher, a neighbour, or doctor.	**1**	**2**	**3**	**4**	**5**
18. I felt that someone in my family hated me.	**1**	**2**	**3**	**4**	**5**
19. People in my family felt close to each other.	**1**	**2**	**3**	**4**	**5**
20. Someone tried to touch me in a sexual way, or tried to make me touch them.	**1**	**2**	**3**	**4**	**5**
21. Someone threatened to hurt me or tell lies about me unless I did something sexual with them.	**1**	**2**	**3**	**4**	**5**
22. I had the best family in the world.	**1**	**2**	**3**	**4**	**5**
23. Someone tried to make me do sexual things or make me watch sexual things.	**1**	**2**	**3**	**4**	**5**
24. Someone molested me.	**1**	**2**	**3**	**4**	**5**
25. I believe that I was emotionally abused.	**1**	**2**	**3**	**4**	**5**
26. There was someone to take me to the doctor if needed.	**1**	**2**	**3**	**4**	**5**
27. I believe that I was sexually abused.	**1**	**2**	**3**	**4**	**5**
28. My family was a source of strength and support	**1**	**2**	**3**	**4**	**5**

Attachment 13: Instructions for the Completion of the Patient-Reported Outcome (PRO) Case Report Forms

The following instructions are intended to assist investigators, study coordinators, and those with monitoring responsibilities with the completion of all patient self-administered (PRO) assessments.

I. General Instructions

1. Patients should complete the patient-reported outcome (PRO) assessments in a quiet, semi-private location with access to study staff for questions.
2. Patients should be allowed approximately 30 minutes to orient him/herself and to self-administer all PRO assessments.
3. Patients should be literate in the language of the PRO assessment(s). Patients must not have any developmental, learning, or behavioral disabilities.
4. Patients should complete all PRO assessments using a black ballpoint pen. Have the patient press firmly and print legibly when writing to ensure that all copies are clear and legible. Have the patient place a piece of cardboard between the pages to ensure no 'run through' pages.
5. Explain to patients the reasons why they are being asked to complete the PRO assessment(s), i.e., they are part of the overall medical assessment and are designed to find out more information about how having their disease has affected their life.
6. Indicate to patients that all of the information on the PRO assessment(s) is confidential, and that someone from the study staff will only check for completeness and not share the results with other clinical staff.
7. Indicate to patients that there are no right or wrong answers.
8. Provide patients with the set of instructions that are provided with the PRO assessment(s) materials. Have patients read the instructions prior to completing the assessment(s). For almost all items, it is necessary for patients to check the box next to the answer that applies. Occasionally, patients will be asked to write in some additional information. Not all of the questions apply to every patient. Where a particular question or set of questions does not apply, there will be instructions on which question to answer next.

II. Assessment Times

1. Each PRO assessment asks the patient for an evaluation of a specified period of time. Therefore, it is important to minimize the influence of feedback from the clinic visit itself. Insofar as it is possible, it is also important to have the PRO assessment(s) be conducted within the flow of the study visit.
2. The PRO instruments have been placed in the correct order of completion in the study CRF. Please ask the subject to complete the PROs in the sequence that they appear in the booklet.

Day -28 to -1 - Screening:

PRO assessment(s) during this time period should be completed immediately after the patient provides his/her informed consent, but before any clinical tests are taken or assessments associated with the study visit are conducted.

All other days:

PRO assessment(s) during this/these time period(s) should be completed before any clinical tests are taken or assessments associated with the study visit are conducted.

III. Quality Control

1. Complete the 'Subject Number,' 'date of birth,' 'Visit' number, and 'Visit Date' at the bottom of every PRO assessment page.

2. Before the patient leaves following the study visit, check for any questions that might have been left blank. If an item has been omitted, point this out and ask whether the item was left blank intentionally, and that these items be completed if appropriate. Occasionally, patients mark more than one answer per item. In such instances, ask the patient if he/she will reconsider the question and try to choose one answer only.

IV. Special Issues

1. Patients should be instructed to complete the PRO assessment(s) without help from anyone, and relatives or caregivers should not be with the subject when the PROs are completed. However, if a patient cannot read the PRO assessment(s) or complete it/them independently, then a designated person can read the items and response choices aloud and mark the appropriate response choices as verbally stated by the patient. The designated person should read each question in its entirety in a neutral voice, avoiding any cues, even if interrupted by the patient with an answer. The designated person should repeat each of the patient's answers, e.g., "A little bit." The patient should not be prompted by the designated person in any other way. No help should be offered to the patient in interpreting the questionnaire.

2. If a person is designated to assist the patient with the PRO assessment(s), this person should remain consistent across assessment instruments and across assessment periods.

3. If a designated person assists the patient with the PRO assessment(s), this should be noted in the footer section on the first page of each PRO assessment instrument.

INVESTIGATOR AGREEMENT

CNTO136 sirukumab
Amendment INT-5 CNTO136MDD2001

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): Giacomo Salvadore

Institution: Janssen Research & Development, a division of Janssen Pharmaceutica N.V.

Signature: [redacted] Date: 23 JAN 2018
(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.

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