Study Title:	An Open-Label Safety Extension Study (OLSES) Evaluating the Long-term Safety and Durability of Response of CHS-0214 (CHS-0214-05)
Protocol Number:	CHS-0214-05
Protocol Date:	19 March 2015
Version 2.0 (Amendment 1): (UK Only)	24 June 2015
Version 3.0 (Amendment 2):	13 July 2015
Version 4.0 (Amendment 3): (Japan only)	29 February 2016
IND Number:	115,675
EudraCT Number:	2015-000665-30
Study Phase:	Phase 3
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INVESTIGATOR

SIGNATURE PAGE

STUDY TITLE: An Open-Label Safety Extension Study (OLSES) Evaluating the Long-term Safety and Durability of Response of CHS-0214 (CHS-0214-05)

By signing below I agree that:

I have read this protocol and agree to conduct the study as outlined herein in accordance with International Conference on Harmonisation Good Clinical Practice, United States Food and Drug Administration regulations, Institutional Review Board regulations, and regional regulatory requirements.

_____ _____
Principal Investigator Signature Date

_____
Principal Investigator Name and Title (please print)

Investigative Site Address

_____
_____
_____

COHERUS BIOSCIENCES, INC.

SIGNATURE PAGE

STUDY TITLE: An Open-Label Safety Extension Study (OLSES) Evaluating the Long-term Safety and Durability of Response of CHS-0214 (CHS-0214-05)

I, the undersigned, have read this protocol and agree that it contains all necessary information required to conduct the study.

Signature Barbara K Finck MD

Date 3 MAR 2016

Barbara Finck, M.D.
Chief Medical Officer
Coherus BioSciences, Inc.

DAIICHI SANKYO CO., LTD.

SIGNATURE PAGE

STUDY TITLE: An Open-Label Safety Extension Study (OLSES) Evaluating Long-Term Safety and Durability of Response of CHS-0214 (CHS-0214-05)

I, the undersigned, have read this protocol and agree that it contains all necessary information required to conduct the study.

Signature _____ Date 3 Mar 2016

Kohei Wada
Vice President, Clinical Execution Department, R&D Division
Daiichi Sankyo Co., Ltd.

SYNOPSIS

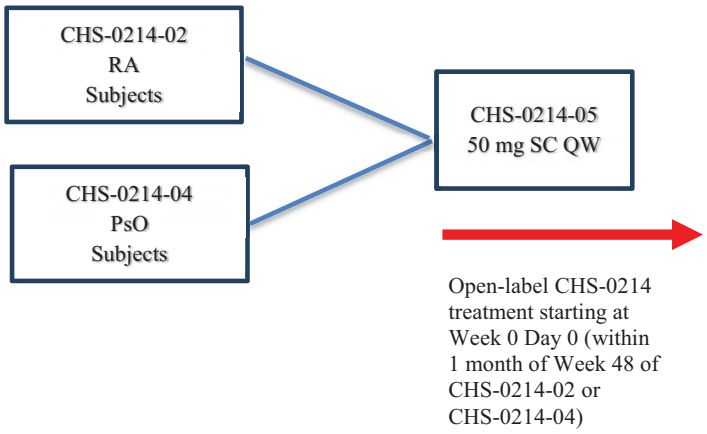
Study Title	An Open-label, Safety Extension Study (OLSES) Evaluating the Long-term Safety and Durability of Response of CHS-0214 (CHS-0214-05)
Sponsors	Coherus BioSciences Inc., Daiichi Sankyo Co., Ltd.
Study Objective	Objectives: To evaluate the longer-term safety and durability of response of subjects who completed 48 weeks of evaluations in the confirmatory safety and efficacy studies, CHS-0214-02 or CHS-0214-04, evaluating CHS-0214 in rheumatoid arthritis (RA) and plaque psoriasis (PsO), respectively.
Study Design	This is an open-label safety extension study. Subjects completing the 48-week evaluation in the clinical studies CHS-0214-02 or CHS-0214-04 may be eligible to enroll into this study and receive open-label CHS-0214 50 mg as a subcutaneous (SC) injection every week (QW). Subjects will receive QW treatment of CHS-0214 for 48 weeks except in Japan, where subjects with RA may receive CHS-0214 until marketing approval of CHS-0214. There will be a follow-up evaluation 28 days after last dose of study drug for any subject discontinuing treatment at any time during the study. Study drug will be supplied either as a prefilled syringe or a prefilled syringe in an auto-injector. Subjects will be evaluated at 1 month and 3 months following enrollment, and every 3 months thereafter for safety, including immunogenicity, and durability of response.
Study Centers	Selected study centers that participated in CHS-0214-02 and/or CHS-0214-04
Sample Size	Approximately 400 subjects will be enrolled.
Study Population	Adult male and female subjects with: • RA who have completed 48 weeks of evaluations in CHS-0214-02 and, at Week 48, had at least a 20% improvement from Baseline (parent study) according to American College of Rheumatology criteria (ACR20) • Moderate to severe, chronic, stable PsO who have completed 48 weeks of evaluations in CHS-0214-04 and, at Week 48, had at least 50% improvement in Psoriasis Area and Severity Index (PASI-50) from Baseline (parent study).
Main Inclusion Criteria	Subjects must meet the following criteria to be enrolled in this study: 1. Have completed 48 weeks of evaluations in CHS-0214-02 and, at Week 48, had at least an ACR20, or completed 48 weeks of evaluations in CHS-0214-04 and, at Week 48, had at least a PASI-50; 2. Women who either: a) Are of childbearing potential with a negative urine pregnancy test at Week 0 Day 0 who agree to use 1 or more approved methods of birth control (hormonal contraception, intrauterine device, diaphragm plus spermicide, condom plus spermicide, or abstinence from heterosexual intercourse—abstinence from heterosexual intercourse will be acceptable only if it is the preferred and usual lifestyle of the subject regardless of study participation; abstinence should be practiced for the duration of the study Follow-up Visit 28 days after the last dose of study drug);

	b) Have been postmenopausal for at least 2 years (with amenorrhea for at least 1 year) or have had a hysterectomy, bilateral salpingo-oophorectomy, or tubal ligation prior to signing the informed consent; and 3. Able and willing to give written informed consent prior to performance of any study related procedures.
Main Exclusion Criteria	Subjects who meet the following criterion will be excluded from participation in this study: 1. Men whose partners may become pregnant (do not agree to use contraception or who are not postmenopausal) or may breastfeed during the study (Japan only specific exclusion).
Study Drug Dosage and Administration	Subjects will receive open-label CHS-0214 50 mg in prefilled syringes or prefilled syringes in auto-injectors. Study drug will be self-injected or administered to the subject by a caregiver at home as a SC injection QW.
Study Endpoints	**Safety:** Safety will be assessed at 1 month and 3 months following enrollment and every 3 months thereafter by: • Assessment of treatment-emergent AEs; • Determination of subject withdrawal information; • Assessment of injection site reactions; • Assessment of changes in safety laboratory parameters, including hematology, clinical chemistry, and pregnancy tests; • Assessment of changes in vital signs, physical examination, and electrocardiogram findings; • Monitoring for tuberculosis (TB) with regular QuantiFERON®-TB Gold test (every 12 months or more frequently for regions with high incidences of TB or to evaluate signs and symptoms that might be due to TB); and • Assessment of immunogenicity (anti-CHS-0214 antibodies) **Retained samples:** Serum samples will be collected at each visit and retained for potential analysis of serum concentration of CHS-0214, anti-drug antibodies, or other tests as necessary to evaluate AEs, loss of response, or compliance. Serum samples will not be used to assess population pharmacokinetics (PK), biomarkers, or genetics. Samples will be stored at Medpace Reference Laboratories, LLC (MRL) and may be transferred to Charles River Laboratories or other reference laboratory for analysis at the request of the Sponsor. All retained samples and remnants of samples will be destroyed 2 years after the completion of the study (database lock). **Efficacy endpoints:** Durability of response will be measured at each visit as follows: Primary endpoint: • For subjects with RA, maintenance of an ACR20 response or greater • For subjects with PsO, maintenance of PASI-50 response or greater Secondary endpoints: • For subjects with RA, Disease Activity Score using 28 tender and swollen joint counts, high sensitivity C-reactive protein, and subject's global assessment (DAS28-CRP [4]) to < 3.2 (low disease activity) assessed at all visits and < 2.6 (remission) assessed on all visits after DAS28-CRP (4) < 2.6 is achieved

Statistical Analysis	Safety analyses will be performed in all subjects who receive at least 1 dose of CHS-0214 in this study (the Safety Population). Separate efficacy analyses will be performed in subjects who receive at least 1 dose of CHS-0214 and who have any efficacy measurements in 3 populations; all subjects with RA who complete the CHS 0214-02 study and meet the entry criteria for this study (the RA Population), all subjects with RA who complete the CHS 0214-02 study at Japanese sites and meet the entry criteria for this study (the Japanese RA Population-a subset of the RA population), and all subjects with PsO who complete the CHS 0214-04 study and meet the entry criteria for this study (the PsO Population). Continuous variables will be summarized using descriptive statistics (N, mean, standard deviation, median, minimum, and maximum, where appropriate). Discrete variables will be summarized using frequency counts and percentages.
Study Duration	Subjects may continue to participate in this study until 1 of the following occurs: • The subject has undergone follow-up evaluations 28 days after the last dose of study drug (the subject has completed the study); • The subject experiences a serious adverse event (SAE) or medically important AE (e.g., serious or opportunistic infection related to study drug) that would preclude further treatment with study drug; • The subject develops a malignancy while on study drug, except as below: ○ Please note, subjects who develop a malignancy while on study drug and receive localized and non-invasive treatment may stay in the study per the Investigator's judgment; • The subject requires medical treatment excluded by the protocol, or that could present a safety risk to the subject; • The subject is not willing to continue participation in the study (withdraws consent); • The subject is lost to follow up; • Lack of compliance with the provisions of the protocol; • The subject experiences an increase in disease activity that requires additional or different therapy; • The subject develops a positive response to the QuantiFERON®-TB Gold test at any time during the study, as defined by 2 consecutive positive tests (>2 IU/mL). During the study (every 12 months or more frequently for regions with a high incidence of TB, or to evaluate signs and symptoms that might be due to TB), if a patient has an indeterminate or low positive (0.35-2 IU/mL) or a positive (>2 IU/mL) QuantiFERON®-TB Gold test result, the QuantiFERON®-TB Gold test should be repeated. If the repeat test is indeterminate or low positive (0.35-2 IU/mL), the patient can continue in the study, providing symptoms and risk factors are all negative, i.e., the subject has not been exposed to TB, the chest x-ray is negative, and the Investigator does not believe the subject has latent TB. Only a conversion to positive (>2 IU/mL) on 2 consecutive tests would result in the subject not qualifying to continue in OLSES; • The subject becomes pregnant while on study medication (the subject will immediately be withdrawn from study drug and all procedures for the Follow-up Visit will be conducted 28 Days after the last dose of study drug); • In the opinion of the Investigator, it is in the best interest of the subject to discontinue study participation; • Subject has positive viral screen results;

	• Subject's Week 48 laboratory results from CHS-0214-02 or CHS 0214-04 are clinically significant; or
	• The Sponsor discontinues the study for any of the following reasons:
	  ○ The Sponsor receives marketing approval in Japan;
	  ○ Development of a previously unknown safety concern
	  ○ The results of analyses indicate that either parent study (CHS-0214-02 or CHS-0214-04) did not meet its primary efficacy endpoints;
	  ○ Other events that have not been anticipated by the Sponsor;
	  ○ Any other reason (e.g., an unexpected SAE not previously observed with etanercept or another tumor necrosis factor inhibitor is observed in the study)

Figure 1: Study Design



Efficacy Primary Endpoints
- **For subjects with RA, maintenance of ACR20 response or greater**
- **For subjects with PsO, maintenance of PASI-50 response or greater**

Efficacy Secondary Endpoints:
- **For subjects with RA, DAS28-CRP (4) < 3.2 (low disease activity) assessed at all visits and DAS28-CRP (4) < 2.6 (remission) assessed on all visits after DAS28-CRP (4) < 2.6 is achieved**

Safety
- **TEAEs; withdrawals; ISRs; changes in laboratory safety parameters and vital sign, physical examination, and ECG findings; QuantiFERON®-TB Gold; immunogenicity**

ACR20 = 20% improvement according to American College of Rheumatology criteria; DAS28-CRP(4) = Disease Activity Score using 28 tender and swollen joint counts, C-reactive protein, and subject's global assessment; ECG = electrocardiogram; ISR = injection site reaction; PASI-50 = 50% improvement in Psoriasis Area and Severity Index; PsO = plaque psoriasis; QW = every week; RA = rheumatoid arthritis; SC = subcutaneous; TEAE = treatment-emergent adverse event.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ACR	American College of Rheumatology
ACR20	20% improvement according to American College of Rheumatology criteria
ADA	Anti-drug antibody
AE	Adverse event
CFR	Code of Federal Regulations
CRA	Clinical Research Associate
CRP	C-reactive protein
DAS28-CRP(4)	Disease Activity Score using 28 tender and swollen joint counts, C-reactive protein, and subject's global assessment
DMARD	Disease-modifying anti-rheumatic drug
DSMB	Data Safety Monitoring Board
EC	Ethics Committee
ECG	Electrocardiogram
ECL	Electrochemiluminescent
eCRF	Electronic Case Report Form
EDC	Electronic data capture
ELISA	Enzyme-linked immunosorbent assay
EU	European Union
EULAR	European League Against Rheumatism
FAP	Full Analysis Population
FDA	United States Food and Drug Administration
GCP	Good Clinical Practice
HAQ-DI	Health Assessment Questionnaire–Disability Index
HBcAb	Hepatitis B core antibody
HBsAg	Hepatitis B surface antigen
HBsAb	Hepatitis B surface antibody
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
hs-CRP	high sensitivity C-reactive protein

ICF	Informed consent form
ICH	International Conference on Harmonisation
ID	Identification number
IMID	Immune mediated inflammatory diseases
IRB	Institutional Review Board
ISR	Injection site reaction
IVRS	Interactive voice response system
IWRS	Interactive web response system
LTα	Lymphotoxin-alpha
JIA	Juvenile idiopathic arthritis
MedDRA	Medical Dictionary for Regulatory Activities
MRL	Medpace Reference Laboratories, LLC
MTX	Methotrexate
NAB	Neutralizing anti-drug antibody
NSAID	Non-steroidal anti-inflammatory drug
OLSES	Open-label safety extension study
p75	75-kilodalton protein
PASI	Psoriasis Area and Severity Index
PASI-50	50% improvement in Psoriasis Area and Severity Index
PGA	Physician's Global Assessment
PSGA	Physician's Static Global Assessment
PK	Pharmacokinetic(s)
PsA	Psoriatic arthritis
PsO	Plaque psoriasis
PUVA	Psoralen plus ultraviolet A
QW	Every week
RA	Rheumatoid arthritis
RF	Rheumatoid factor
SAE	Serious adverse event
SC	Subcutaneous
SGA	Subject's global assessment of disease activity
SJC	Swollen joint count

SUSAR	Suspected unexpected serious adverse reaction
TB	Tuberculosis
TEAE	Treatment-emergent adverse event
TJC	Tender joint count
TNF	Tumor necrosis factor
TNFα	Tumor necrosis factor-alpha
TNFβ	Tumor necrosis factor-beta
TNFR	Tumor necrosis factor receptor
ULN	Upper limit of normal
US, USA	United States
UVA	Ultraviolet A
UVB	Ultraviolet B
VAS	Visual analog scale
WHO-DD	World Health Organization Drug Dictionary

1 INTRODUCTION

1.1 Overview

Coherus BioSciences is developing CHS-0214 as a proposed biosimilar product to etanercept, Enbrel®, under a global development and regulatory strategy for rheumatoid arthritis (RA), plaque psoriasis (PsO), and other indications for which Enbrel is approved in various regulatory territories.

1.2 Background

The purposes of this open-label safety extension study (OLSES) are to evaluate the longer-term safety and durability of response of subjects who completed 48 weeks of evaluations in the confirmatory CHS-0214 safety and efficacy studies, CHS-0214-02 and CHS-0214-04 in RA and PsO, respectively. This study will only be offered in selected countries.

Tumor necrosis factor (TNF) is a naturally occurring cytokine that plays an important role in the inflammatory processes of immune mediated inflammatory diseases (IMID) such as PsO, psoriatic arthritis (PsA), juvenile idiopathic arthritis (JIA), Crohn's disease, ulcerative colitis, and RA. Elevated levels of TNF are found in involved tissues and fluids of subjects with PsO and other IMIDs (Krueger, Krane, Carter, & Gottlieb, 1990), (Brotas, Cunha, Lago, Machado, & Carneiro, 2012), (Keystone & Ware, 2010). Two distinct tumor necrosis factor receptors (TNFRs), a 55-kilodalton protein and a 75-kilodalton protein (p75), exist naturally as monomeric molecules on cell surfaces and in soluble forms. Biological activity of TNF is dependent upon binding to either cell surface TNFR (Bluml, Scheinecker, Smolen, & Redlich, 2012).

Etanercept (Enbrel®, Amgen Inc.), is a dimeric soluble form of the p75 TNFR that can bind TNF molecules. Etanercept inhibits binding of tumor necrosis factor-alpha (TNFα) and tumor necrosis factor-beta (TNFβ) (also known as lymphotoxin-alpha, LTα) to cell surface TNFRs, rendering TNF biologically inactive. In in vitro studies, large complexes of etanercept with TNFα were not detected, and cells expressing transmembrane TNF (that binds etanercept) are not lysed in the presence or absence of complement (Horiuchi, Mitoma, Harashima, Tsukamoto, & Shimoda, 2010).

Enbrel was approved in the United States (US) in 1998 (Amgen, 2015), in the EU in 2000 (European Medicines Agency, 2014), and in Japan in 2005 (Pfizer, 2015). Enbrel is indicated in Japan for patients with RA and Juvenile RA and is indicated in Europe for patients with RA, JIA, PsA, axial spondyloarthritis, ankylosing spondylitis, non-radiographic axial spondyloarthritis, PsO, and pediatric PsO.

Across clinical studies and postmarketing experience, the most serious adverse reactions related to Enbrel were infections, neurologic events, congestive heart failure, hematologic events, malignancies, and autoimmune reactions. The most common adverse reactions were infections, injection site reactions (ISRs), allergic reactions, development of autoantibodies, pruritus, and fever. Further details are

provided in the prescribing information for Enbrel (see Appendix L). Antibodies to the TNFR portion or other protein components of the Enbrel drug product were detected in sera of approximately 6% of adult subjects treated with Enbrel using an enzyme-linked immunosorbent assay (ELISA) (Amgen, 2015). These antibodies were all non-neutralizing. The clinical significance of this finding is unknown.

Please refer to the CHS-0214 Investigator's Brochure for information on adverse events (AEs) and anti-drug antibodies observed in clinical trials of CHS-0214.

1.3 Development of CHS-0214

CHS-0214 has been evaluated in the following studies thus far. All 4 studies have met their primary endpoints.

1. CHS-0214-01: A Randomized, Double-Blind, Single-Dose, Two-Period Crossover Study to Assess the Pharmacokinetic Similarity of CHS-0214 DP and EU approved etanercept, Enbrel® (EU), in Healthy Male and Female Subjects-This study has been completed.
2. CHS-0214-02: A Double-Blind, Randomized, Parallel-Group, Active-Control Study to Compare the Efficacy and Safety of CHS-0214 Versus Enbrel® in Subjects With Rheumatoid Arthritis and Inadequate Response to Treatment With Methotrexate (RApsody). This study is ongoing
3. CHS-0214-03: A Randomized, Double-Blind, Single-Dose, 2-Period Crossover Study to Assess the Pharmacokinetic Similarity of CHS-0214 (European Union [EU]) and EU-Approved Etanercept (Enbrel® [EU]) and the Safety and Tolerability of CHS-0214 (EU) in Healthy Male and Female Subjects. This study has been completed.
4. CHS-0214-04: A Double-Blind, Randomized, Parallel-Group, Active-Control Study to Compare the Efficacy and Safety of CHS-0214 Versus Enbrel® in Subjects With Chronic Plaque Psoriasis (CHS-0214-04) RaPSOdy. This study is ongoing.

See the Investigator's Brochure for more details.

2 STUDY OBJECTIVES

The purpose of this OLSES is to evaluate the longer-term safety and durability of response of subjects who completed 48 weeks of evaluations in the confirmatory CHS-0214 safety and efficacy studies, CHS-0214-02 and CHS-0214-04 in RA and PsO, respectively.

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

This multicenter, global OLSES is being conducted in the following subjects:

- Adult subjects with RA who have completed 48 weeks of evaluations in Study CHS-0214-02 and, at Week 48, had at least a 20% improvement from Baseline according to American College of Rheumatology criteria (ACR20)
- Adult subjects with moderate to severe, chronic, stable PsO who have completed 48 weeks of evaluations in Study CHS-0214-04 and, at Week 48, had at least a 50% improvement in Psoriasis Area and Severity Index (PASI-50) from Baseline (see Appendix J)
- Study drug administration may continue uninterrupted for eligible subjects who decide to enroll into OLSES following participation in either Study CHS-0214-02 or Study CHS-0214-04.
  - Subjects will either enroll directly into OLSES on their Week 48 Visit of the parent study (either Study CHS-0214-02 or Study CHS-0214-04) or within 1 month of their Week 48 Visit of the parent study.
  - In both cases described above, data collected from procedures conducted at the Week 48 Visit of the parent study will also be considered Week 0 Day 0 data in OLSES.
  - If eligibility is not determined and consent is not obtained during the Week 48 Visit of the parent study, subjects will come back for an additional visit as soon as possible (within 1 month of the Week 48 Visit) to complete the procedures/testing required for the OLSES study start, i.e., consent and viral laboratory and urine pregnancy (if applicable) tests. At that time, subjects will also be dispensed study drug supply as part of the OLSES study.

Subjects will receive open-label CHS-0214 50 mg every week (QW) in prefilled syringes with passive needle guard or prefilled syringes in auto-injectors administered by self-injection or by a caregiver at home as a subcutaneous (SC) injection. Subjects will receive study drug for 48 weeks except in Japan, where subjects may receive study drug until marketing approval. Note that all subjects in Japan enrolled in OLSES are from the CHS-0214-02 parent study.

Any subject discontinuing treatment at any time during the study will undergo follow-up evaluations 28 days after last dose of study drug.

Safety will be assessed throughout the study by:

- Assessment of treatment-emergent adverse events (TEAEs);
- Determination of subject withdrawal information;
- Assessment of ISRs;

- Assessment of changes in safety laboratory parameters, including hematology, clinical chemistry, and pregnancy tests;
- Assessment of changes in vital sign, physical examination, and electrocardiogram (ECG) findings;
- During the study (every 12 months or more frequently for regions with a high incidence of TB, or to evaluate signs and symptoms that might be due to TB), if a patient has an indeterminate or low positive (0.35-2 IU/mL) or a positive (>2 IU/mL) QuantiFERON®-TB Gold test result, the QuantiFERON®-TB Gold test should be repeated. If the repeat test is indeterminate or low positive (0.35-2 IU/mL), the patient can continue in the study, providing symptoms and risk factors are all negative, i.e., the subject has not been exposed to TB, the chest x-ray is negative, and the Investigator does not believe the subject has latent TB. Only a conversion to positive (>2 IU/mL) on 2 consecutive tests would result in the subject not qualifying to continue in OLSES;
- Assessment of immunogenicity (anti-CHS-0214 antibodies).

Durability of response will be measured at each visit as follows:

- For subjects with RA, maintenance of an ACR20 response or greater
- For subjects with PsO, maintenance of PASI-50 (see Appendix J) response or greater

Serum samples will be collected at each visit and retained for potential analysis of serum concentration of CHS-0214, anti-drug antibodies (ADAs), or other tests as necessary to evaluate AEs, loss of response, or compliance. Serum samples will not be used to assess population pharmacokinetics (PK), biomarkers, or genetics. Samples will be stored at Medpace Reference Laboratories, LLC (MRL) and may be transferred to Charles River Laboratories or other reference laboratory for analysis at the request of the Sponsor. All retained samples and remnants of samples will be destroyed 2 years after the completion of the study (database lock).

3.2 Rationale for Study Design/Dose Level

The rationale for the study design is to evaluate the longer-term safety and durability of response of subjects who completed 48 weeks of evaluations in the confirmatory safety and efficacy studies, CHS-0214-02 or CHS-0214-04, evaluating CHS-0214 in RA and PsO, respectively.

The dose selected for this safety study is 50 mg QW. Studies comparing dosing at 50 mg twice weekly to 50 mg QW in subjects with PsO have demonstrated that decreasing the dose after 12 weeks does not result in a loss of or diminishment of response or an exacerbation of disease for most subjects (Leonardi, et al., 2003) (Papp, et al., 2005). Also, in subjects with RA, the dosage form used is 50 mg QW, rather than 25 mg twice weekly, as this dosing has been determined to be

similar with respect to PK, efficacy (ACR20 responders at Week 8), and safety (Keystone, et al., 2004).

3.3 Selection of Study Population

3.3.1 Inclusion Criteria

Subjects with RA or PsO must meet the following criteria to be enrolled in this study:

1. Have completed 48 weeks of evaluations in CHS-0214-02 and, at Week 48, had at least an ACR20, or completed 48 weeks of evaluations in CHS-0214-04 and, at Week 48, had at least a PASI-50;
2. Women who either:
   a) Are of childbearing potential with a negative urine pregnancy test at Week 0 Day 0 who agree to use 1 or more approved methods of birth control (hormonal contraception, intrauterine device, diaphragm plus spermicide, condom plus spermicide, or abstinence from heterosexual intercourse—abstinence from heterosexual intercourse will be acceptable only if it is the preferred and usual lifestyle of the subject regardless of study participation; abstinence should be practiced for the duration of the study [study duration includes the Follow-up Visit 28 days after the last dose of study drug]); or
   b) Have been postmenopausal for at least 2 years (with amenorrhea for at least 1 year) or have had a hysterectomy, bilateral salpingo-oophorectomy, or tubal ligation prior to signing the informed consent; and
3. Able and willing to give written informed consent prior to performance of any study related procedures.

3.3.2 Exclusion Criteria

Subjects who meet the following criterion will be excluded from participation in this study:

1. Men whose partners may become pregnant (do not agree to use contraception or who are not postmenopausal) or who may breastfeed during the study (Japan only specific exclusion).

3.3.3 Removal of Subjects from Therapy or Assessment

Subjects will be advised that they are free to withdraw from the study at any time for any reason. Subjects who discontinue study drug at any time will be encouraged to return for the Follow-up Visit 28 days after the last dose of study drug for safety and immunogenicity evaluations. Subjects may be withdrawn from study therapy or assessment prematurely for any of the following reasons:

- The subject experiences a serious adverse event (SAE) or medically important AE (e.g., serious or opportunistic infection related to study drug) that would preclude further treatment with study drug;
    - The subject develops a malignancy while on study drug, except as below:Please note, subjects who develop a malignancy while on study drug and who receive localized and non-invasive treatment may stay in the study per the Investigator's judgment;
- The subject requires medical treatment excluded by the protocol or that could present a safety risk to the subject;
- The subject is not willing to continue participation in the study (withdraws consent);
- The subject is lost to follow up;
- Lack of compliance with the provisions of the protocol;
- The subject experiences an increase in disease activity that requires additional or different therapy;
- The subject develops a positive response to the QuantiFERON®-TB Gold test at any time during the study, as defined by 2 consecutive positive tests (>2 IU/mL). During the study (every 12 months or more frequently for regions with a high incidence of TB, or to evaluate signs and symptoms that might be due to TB), if a patient has an indeterminate or low positive (0.35-2 IU/mL) or a positive (>2 IU/mL) QuantiFERON®-TB Gold test result, the QuantiFERON®-TB Gold test should be repeated. If the repeat test is indeterminate or low positive (0.35-2 IU/mL), the patient can continue in the study, providing symptoms and risk factors are all negative, i.e., the subject has not been exposed to TB, the chest x-ray is negative, and the Investigator does not believe the subject has latent TB. Only a conversion to positive (>2 IU/mL) on 2 consecutive tests would result in the subject not qualifying to continue in OLSES;
- The subject becomes pregnant while on study medication (the subject will immediately be withdrawn from study drug and all procedures for the Follow-up Visit will be conducted 28 days after the last dose of study drug);
- In the opinion of the Investigator, it is in the best interest of the subject to discontinue study participation;
- The subject has positive viral screen results; or
- The subject's Week 48 laboratory results of CHS-0214-02 or CHS-0214-04 are clinically significant.

If a subject withdraws prematurely from the study, study staff should make every effort to complete the full panel of assessments scheduled for the Follow-up Visit 28 days after the last dose of study drug (see Section 5.2.5).

The subject will be considered to have completed the study after undergoing follow-up evaluations 28 days after the last dose of study drug.

3.3.4 Discontinuation of Study by Sponsor

The Sponsor may suspend temporarily or terminate the study for any of the following reasons:

- The Sponsor receives marketing approval for CHS-0214 in Japan;
- Development of a previously unknown safety concern;
- The results of analyses indicate that either parent study (CHS-0214-02 or CHS-0214-04) did not meet its primary efficacy endpoints;
- Other events that have not been anticipated by the Sponsor; or
- Any other reason (e.g., an unexpected SAE not previously observed with etanercept or another TNF inhibitor is observed in the study).

4 TREATMENTS

4.1 Treatments Administered

CHS-0214 50 mg will be administered SC QW from Week 0 Day 0 through Week 48 except in Japan, where subjects may receive study drug until marketing approval. Note that all subjects in Japan enrolled in OLSES are from the CHS-0214-02 parent study.

4.2 Identity of Investigational Product

CHS-0214 50-mg prefilled syringes with passive needle guards or prefilled syringes in auto-injectors for SC injection (manufactured by Coherus BioSciences, Inc., Redwood City, CA 94065) will be supplied by the Sponsor.

CHS-0214 should be refrigerated between 2°C and 8°C (36°F and 46°F) in the kit provided to protect from light.

4.3 Labeling

Each study drug kit and syringe will be labeled according to country specific requirements.

4.4 Method of Assigning Subjects to Treatment Groups

Once the subject has signed the informed consent form (ICF), site personnel will assign a subject identification number (ID). The subject ID will include the site number (3 digits) and a 3-digit subject number assigned sequentially starting with 001. This number and the subject's initials will be utilized to identify the subject throughout the study period. Once the subject ID has been assigned, the site will contact the Interactive Voice Response System/Interactive Web-based Response System (IVRS/IWRS) to register the subject. They will also be requested to input the subject's ID from the parent study, CHS-0214-02 or CHS-0214-04.

Approximately 400 subjects will be assigned to receive CHS-0214 50 mg SC QW.

4.5 Selection of Doses in the Study

The recommended dose of Enbrel for adult subjects with RA is 50 mg given QW or 25 mg given twice weekly as a SC injection. (In Japan, the recommended dosage is 25 mg or 50 mg weekly or 10 mg or 25 mg twice weekly.) In this study, CHS-0214 will be administered at a recommended dose of 50 mg SC QW.

The recommended dosage of Enbrel for subjects with chronic moderate to severe PsO is 50 mg as a SC injection QW as a maintenance dose. In this study, CHS-0214 will be administered per the approved dosing regimen for chronic PsO at a dose of 50 mg QW.

4.6 Selection and Timing of Dosing for Each Subject

Study drug will consist of CHS-0214 50 mg and will be self-administered (or administered by a caregiver) SC QW for 48 weeks except in Japan, where subjects may receive study drug until marketing approval. Note that all subjects in Japan enrolled in OLSES are from CHS-0214-02 parent study

Subjects and/or caregivers will be instructed to continue to administer the study drug on approximately the same day and time QW. However, if an injection is planned on the day of a study visit, this injection should be performed after the completion of all visit procedures, so that the blood sample collected represents a trough serum sample (see Section 4.10). Subjects who miss a dose of study drug, for whatever reason, should administer or receive the missed dose before the next week's dose.

4.7 Blinding

The study will be conducted in an open-label manner. All subjects will receive CHS-0214.

4.8 Study Drug Dispensing

The study site will be supplied with a sufficient quantity of study drug to treat enrolled subjects. Open-label study drug will be shipped under appropriate storage conditions to site personnel according to the regulations of the study country. Each delivery must be acknowledged by the addressee by confirming receipt of the study drug shipment in IVRS/IWRS. Study drug will not be assigned to a subject until the site confirms receipt in the IVRS/IWRS system. Site personnel or the investigational storage manager will dispense study drug to each subject.

Prior to dispensing study drug, study personnel or the investigational storage manager should visually inspect each syringe for foreign particulate matter and discoloration. The solution may be colorless to pale yellow and clear to slightly opalescent in appearance. There may be small white particles of protein in the solution. This is not unusual for proteinaceous solutions. The syringes should not be dispensed if discolored or cloudy or if foreign or dark particulate matter is present, but other unaffected syringes in the kit should be dispensed at the discretion of the Investigator.

A dispensing log will be kept by site personnel or the investigational storage manager who will record the dates and quantity of the study drug kits dispensed to each subject at each visit. All used and unused syringes will be accounted for during the study using the subject's e-Diary entries and/or the numbers of provided and returned syringes. Study monitors will review and reconcile study

drug receipts, dispensing logs, and records of any study drug destruction to study drug on-hand.

The subject and/or caregiver will be instructed to place used syringes into the sharps container provided and return the sharps container to the clinic once it is full. A new sharps container will be provided to the subject and/or caregiver. The subject and/or caregiver will also be provided with cool packs should there be a need to bring unused study drug to the clinic for any reason (e.g., further training with self-injection or issues with study drug). At each study visit, sufficient syringes for dosing through the next study visit will be provided to the subject and/or caregiver.

Used and unused syringes may be destroyed on site per each Institution's Standard Operating Procedure or policy once the site's monitor has reviewed and confirmed drug accountability. Site personnel or the investigational product storage manager may also return any unused syringes to the Sponsor or designee once the site's monitor has reviewed and confirmed accountability.

4.9 Concomitant Medications

Any medications, both prescription and non-prescription, taken during this study will be recorded in the source documents and entered into the eCRFs.

Required or allowed and prohibited concomitant medications are listed below. These lists are not intended to be all-inclusive; Investigators must review each subject's case individually and use their clinical judgment.

4.9.1 Rheumatoid Arthritis

For subjects with RA, the following **concomitant medications are required or allowed** during the study provided that the subject has been on a stable dose (unless otherwise noted) (see Appendix C):

- A single non-steroidal anti-inflammatory drug (NSAID) at a dose not exceeding the maximum dose allowed per the prescribing instructions for that NSAID. *NOTE:* A topical NSAID used on a regular basis (at least daily) will be considered the subject's single NSAID permitted during the study. Topical NSAIDs taken on a regular basis should not be applied within 24 hours prior to each study visit. Occasional use of topical NSAIDs (less frequently than once per day) will not be considered as the subject's single NSAID and may be used in conjunction with another systemic NSAID (*NOTE*: a change in NSAID dose may be allowed for safety considerations only);
- Oral corticosteroid (≤ 10 mg prednisone per day or equivalent corticosteroid) providing the dose of prednisone or equivalent corticosteroid will remain stable for the duration of the study (*NOTE*: a change in prednisone dose may be allowed for safety considerations only);

- Methotrexate (MTX) at stable dose (≥ 8 mg/week to ≤ 25 mg/week, not to exceed local approved dose level) and at the dose the subject was receiving throughout the parent study (*NOTE*: a change in MTX dose may be allowed for safety considerations only). If the MTX dose was reduced below 8 mg/week in the parent study and remains stable, the subject may enter the OLSES study at that reduced dose;
- Folic or folinic acid at the dose and schedule prescribed by the subject's primary or personal physician to prevent MTX toxicity;
- Steroid injections should be kept at a minimum. The injected joint should be noted as swollen and tender in all subsequent joint counts going forward;
- Insulin for diabetes mellitus, replacement hormone therapy, and hormonal contraception; and
- All medications required to adequately treat AEs or concurrent medical conditions at the discretion of the Investigator.

For subjects with RA, the following **concomitant medications are prohibited** during the study (see Appendix C):

- Any biologic medication for any indication (other than insulin or hormones), other than study drug (including but not limited to tocilizumab [RoACTEMRA, Actemra], certolizumab pegol [CIMZIA], adalimumab [HUMIRA], anakinra [Kineret], abatacept [ORENCIA], infliximab [Remicade], rituximab [MabtThera, Rituxan], golimumab [SIMPONI]);
- Any kinase inhibitor for RA (e.g., tofacitinib citrate [XELJANZ]);
- Non-biological disease-modifying anti-rheumatic drugs (DMARDS), other than MTX (Rheumatrex, Trexall) (e.g., hydroxychloroquine [Plaquenil], oral or injectable gold, D-penicillamine, sulfasalazine [Azulfidine], leflunomide [Arava], and iguratimod [Careram, Kolbet]).;
- Parenteral steroids, intra-articular steroids (except as described above), or oral steroids > 10 mg prednisone per day or equivalent corticosteroid;
- Cyclophosphamide, azathioprine (Imuran), or any other chemotherapies or immunosuppressants; or
- Live vaccines.

4.9.2 Plaque Psoriasis

For subjects with PsO, the following **concomitant medications are allowed** during the study (see Appendix C):

- Mild (class 6-7 based on US classification system of topical steroids) topical corticosteroids on scalp, face, axillae, groin, and genitalia are allowed except within 24 hours prior to study visits;

- Mild/bland moisturizers/lubricants are allowed at any time except within 24 hours prior to study visits;
- Single NSAID use is not prohibited in this protocol; however, the dose should not exceed the maximum dose recommended for that NSAID; and
- All medications required to adequately treat AEs or concurrent medical conditions at the discretion of the Investigator.

For subjects with PsO, the following **concomitant medications are prohibited** during the study (see Appendix C):

- All biologics (other than study drug, insulin and hormone replacement therapy) for any indication (including but not limited to tocilizumab [RoACTEMRA, Actemra], certolizumab pegol [CIMZIA], etanercept [Enbrel], adalimumab [HUMIRA], anakinra [Kineret], abatacept [ORENCIA], infliximab [Remicade], rituximab [Mathera, Rituxan], golimumab [Simponi ARIA], ustekinumab [STELARA]);
- Any kinase inhibitor for any reason (e.g., tofacitinib citrate [XELJANZ]);
- Any PDE4 inhibitor (e.g., apremilast [Otezla]);
- Systemic psoriasis treatments such as oral retinoids, MTX, or cyclosporine; systemic glucocorticoids, vitamin A or D analog preparations; dithranole; psoralen plus ultraviolet A (PUVA); ultraviolet B (UVB) phototherapy;
- Drugs that may cause new onset or exacerbation of psoriasis (including but not limited to; beta-blockers, lithium and anti-malarials) unless the subject has been on a stable dose for 6 months prior to enrollment in OLSES without exacerbation of psoriasis;
- Use of topical corticosteroids (class 1-5); and
- Live vaccines

4.10 Treatment Compliance

Study drug will be dispensed in single-use prefilled syringes with passive needle guards or as a prefilled syringe in an auto-injector in a quantity required for the period of time until the next visit. Subjects and/or caregivers will be reminded how to transport and store the study drug, to place used study drug syringes in the provided sharps container, and to return all used study drug syringes when the sharps container is full. If the subject is required to return any unused study drug to the site, the unused study drug should be transported using the provided cold packs and insulated cooler.

Subjects and/or caregivers will utilize an e-Diary to record information about the weekly injections through Week 48 and possible ISRs. The study staff will help the subject and/or caregiver re-register into the e-Diary system at the time of the

first visit. Subjects will access the e-Diary via a web-based system or telephone, if available in the region/country.

Study staff and subjects will be notified if the subject and/or caregiver does not enter information into the e-Diary system within 24 hours of the expected date/time of a dose. Site staff should follow up with subjects to ensure subjects are receiving doses per protocol and provide retraining as necessary. At each post-dosing study visit through Week 48 and at the Follow-up Visit 28 days after the last dose of study drug for subjects who discontinue study drug prior to or at Week 48, study staff will review the e-Diary entries with the subject and/or caregiver and provide retraining as necessary.

Compliance and possible ISRs to study drug during the first 48 weeks of receipt of study drug will be assessed by the Investigator and study staff based on study drug use recorded by the subject and/or caregiver in the e-Diary. Subjects and/or caregivers who have had any compliance issues will be re-educated by the Investigator or study staff on the importance of taking study drug weekly.

Subjects and/or caregivers should be instructed to inject study drug on a regular weekly schedule and not to inject study drug on the day of a study visit until all visit procedures are complete so that a trough serum sample may be obtained prior to dosing.

5 MEASUREMENTS AND EVALUATIONS

5.1 Schedules of Procedures

The schedules of procedures performed at each clinic visit are presented in **Error! eference source not found.** for RA subjects and **Error! Reference source not found.** for PsO subjects.

Note that all subjects in Japan enrolled in OLSES are from CHS-0214-02 parent study.

All PsO subjects will receive CHS-0214 for a no longer than 48 weeks.

Table 1: Schedule of Procedures for Subjects with Rheumatoid Arthritis

Day	0	28	84	168	252	336		
Week	0*	4	12	24	36	48	Quarterly Visits[a]	28 Days Post Last Dose
Window	Dosing	± 3 Days	± 7 Days	± 7 Days	± 7 Days	± 7 Days	± 7 Days	± 3 Days
Study Procedures								
Informed consent	X[b]					X[c]		
Assign subject ID	X[b]							
Contact IVRS/IWRS	X[b]	X	X	X	X	X	X	X
Physical examination[d]	**	X	X	X	X	X	X	X[e]
Vital signs[f]	**	X	X	X	X	X	X	X
Concomitant medications	**	X	X	X	X	X	X	X
ECG	**					X	X[g]	X[h]
Hematology[i]	**			X		X	X[j]	X
Chemistry[k]	**			X		X	X[j]	X
Urinalysis[l]	**			X		X	X[j]	X
Viral Screening (HBsAg, HBcAb, HBsAb[m], HCV, HIV)[n]	X[b]					X[o]	X[g]	
QuantiFERON®-TB Gold	**					X	X[g]	
66/68 SJC/TJC assessment	**	X	X	X	X	X	X	
Subject's pain assessment (VAS)	**	X	X	X	X	X	X	
hs-CRP	**	X	X	X	X	X	X	
HAQ-DI	**	X	X	X	X	X	X	
SGA (VAS)[p]	**	X	X	X	X	X	X	
PGA (VAS)[p]	**	X	X	X	X	X	X	
Serum sample (trough retention sample)[q]	**	X	X	X	X	X	X[j]	X
Serum sample for ADA (pre-dose on dosing days)[q]	**	X	X	X	X	X	X[j]	X
Urine pregnancy test[r]	**[s]	X	X	X	X	X	X	X
Assess AEs	**	X	X	X	X	X	X	X
Injection site assessment[t]	**	X	X	X	X	X	X	X
e-Diary review and/or compliance evaluation	**	X	X	X	X	X		
Drug dispensing	X[b]	X	X	X	X	X[u]	X[u]	

ACR20 = at least a 20% improvement from Baseline according to American College of Rheumatology criteria; ADA = anti-drug antibody; AE = adverse event; ECG = electrocardiogram; HAQ-DI = Health Assessment Questionnaire-Disability Index; HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HBsAb=Hepatitis B surface antibody; HCV = hepatitis C virus; HIV = human immunodeficiency virus; hs-CRP = high sensitivity C-reactive protein; ID = identification number; ISR = injection site reaction; IVRS = interactive voice response system; IWRS = interactive web response system; OLSES = open-label safety extension study; PGA = Physician's Global Assessment; QW = every week; RA = rheumatoid arthritis; SGA = subject's global assessment of disease activity; SJC = swollen joint count; TJC = tender joint count; VAS = visual analog scale.

* The Week 0 Visit of OLSES is considered to correspond to the Week 48 Visit of CHS-0214-02. An interval of ≤1 month (unless an interval >1 month is approved by the Sponsor per subject) between completion of CHS-0214-02 and start of OLSES is allowed. Subjects awaiting hs-CRP results to determine if they meet ACR20 criteria can enroll in OLSES after hs-CRP results are available and it is determined ACR20 criteria are met. Therefore, for these subjects, the Day 0 Visit for OLSES will not coincide exactly with (but, for assessments, will be considered to correspond to) the Week 48 Visit of CHS-0214-02.

** Same evaluations/procedures as for Week 48 of CHS-0214-02; these evaluations will serve as baseline evaluations for this study.

a Begins with the Week 60 Visit for subjects in Japan who continue participation in OLSES beyond Week 48.

b A subject who meets ACR20 criteria based on hs-CRP results not available at the Week 48 Visit of CHS-0214-02 will be asked to return to the clinic for a separate OLSES Week 0 Day 0 Visit in addition to the Week 48 Visit of CHS-0214-02, at which time informed consent will be obtained, subject ID will be assigned, blood samples for viral screening will be obtained, IVRS/IWRS will be contacted to register the subject

Table 1: Schedule of Procedures for Subjects with Rheumatoid Arthritis

in the study, and study drug will be dispensed.

c Subjects in Japan will consent on or before their OLSES Week 48 Visit to be able to continue participation in OLSES beyond Week 48.

d Abbreviated physical examinations are conducted at the Week 48 Visit in the parent study (considered to correspond to the Week 0 Day 0 Visit in this study) and all the subsequent visits. Abbreviated physical examinations will consist of respiratory, gastrointestinal, musculoskeletal, and cardiovascular system evaluations and evaluations of other physical conditions of note.

e Weight will be recorded at the Follow-up Visit 28 days after the last dose of study drug.

f Vital signs include blood pressure (*NOTE*: an arm or wrist cuff is acceptable); heart rate; respiratory rate; and oral, aural, or axillary temperature and are to be obtained after the subject has rested in a seated position for at least 5 minutes.

g Repeat every 12 months for subjects in Japan who continue participation in OLSES beyond Week 48.

h Perform ECG at the Follow-up Visit 28 days after the last dose of study drug for those subjects who discontinue study drug

i Hematology parameters include hematocrit, hemoglobin, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, and mean corpuscular volume, red blood cell count, white blood cell count with differential, reticulocyte count, and platelet count.

j Perform every 6 months for subjects in Japan who continue participation in OLSES beyond Week 48.

k Chemistry parameters include alkaline phosphatase; sodium; potassium; total protein; calcium; chloride; bicarbonate; glucose; creatine phosphokinase; lactate dehydrogenase; alanine aminotransferase; aspartate aminotransferase; albumin; total, direct and indirect bilirubin; blood urea nitrogen; creatinine; and uric acid.

l Urinalysis parameters include pH, specific gravity, protein, glucose, leukocyte esterase, bilirubin, blood, nitrite, and ketones. A urine microscopic examination will be performed when there are any abnormalities on any of the following 3 dipstick results: leukocyte esterase, blood, or nitrite.

m Japan only (see Section 5.2.1).

n Perform HIV and hepatitis screen testing prior to subject enrolling in OLSES (the subject may be enrolled in OLSES prior to receipt of results); assess ongoing participation in OLSES upon receipt of results.

o Perform for subjects in Japan who continue participation in OLSES beyond Week 48.

p Perform PGA (VAS) prior to SGA (VAS).

q Blood samples will be collected (pre-dose on dosing days) and serum retained at each visit through Week 48 and every 6 months for subjects in Japan who continue participation in OLSES beyond Week 48 for possible evaluation of CHS-0214 serum concentrations, ADA, or other tests as necessary to evaluate adverse effects or compliance. The exact date and time of each sample collection will be recorded.

r Perform for female subjects who are of childbearing potential and not surgically sterile at the Week 0 Day 0 Visit, and at the Follow-up Visit 28 days after the last dose of study drug; for these subjects using abstinence as birth control, perform at every visit.

s A urine pregnancy test will be required on Week 0 Day 0 if Week 0 does not coincide with Week 48 of the parent study.

t Record ISRs observed by site personnel as AEs.

u Perform only for the subjects in Japan who consent to continue participation in OLSES beyond Week 48. If this visit is the subject's last visit, do not dispense study drug.

Table 2: Schedule of Procedures for Subjects with Plaque Psoriasis

Day	**0**	**28**	**84**	**168**	**252**	**336**	**28 Days Post Last Dose**
Week	**0***	**4**	**12**	**24**	**36**	**48**	**4 Weeks Post Last Dose**
Window	**Dosing**	**± 3 Days**	**± 7 Days**	**± 7 Days**	**± 7 Days**	**± 7 Days**	**± 3 Days**
Study Procedures							
Informed consent	X						
Assign subject ID	X						
Contact IVRS/IWRS	X	X	X	X	X	X	X
Physical examination[a]	**	X	X	X	X	X	X[b]
Vital signs[c]	**	X	X	X	X	X	X
Concomitant medications	**	X	X	X	X	X	X
ECG	**					X	X[d]
Hematology[e]	**			X		X	X
Chemistry[f]	**			X		X	X
Urinalysis[g]	**			X		X	X
Viral Screening (HBsAg, HCV, HIV)[h]	X						
QuantiFERON®-TB Gold	**					X	
PASI assessment for subjects with PsO	**	X	X	X	X	X	
SGA (VAS)	**	X	X	X	X	X	
PSGA	**	X	X	X	X	X	
Serum sample (trough retention sample)[i]	**	X	X	X	X	X	X
Serum sample for ADA (pre-dose on dosing days)	**	X	X	X	X	X	X
Urine pregnancy test[j]	**[k]	X	X	X	X	X	X
Assess AEs	**	X	X	X	X	X	X
Injection site assessment[l]	**	X	X	X	X	X	X
e-Diary Review and/or Compliance Evaluation	**	X	X	X	X	X	X
Drug dispensing	X	X	X	X	X		

ADA = anti-drug antibody; AE = adverse event; ECG = electrocardiogram; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HIV = human immunodeficiency virus; ID = identification number; ISR = injection site reaction; IVRS = interactive voice response system; IWRS = interactive web response system; OLSES = open-label safety extension study; PASI = Psoriasis Area and Severity Index; PSGA = Physician's Static Global Assessment; PsO = plaque psoriasis; QW = every week; SGA = subject's global assessment of disease activity; VAS = visual analog scale.

* The Week 0 Visit of this study is considered to correspond to the Week 48 Visit of CHS-0214-04. An interval of ≤1 month (unless an interval >1 month is approved by the Sponsor per subject) between completion of the CHS-0214-04 and start of OLSES is allowed.

** Same evaluations/procedures as for Week 48 of CHS-0214-04; these evaluations will serve as baseline evaluations for this study.

a. Abbreviated physical examinations are conducted at the Week 48 Visit in the parent study (considered to correspond to the Week 0 Day 0 Visit in this study) and all the subsequent visits. Abbreviated physical examinations will consist of respiratory, gastrointestinal, musculoskeletal, and cardiovascular system evaluations and evaluations of other physical conditions of note.

b. Weight will be recorded at the Follow-up Visit 28 days after the last dose of study drug.

c. Vital signs include blood pressure(NOTE: an arm or wrist cuff is acceptable); heart rate; respiratory rate; and oral, aural, or axillary temperature and are to be obtained after the subject has rested in a seated position for at least 5 minutes.

d. Perform ECG 28 days after last dose of study drug for those subjects who discontinue study drug prior to Week 48.

e. Hematology parameters include hematocrit, hemoglobin, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, and mean corpuscular volume, red blood cell count, white blood cell count with differential, reticulocyte count, and platelet count.

f. Chemistry parameters include alkaline phosphatase; sodium; potassium; total protein; calcium; chloride; bicarbonate; glucose; creatine phosphokinase; lactate dehydrogenase; alanine aminotransferase; aspartate aminotransferase; albumin; total, direct and indirect bilirubin; blood urea nitrogen; creatinine; and uric acid.

Table 2: Schedule of Procedures for Subjects with Plaque Psoriasis

g. Urinalysis parameters include pH, specific gravity, protein, glucose, leukocyte esterase, bilirubin, blood, nitrite, and ketones. A urine microscopic examination will be performed when there are any abnormalities on any of the following 3 dipstick results: leukocyte esterase, blood, or nitrite.
h. Perform HIV and hepatitis screen testing prior to subject enrolling in OLSES (the subject may be enrolled in OLSES prior to receipt of results); assess ongoing participation in OLSES upon receipt of results.
i. Blood samples will be collected (pre-dose on dosing days) and serum retained at each visit for possible evaluation of CHS-0214 serum concentrations, ADA, or other tests as necessary to evaluate adverse effects or compliance. The exact date and time of each sample collection will be recorded.
j. Perform for female subjects who are of childbearing potential and not surgically sterile at the Week 0 Day 0 Visit and at the Follow-up Visit 28 days after the last dose of study drug; for these subjects using abstinence as birth control, perform at every visit.
k. A urine pregnancy test will be required on Week 0 Day 0 if Week 0 does not coincide with Week 48 of the parent study.
l. Record ISRs observed by site personnel as AEs.

5.2 Study Schedule

5.2.1 Week 0 Day 0

The Week 0 Day 0 Visit of this study is considered to correspond to the Week 48 Visit of the parent study, CHS-0214-02 or CHS-0214-04. An interval of ≤1 month (unless an interval >1 month is approved by the Sponsor for the subject) between completion of the parent study and start of OLSES is allowed. The following procedures will be performed:

- Obtain written informed consent;
- Assign subject ID in sequential order;
- Collect blood samples for viral screening (hepatitis B surface antigen [HBsAg], hepatitis B core antibody [HBcAb], hepatitis B surface antibody [HBsAb; Japan only], hepatitis C virus, and human immunodeficiency virus)
- If Week 0 does not coincide with Week 48 of the parent study, perform urine pregnancy test for female subjects who are of childbearing potential and not surgically sterile (see Appendix I);
- **In Japan**
  - In accordance with current Japanese Society of Hepatology guidelines for the management of hepatitis B virus (HBV) infection (Drafting Committee for Hepatitis Management Guidelines and the Japan Society of Hepatology, 2014):
    - In an HBsAg negative subject, if HBsAb is positive and there is documented evidence of HBV vaccination, do not initiate nucleotide/nucleoside analogue therapy and continue the subject in the study.
    - If HBsAb is positive and there is no documented evidence of HBV vaccination, HBV DNA will be evaluated.
    - If HBV DNA is ≥2.1 log copies per mL, initiate nucleotide/nucleoside analogue therapy and continue the subject in the study.
    - If HBV DNA is <2.1 log copies/mL, the subject can continue in the study.
  - In all cases, monitor liver function tests per current protocol.
- Contact the IVRS/IWRS to register the subject in the study; and
- Dispense study drug (see Section 4.8).

The Investigator should review CHS-0214-02 or CHS-0214-04 Week 48 (OLSES Week 0/Day 0) assessment results (including viral and QuantiFERON®-TB Gold test results) when they are available to ensure the subject's continuation in

OLSES is appropriate. The QuantiFERON®-TB Gold test can be repeated once using a fresh sample in a subject with an indeterminate result or low positivity (defined as QuantiFERON®-TB antigen minus Nil value = 0.35-2 IU/mL).

If the repeat test is indeterminate or low positive (0.35-2 IU/mL), the patient can continue in the study, providing symptoms and risk factors are all negative, i.e., the subject has not been exposed to TB, the chest x-ray is negative, and the investigator does not believe the subject has latent TB. Only a conversion to positive (>2 IU/mL) on 2 consecutive tests would result in the subject being terminated from the study (Raychaudhuri, Nguyen, Raychaudhuri, & Gershwin, 2009). Subjects with a history of adequately treated TB may have signs of obsolete pulmonary TB (consistent with scarring) on chest x-ray. These subjects may continue on OLSES provided that their QuantiFERON®-TB Gold test results is negative or low positive (< 2.0 IU/mL). A repeat chest x-ray may be obtained to ensure that there is no change in the obsolete lesions. In addition:

- Subjects with RA are eligible for continuation into OLSES if they meet the ACR20 criteria at the Week 48 Visit of the parent study. If Week 48 hs-CRP results are needed to determine whether or not ACR20 criteria are met and not yet available, enrollment into OLSES will be delayed until hs-CRP results are available and it is determined that ACR20 criteria are met. In this case, the subject will be asked to return to the clinic for a separate OLSES Week 0 Day 0 Visit. At this visit, informed consent will be obtained, subject ID will be assigned, blood samples for viral screening will be obtained, urine pregnancy testing will be performed for females who are of childbearing potential and not surgically sterile; IVRS/IWRS will be contacted to register the subject in the study; and study drug will be dispensed. Every effort should be made to maintain the QW dosing schedule.
- For subjects with PsO, eligibility for continuation will be determined by calculation of Psoriasis Area and Severity Index (PASI). Subjects are required to have had at least a PASI-50 from Baseline at Week 48 in the parent study.

5.2.2 Week 4 Day 28 (± 3 Days), Week 12 Day 84 (± 7 Days) and Week 36 Day 252 (± 7 Days)

The following procedures will be performed:

- Perform abbreviated physical examination (see Section7.2);
- Obtain vital sign measurements, including blood pressure (*NOTE:* an arm or wrist cuff is acceptable), heart rate, respiratory rate, and body temperature (using oral, aural, or axillary thermometer), after the subject has rested in a seated position for at least 5 minutes (see Section 7.3);
- Record concomitant medications (see Section 4.9);

- Collect pre-dose (trough) blood sample for retained serum (see Section 7.8);
- Collect pre-dose blood sample for ADA testing (see Section 7.6);
- Perform urine pregnancy test for female subjects who are of childbearing potential and not surgically sterile using who are using abstinence as birth control (see Appendix I);
- Assess and record AEs (see Section 7.1);
- Perform injection site assessment and record ISRs observed during the examination as AEs (see Section 7.1 and Section 7.2);
- Review subject's e-Diary for any issues with compliance or with injecting study drug;
- Contact the IVRS/IWRS to assign study drug kits to be dispensed;
- Dispense study drug (see Section 4.8);
- At Week 36, remind subject to bring all used and unused study drug to their Week 48 Visit;
- For subjects with RA:
    - Perform Physician's Global Assessment (PGA) visual analog scale (VAS) (see Appendix G) prior to subject's global assessment of disease activity (SGA) (VAS) (see Appendix F);
    - Perform SGA (VAS) (see Appendix F) after PGA (VAS) (see Appendix G);
    - Perform joint assessment (66/68 SJC/TJC assessment) (see Appendix D);
    - Obtain blood sample for hs-CRP (see Section 6.1.1.6 and Appendix I)
    - Administer HAQ-DI (see Appendix K); and
    - Perform subject's pain assessment (VAS) (see Appendix E).
- For subjects with PsO:
    - Perform PASI assessment (see Appendix J);
    - Perform Physician's Static Global Assessment (PSGA) (see Appendix H) prior to SGA (VAS) (see Appendix F); and
    - Perform SGA (VAS) (see Appendix F) after PSGA (see Appendix H).

5.2.3 Week 24 Day 168 (± 7 Days)

The following procedures will be performed:

- Perform abbreviated physical examination (see Section 7.2);
- Obtain vital sign measurements, including blood pressure (*NOTE:* an arm or wrist cuff is acceptable), heart rate, respiratory rate, and body temperature (using oral, aural, or axillary thermometer), after the subject has rested in a seated position for at least 5 minutes (see Section 7.3);
- Record concomitant medications (see Section 4.9);
- Collect blood samples for chemistry and hematology assessments (see Appendix I);
- Collect urine sample for urinalysis (see Appendix I);
- Collect pre-dose (trough) blood sample for retained serum (see Section 7.8);
- Collect pre-dose blood sample for ADA testing (see Section 7.6);
- Perform urine pregnancy test for female subjects who are of childbearing potential and not surgically sterile who are using abstinence as birth control (see Appendix I);
- Assess and record AEs (see Section 7.1);
- Perform injection site assessment and record ISRs observed during the examination as AEs (see Section 7.1 and Section 7.2);
- Review subject's e-Diary for any issues with compliance or with injecting study drug;
- Contact the IVRS/IWRS to assign study drug kits to be dispensed;
- Dispense study drug (see Section 4.8);
- For subjects with RA:
    - Perform PGA (VAS) (see Appendix G) prior to SGA (VAS) (see Appendix F);
    - Perform SGA (VAS) (see Appendix F) after PGA (VAS) (see Appendix G);
    - Perform joint assessment (66/68 SJC/TJC assessment) (see Appendix D);
    - Obtain blood sample for hs-CRP (see Section 6.1.1.6 and Appendix I);
    - Administer HAQ-DI (see Appendix K); and
    - Perform subject's pain assessment (VAS) (see Appendix E).

- For subjects with PsO:
  - Perform PASI assessment (see Appendix J);
  - Perform PSGA (see Appendix H) prior to SGA (VAS) (see Appendix F); and
  - Perform SGA (VAS) (see Appendix F) after PSGA (see Appendix H).

5.2.4 Week 48 Day 336 (± 7 days)

The following procedures will be performed:

- Perform abbreviated physical examination (see Section 7.2);
- Obtain vital sign measurements, including blood pressure (*NOTE:* an arm or wrist cuff is acceptable), heart rate, respiratory rate, and body temperature (using oral, aural, or axillary thermometer), after the subject has rested in a seated position for at least 5 minutes (see Section 7.3);
- Record concomitant medications (see Section 4.9);
- Perform resting 12-lead ECG (see Section 7.4);
- Collect blood samples for chemistry and hematology assessments (see Appendix I);
- Collect urine sample for urinalysis (see Appendix I);
- Obtain blood sample for QuantiFERON®-TB Gold test to rule out active or latent TB (see Appendix I);
- Collect pre-dose (trough) blood sample for retained serum (see Section 7.7);
- Collect pre-dose blood sample for ADA testing (see Section 7.6);
- Perform urine pregnancy test for female subjects who are of childbearing potential and not surgically sterile who are using abstinence as birth control (see Appendix I);
- Assess and record AEs (see Section 7.1);
- Perform injection site assessment and record ISRs observed during the examination as AEs (see Section 7.1 and Section 7.2);
- Review subject's e-Diary for any issues with compliance or with injecting study drug; and
- For subjects not continuing study participation beyond Week 48, contact the IVRS/IWRS to register subject's completion of treatment.
- For subjects with RA:

  - Perform PGA (VAS) (see Appendix G) prior to SGA (VAS) (see Appendix F);
  - Perform SGA (VAS) (see Appendix F) after PGA (VAS) (see Appendix G);
  - Perform joint assessment (66/68 SJC/TJC assessment) (see Appendix D);
  - Obtain blood sample for hs-CRP (see Section 6.1.1.6 and Appendix I);
  - Administer HAQ-DI (see Appendix D);
  - Perform subject's pain assessment (VAS) (see Appendix E);
- For subjects in Japan continuing study participation beyond Week 48:
  - Obtain written informed consent on or before the Week 48 Visit;
  - Collect blood samples for viral screening (HBsAg, HBcAb, HBsAb, hepatitis C virus, and human immunodeficiency virus);
  - Contact the IVRS/IWRS for study drug kit assignment; and
  - Dispense study drug (see Section 4.8).
- For subjects with PsO:
  - Perform PASI assessment (see Appendix J);
  - Perform PSGA (see Appendix H) prior to SGA (see Appendix F); and
  - Perform SGA (VAS) (see Appendix F) after PSGA (see Appendix H).

Quarterly Visits (± 7 days)—Subjects in Japan with RA Only, Beginning at Week 60The following procedures will be performed quarterly:

- Perform abbreviated physical examination (see Section 7.2);
- Obtain vital sign measurements, including blood pressure (*NOTE:* an arm or wrist cuff is acceptable), heart rate, respiratory rate, and body temperature (using oral, aural, or axillary thermometer), after the subject has rested in a seated position for at least 5 minutes (see Section 7.3);
- Record concomitant medications (see Section 4.9);
- Perform urine pregnancy test for female subjects who are of childbearing potential and not surgically sterile who are using abstinence as birth control (see Appendix I);
- Assess and record AEs (see Section 7.1);

- Perform injection site assessment and record ISRs observed during the examination as AEs (see Section 7.1 and Section 7.2);
- Perform PGA (VAS) (see Appendix G) prior to SGA (VAS) (see Appendix F);
- Perform SGA (VAS) (see Appendix F) after PGA (VAS) (see Appendix G);
- Obtain blood sample for hs-CRP (see Section 6.1.1.6 and Appendix I)
- Perform joint assessment (66/68 SJC/TJC assessment) (see Appendix D);
- Administer HAQ-DI (see Appendix D);
- Perform subject's pain assessment (VAS) (see Appendix E); and
- Contact the IVRS/IWRS to assign study drug kits to be dispensed unless subject is discontinuing in the study; if so, contact the IVRS/IWRS to register subject's completion of treatment.
- Dispense study drug for subjects continuing in the study unless this is subject's last visit (see Section 4.8).

The following procedures will be performed every 6 months:

- Collect blood samples for chemistry and hematology assessments (see Appendix I);
- Collect urine sample for urinalysis (see Appendix I);
- Collect pre-dose (trough) blood sample for retained serum (see Section 7.7);
- Collect pre-dose blood sample for ADA testing (see Section 7.6); and

The following procedures will be performed annually beyond Week 48:

- Perform resting 12-lead ECG (see Section 7.4);
- Collect blood samples for viral screening (HBsAg, HBcAb, HBsAb, hepatitis C virus, and human immunodeficiency virus); and
- Obtain blood sample for QuantiFERON®-TB Gold test to rule out active or latent TB (see Appendix I).

5.2.5 Follow-up Visit 28 Days (± 3 Days) Post Last Dose of Study Drug

The following procedures will be performed:

- Contact the IVRS/IWRS to register subject's discharge from the study;
- Perform abbreviated physical examination (see Section 7.2);
- Measure weight (see Section 7.2);

- Obtain vital sign measurements, including blood pressure (*NOTE:* arm or wrist cuff is acceptable), heart rate, respiratory rate, and body temperature (using oral, aural, or axillary thermometer), after the subject has rested in a seated position for at least 5 minutes (see Section 7.3);
- Record concomitant medications (see Section 4.9);
- Perform resting 12-lead ECG at the Follow-up Visit 28 days after the last dose of study drug for subjects who discontinue study drug (see Section 7.4);
- Collect blood samples for chemistry and hematology assessments (see Appendix I);
- Collect urine sample for urinalysis (see Appendix I);
- Collect trough blood sample for retained serum (see Section 7.7);
- Collect blood sample for ADA testing (see Section 7.6);
- Perform urine pregnancy test for female subjects who are of childbearing potential and not surgically sterile (see Appendix I);
- Assess and record AEs (see Section 7.1);
- Perform injection site assessment and record ISRs observed during the examination as AEs (see Section 7.1 and Section 7.2); and

5.3 Informed Consent

All subjects will be informed of the nature and purpose of the study prior to any study-related assessments or procedures and requested to review and to sign an Institutional Review Board/Ethics Committee (IRB/EC) approved consent form specific for either RA or PsO. Subjects in Japan with RA will consent on or before their Week 48 Visit to be able to continue participation in OLSES beyond Week 48.

5.4 Medical and Surgical History

The subject's medical and surgical history will not be collected in OLSES but can be referenced from the parent study if required.

6 EFFICACY MEASUREMENTS

6.1 Primary Efficacy Endpoints

6.1.1 Rheumatoid Arthritis

In subjects with RA, durability of response (maintenance of an ACR20 response or greater at each assessment) will be measured at each visit based on the following assessments:

- SJC;
- TJC;
- Subject's pain assessment (VAS);
- SGA (VAS);
- PGA (VAS);
- HAQ-DI; and
- hs-CRP.

6.1.1.1 66/68 Swollen Joint Count/Tender Joint Count Assessments

All joint count assessors must demonstrate proficiency at performing joint counts. Every attempt should be made to use the same assessor for each subject throughout the study. Joints that were injected during the CHS-0214-02 study should be noted as swollen and tender during the OLSES (see Appendix D). The 66/68 SJC/TJC will be assessed at Weeks 0 (as the Week 48 assessment of the parent study), 4, 12, 24, 36, and 48 and, for subjects in Japan who continue participation in OLSES beyond Week 48, at each quarterly visit thereafter.

6.1.1.2 Subject's Pain Assessment (Visual Analog Scale)

The subject will rate the severity of pain at the time of visit using a horizontal 10-cm VAS with the best anchor and lowest score on the left side and worst anchor and highest score on the right side (Felson, et al., 2011). The subject's pain VAS should be completed by the subject (see Appendix E) at Weeks 0 (as the Week 48 assessment of the parent study), 4, 12, 24, 36, and 48 and, for subjects in Japan who continue participation in OLSES beyond Week 48, at each quarterly visit thereafter.

6.1.1.3 Subject's Global Assessment (Visual Analog Scale)

The subject will rate the actual state of disease activity by indicating the answer to the question "Considering all of the ways your arthritis has affected you, how do you feel your arthritis is today?" on a horizontal 10-cm VAS with the anchors "very well" and "very poor" (see Appendix F) (Felson, et al., 2011). The SGA (VAS) will be conducted at Weeks 0 (as the Week 48 assessment of the parent study), 4, 12, 24, 36, and 48 and, for subjects in Japan who continue participation in OLSES beyond Week 48, at each quarterly visit thereafter.

6.1.1.4 Physician's Global Assessment (Visual Analog Scale)

The clinician will assess the subject's disease activity at the time of the visit by indicating the answer to the question "What is your assessment of the subject's current disease activity?" on a horizontal 10-cm VAS with the anchors "none" and "extremely active" (see Appendix G) (Felson, et al., 2011). The PGA should be conducted prior to conducting the SGA at Weeks 0 (as the Week 48 assessment of the parent study), 4, 12, 24, 36, and 48 and, for subjects in Japan who continue participation in OLSES beyond Week 48, at each quarterly visit thereafter.

6.1.1.5 HAQ-DI

The HAQ-DI is a validated 20-item assessment of a subject's functional abilities in 8 categories (Dressing and Grooming, Hygiene, Arising, Reach, Eating, Grip, Walking, Common Daily Activities) (see Appendix K). There are 4 response options ranging from "Without any Difficulty" to "Unable to Do," scored 0 to 3 (Fries, Spitz, Kraines, & Holman, 1980) (Kawai, 1995). In subjects with RA, the HAQ-DI will be administered at Weeks 0 (as the Week 48 assessment of the parent study), 4, 12, 24, 36, and 48 and, for subjects in Japan who continue participation in OLSES beyond Week 48, at each quarterly visit thereafter.

6.1.1.6 High Sensitivity C-Reactive Protein

Blood samples for measurement of hs-CRP will be collected at Weeks 0 (as the Week 48 assessment of the parent study), 4, 12, 24, 36, and 48 and, for subjects in Japan who continue participation in OLSES beyond Week 48, at each quarterly visit thereafter. In this study, hs-CRP is a marker of inflammation and is not being used as an assessment of cardiovascular risk. As such, the results of the hs-CRP test will not be shared with subjects.

6.1.2 Plaque Psoriasis

6.1.2.1 Psoriasis Area and Severity Index Score

All PASI score assessors must demonstrate proficiency at performing the PASI. Every attempt should be made to use the same assessor for each subject throughout the study.

In subjects with PsO, durability of response (maintenance of a PASI-50 response or greater at each assessment) will be based on scoring the PsO lesions on a scale of 0 to 4 for 3 characteristics: erythema, infiltration, and desquamation, weighted by the area of involvement (Fredriksson & Pettersson, 1978) (Feldman & Krueger, 2005) (see Appendix J). The lesions are scored within 4 anatomical regions: head, upper extremities, trunk, and lower extremities including buttocks. Within each of these regions, the area of involvement is scored on a scale of 0-6. The clinician will assess the subject's PsO lesions according to the PASI at Weeks 0 (as the Week 48 assessment of the parent study), 4, 12, 24, 36, and 48.

6.1.2.2 Physician's Static Global Assessment

The PSGA of Psoriasis will be assessed on a scale of 0 to 5, with 0 indicating no psoriasis (clear of disease), 1 (almost clear), and 2 or higher indicating more severe disease (see Appendix H).

The clinician's assessment should be made and recorded before attaining the subject's assessment (the SGA) at all visits. The PSGA will be performed at Weeks 0 (as the Week 48 assessment of the parent study), 4, 12, 24, 36, and 48.

6.1.2.3 Subject's Global Assessment

The SGA of Psoriasis will be assessed on a scale ranging from 0 (good) to 5 (severe) (Leonardi, et al., 2003) (see Appendix F). The SGA should be assessed at Weeks 0 (as the Week 48 assessment of the parent study), 4, 12, 24, 36, and 48.

6.2 Secondary Efficacy Endpoints (Rheumatoid Arthritis)

The secondary efficacy variable for RA subjects will include DAS28-CRP(4) <3.2 at Weeks 0, 4, 12, 24, 36, and 48 and, for subjects in Japan who continue participation in OLSES beyond Week 48, at each quarterly visit thereafter (Fransen & van Riel, 2009) (van Gestel, Haagsma, & van Riel, 1998) (Wells, et al., 2009) and remission rate (defined as DAS28-CRP[4] < 2.6 on all visits after DAS28-CRP(4) < 2.6 is achieved) (Fransen & van Riel, 2009) (Fries, Spitz, Kraines, & Holman, 1980), DAS28-CRP(4).

6.2.1 DAS28-CRP(4)

The DAS28-CRP(4) is a composite score (ranging from 0-9.4) calculated using the results of the 28 joint subset of the 66/68 SJC/TJC, hs-CRP level (mg/L), and Subject's Global Assessment (0-100 scale). The DAS28-CRP(4) is calculated using the following formula (DAS, 2013):

*0.56*sqrt(28TJC) + 0.28*sqrt(28SJC) + 0.36*ln(CRP+1) + 0.014* pt global VAS + 0.96.*

For DAS28-CRP(4), scores indicating high disease activity are > 5.1; low disease activity, < 3.2; and remission, < 2.6.

7 SAFETY MEASUREMENTS

Safety will be assessed by evaluating the incidence of and reason for discontinuations from study drug; TEAEs; ISRs; conversion of QuantiFERON®-TB Gold test to positive; changes in safety laboratory test, vital sign, 12-lead ECG, and physical examination findings; and immunogenicity (anti-CHS-0214 antibodies).

A list of the analytes to be measured for the safety evaluation is found in Appendix I. Laboratory test results must be evaluated by the Investigator as to their clinical significance. Any laboratory value considered by the Investigator to be clinically significant should be considered an AE.

7.1 Adverse Events

Ongoing AEs from the subject's involvement in CHS-0214-02 or CHS-0214-04 will continue to be followed in the OLSES. New AEs will be collected from the time the ICF is signed at the Week 0 Day 0 Visit through the Follow-up Visit 28 days after the last dose of study drug. New TEAEs will be those starting with OLSES dosing (Week 0 Day 0). An AE is any unfavorable medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product, which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product. All AEs, including observed or suspected problems, complaints, or symptoms, are to be recorded on the appropriate eCRF. Documentation must be supported by an entry in the subject's source document. Each AE is to be evaluated for duration, severity, and causal relationship with the study drug or other factors.

Whenever possible, a specific disease or syndrome rather than individual associated signs and symptoms should be identified by the Investigator and recorded on the eCRF. However, if an observed or reported sign or symptom is not considered a component of a specific disease or syndrome by the Investigator, it should be recorded as a separate AE on the eCRF.

Any ongoing AE from the CHS-0214-02 study or the CHS-0214-04 study should continue to be followed as an AE in OLSES.

Any clinically significant abnormal laboratory or other examination (e.g., ECG) findings that are detected at Week 48 of the CHS-0214-02 or CHS-0214-04 study or at any time during OLSES will be reported as an AE. The Investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant.

The ISRs observed during examination of injection sites by study staff should be recorded as AEs. The AE term "Injection Site Reaction" with the grade of AE consistent with the worst grade for any 1 of the characteristics of the ISR (pain, swelling, erythema, etc.) should be reported.

The ISRs reported by subjects will be recorded in each subject's e-Diary for study drug received through Week 48 and will not be recorded as AEs unless also observed by study staff.

7.1.1 Unexpected Adverse Drug Reaction

An unexpected adverse drug reaction is defined as an adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved product).

7.1.2 Grading and Intensity of Adverse Events

The Investigator will rate the intensity of each AE as mild, moderate, severe, or life threatening as outlined in the Guidance for Industry (FDA, 2007).

Severity or Toxicity Grading:

Grade 1: Mild – An event that is usually transient in nature and generally does not interfere with activities.

Grade 2: Moderate – An event that is sufficiently discomforting to interfere with activities.

Grade 3: Severe – An event that is incapacitating, with inability to work or perform normal daily activity.

Grade 4: Life Threatening – An event that is potentially life threatening and generally requires emergency medical treatment or hospitalization.

7.1.3 Relationship to Study Drug

The assessment of the relationship of an AE to the administration of study drug (yes, no) is a clinical decision based on all available information at the time of the completion of the eCRF.

No (unrelated, not related, no relation):
The time course between the administration of study drug and the occurrence or worsening of the AE rules out a causal relationship and another cause (concomitant drugs, therapies, complications, etc.) is suspected.

Yes (related):
The time course between administration of study drug and the occurrence or worsening of the AE is consistent with a causal relationship and no other cause can be identified (concomitant drugs, therapies, complications, etc.).

The following factors should also be considered:

- Temporal sequence from drug administration

The event should occur after study drug is given. The length of time from drug exposure to event should be evaluated in the clinical context of the event.

- Underlying, concomitant, intercurrent diseases

Each report should be evaluated in the context of the natural history and course of the disease being treated and any other disease the subject may have.

- Concomitant medication

Other drugs the subject is taking or the treatment the subject receives should be examined to determine whether any of them might be recognized to cause the event in question.

- Known response pattern for this class of drug

Clinical and/or preclinical data may indicate whether a particular response is likely to be a class effect.

- Exposure to physical and/or mental stresses

Exposure to stress might induce adverse changes in the recipient and provide a logical and better explanation for the event.

- Pharmacology and PK of the test drug

Known properties (absorption, distribution, metabolism, and excretion) of the test drug should be considered.

Unexpected Adverse Event—An unexpected AE is an experience not previously reported or an AE that occurs with specificity, severity, or frequency that is not consistent with the current Investigator's Brochure.

7.1.4 Serious Adverse Event Reporting

An SAE is any untoward medical occurrence that, at any dose:

- Results in death;
- Is life-threatening;

  NOTE: An AE or adverse reaction is considered "life-threatening" if, in the view of either the Investigator or Sponsor, its occurrence places the subject at immediate risk of death. It does not include an event that, had it occurred in a more severe form, might have caused death.

- Requires hospitalization or prolongation of an existing hospitalization;

  NOTE: Any hospital admission with at least 1 overnight stay will be considered an inpatient hospitalization. An emergency room visit without hospital admission will not be recorded as an SAE under this criterion, nor will hospitalization for a procedure planned or scheduled before signing of the ICF. However, unexpected complications and/or prolongation of hospitalization that occur during elective surgery should be recorded as AEs and assessed for seriousness.

  Admission to the hospital for social or situational reasons (i.e., no place to stay, live too far away to come for hospital visits) will not be considered inpatient hospitalizations.

- Results in a disability/incapacity;
- Is a congenital anomaly/birth defect; or
- Is an important medical event.

  NOTE: Medical or scientific judgment should be exercised in deciding whether reporting is 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 medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, development of drug dependency, or drug abuse.

7.1.5 Adverse Event Outcome

The Investigator will record the outcome of each AE as follows:

- Resolved
- Resolved with sequelae
- Ongoing
- Death
- Unknown

7.1.6 Serious Adverse Event Reporting – Procedure for Investigators

All SAEs occurring from the Week 0 Day 0 Visit through 28 days following the last administration of study drug must be reported to Medpace Clinical Safety within 24 hours of the knowledge of the occurrence. All SAEs occurring after the 28-day follow-up period, which the Investigator considers related to study drug, must also be reported to Medpace.

To report the SAE, the Investigator will complete the SAE form electronically in the electronic data capture (EDC) system for the study. When the form is completed, Medpace Safety personnel will be notified electronically and will retrieve the form. If the event meets serious criteria and it is not possible to access the EDC system, an e-mail should be sent to the e-mail address listed below or a call made to the Medpace SAE hotline (phone number listed below), and fax or e-mail the completed paper SAE form to Medpace (fax number/e-mail listed below) within 24 hours of awareness. When the EDC system becomes available, the SAE information must be entered within 24 hours of the system becoming available.

The Investigator will be requested to supply detailed information regarding the event. The SAE must also be reported to the reviewing IRB/EC per IRB/EC requirements and a copy of that report must be retained at the investigative site

and filed in the Investigator Site File in accordance with the requirements of that institution.

Safety Contact Information:

Medpace Clinical Safety
Medpace
5375 Medpace Way
Cincinnati, Ohio 45227
USA

Medpace SAE – USA:
Tel: +1-800-730-5779, ext. 2999 or +1-513-579-9911, ext. 2999
Fax: +1-866-336-5320 or +1-513-579-0444
e-mail: medpace-safetynotification@medpace.com

Medpace SAE hotline – Europe:
Telephone: +49 89 89 55 718 44
Fax: +49 89 89 55 718 104
e-mail: EUsafetynotification@medpace.com

Country specific toll-free numbers will be provided to the Investigators.

7.1.7 Serious Adverse Events Follow-up

The Investigator must continue to follow the subject until the SAE has subsided or until the condition becomes chronic in nature, stabilizes (in the case of persistent impairment) or the subject dies.

Within 24 hours of receipt of follow-up information, the Investigator must update the SAE form electronically in the EDC system for the study and submit any supporting documentation (e.g., subject discharge summary or autopsy reports) to Medpace Safety personnel via fax or e-mail. If it is not possible to access the EDC system, refer to the procedures outlined above (see Section 7.1.6) for initial reporting of SAEs.

7.1.8 Serious Adverse Event Reporting-Procedure for Sponsor

The Sponsor will send copies of reports of SAEs and/or suspected unexpected serious adverse reactions (SUSARs) as required to regulatory authorities, Investigators/institutions, and IRBs/ECs in compliance with all reporting requirements according to local regulations and Good Clinical Practice (GCP). For all active Investigators located in Europe, the Sponsor or designee will be responsible for reporting SUSARs and any other applicable SAEs to regulatory authorities including the European Medicines Agency, Investigators, and central or local ECs, as applicable, in accordance with national regulations in the countries where the study is conducted. SUSARs will be submitted within 7 days for fatal and life-threatening events and within 15 days for other serious events, unless otherwise required by national regulations.

7.2 Physical Examination

An abbreviated physical examination will be performed at each visit and will consist of respiratory, gastrointestinal, musculoskeletal, and cardiovascular system evaluations and evaluations of other physical conditions of note.

Study drug injection sites will be assessed at each study visit. An ISR observed during the examination of injection sites at each visit should be recorded on the ISR worksheet and be reported as an AE with the AE term "Injection Site Reaction" and the grade of AE consistent with the worst grade for any 1 of the characteristics of the ISR (pain, swelling, erythema, etc.).

Weight (kg) will be measured at Week 0 Day 0 (considered to correspond to the Week 48 Visit of the parent study). Subjects should be weighed wearing indoor, daytime clothing with no shoes. Before being weighed, subjects should empty their bladders.

In addition, weight will also be measured at the Follow-up Visit 28 days after the last dose of study drug for all subjects.

7.3 Vital Signs

Vital signs, including blood pressure (arm or wrist cuff are acceptable), heart rate, respiratory rate, and body temperature (C°) (using an oral, aural, or axillary thermometer), will be measured at Weeks 0 (as the Week 48 assessment of the parent study), 4, 12, 24, 36, and 48 as well as at the Follow-up Visit 28 days after the last dose of study drug for all subjects. In addition, for subjects in Japan who continue participation in OLSES beyond Week 48, vital signs will be measured at each quarterly visit after Week 48. The following standardized processes will be used:

- The subject should sit for 5 minutes with feet flat on the floor and his/her measurement arm supported so that the midpoint of the manometer cuff is at heart level;
- A mercury sphygmomanometer or automatic blood pressure device with an appropriately sized cuff with the bladder centered over the brachial artery (*NOTE:* a wrist cuff centered over the radial artery is also acceptable) should be used;
- Blood pressure and heart rate should then be measured and recorded.

Blood pressure should be recorded to the nearest 2 mm Hg mark on the manometer or to the nearest whole number on an automatic device.

7.4 Electrocardiogram

A resting 12-lead ECG will be performed after the subject has been in the supine position for at least 10 minutes. The ECG will include all 12 standard leads and will be recorded at a paper speed of 25 mm/sec. Standard ECG parameters will be measured, including RR, PR, QTc intervals, and QRS duration. All ECGs must be

evaluated by a qualified physician for the presence of abnormalities. ECGs will be performed at Week 0 Day 0 (considered to correspond to the Week 48 Visit of the parent study) and at Week 48 or for subjects terminating the study at the Follow-up Visit 28 days after the last dose of study drug. In addition, for subjects in Japan who continue participation in OLSES beyond Week 48, ECGs will be performed every 12 months after Week 48.

7.5 Pregnancy Reporting

If a subject becomes pregnant during the study or within 28 days of discontinuing study drug, the Investigator should report the pregnancy to Medpace Clinical Safety within 24 hours of being notified (see Section 7.1.6 for contact information). Medpace Clinical Safety will then forward the Exposure In Utero form to the Investigator for completion.

A subject becoming pregnant while on study medication will immediately be withdrawn from the study drug and Follow-up Visit study procedures will be performed 28 days after the last dose of study drug.

The subject should be followed by the Investigator until completion of the pregnancy. If the pregnancy ends for any reason before the anticipated date, the Investigator should notify the Sponsor. At the completion of the pregnancy, the Investigator will document the outcome of the pregnancy. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (i.e., postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly), the Investigator should follow the procedures for reporting an SAE.

7.6 Anti-Drug Antibody Assessment

Antibodies to CHS-0214 will be measured in the sera of subjects enrolled in this study at each study visit through Week 48 and at the Follow-up Visit 28 days after the last dose of study drug. In addition, for subjects in Japan who continue participation in OLSES beyond Week 48, ADA testing will be performed every 6 months after Week 48. The immunogenicity testing will be performed using validated electrochemiluminescent (ECL) ADA assays. Presence of ADA based on this confirmatory assay will be assessed and compared with published data (Amgen, 2015). A cell-based neutralizing anti-drug antibody (NAB) assay is under development. NAB may be evaluated for samples testing positive in the confirmatory ADA assay and for subjects with loss of clinical response.

7.7 Serum Retention Samples

Serum samples will be collected from all subjects prior to dosing at each study visit through Week 48 and at the Follow-up Visit 28 days after the last dose of study drug. In addition, for subjects in Japan who continue participation in OLSES beyond Week 48, SRS samples will be collected every 6 months after Week 48. The exact date and time of each sample collection will be recorded. Serum samples may be used to evaluate an AE or loss of response to study drug, to confirm compliance to the dosing regimen, or for tests required by regulatory agencies. No population PK assessment is planned for these samples. These samples will not be used to assess biologic or genetic markers of disease. All of these samples will be stored at MRL and may be transferred to Charles River Laboratories or other reference laboratory for analysis at the request of the Sponsor. All retained samples and remnants of retained samples will be destroyed 2 years after completion of the study (database lock).

7.8 Sample Collection Procedures and Bioanalytical Methods

Instructions for sample collection and handling are included in the laboratory manual. All clinical laboratory evaluations (e.g., hematology, chemistry, urinalysis, QuantiFERON®-TB Gold test, hs-CRP) will be performed at a central clinical laboratory throughout the study. The ADA and PK evaluations will be performed at a central bioanalytical laboratory. In the event that immediate laboratory analyses are required to assess an AE, a local laboratory may be used; however, duplicate blood sample(s) should also be sent to the central laboratory.

8 PLANNED ANALYSES

8.1 Analysis Populations

8.1.1 Enrolled Subject Population

The Enrolled Subject Population will include all subjects enrolled from the parent CHS-0214-02 Study or CHS-0214-04 Study.

8.1.2 Full Analysis Population

The Full Analysis Population (FAP) will include all enrolled subjects who receive 1 or more doses of study drug in this study. The FAP is the efficacy analysis population.

8.1.3 Safety Population

The Safety Population is defined the same as the FAP Population. The Safety Population is the safety analysis population.

8.1.4 Pharmacokinetic Population

The PK Concentration Population will include any subjects with serum PK data measured because of AEs or loss of response or to fulfill a regulatory requirement.

8.1.5 Per-Protocol Population

The Per-Protocol Population will include all subjects who complete the 48-week treatment period and have no protocol violations that may affect the interpretation of efficacy endpoints. These violations will be identified by the Sponsor prior to database lock.

8.1.6 Rheumatoid Arthritis Population

The RA Population will include all subjects with RA who complete the CHS-0214-02 study, meet the entry criteria for this study, receive at least 1 dose of study drug of CHS-0214 and have any efficacy measurements.

8.1.7 Japanese Rheumatoid Arthritis Population

The Japanese RA Population will include all subjects with RA who complete the CHS-0214-02 study at Japanese sites, meet the entry criteria for this study, receive at least 1 dose of study drug of CHS-0214 and have any efficacy measurements.

8.1.8 Plaque Psoriasis Population

The PsO Population will include all subjects with PsO who complete the CHS-0214-04 study, meet the entry criteria for this study, receive at least 1 dose of study drug of CHS-0214 and have any efficacy measurements.

8.2 Statistical Methods

Continuous variables will be summarized using descriptive statistics (N, mean, standard deviation, median, minimum, and maximum, where appropriate). Discrete variables will be summarized using frequency counts and percentages.

8.2.1 Demographic and Baseline Characteristics

Descriptive summaries of demographic and Baseline characteristics will be presented. A detailed description of subject disposition will also be provided.

8.2.2 Efficacy Analysis

8.2.2.1 Rheumatoid Arthritis

8.2.2.1.1 Primary Endpoint

Proportion of subjects with durability of response will be calculated in the RA Population, Per-Protocol RA Population, Japanese RA Population, and Per-Protocol Japanese RA Population.

Durability of response is defined as the maintenance of the 20% improvement in the ACR score (ACR20) (or greater) at Week 4, Week 12 and every 3 months thereafter during the study. The baseline values to assess the ACR20 during this study will be the same baseline value used to assess the ACR20 during the parent study (i.e., the Week 0 assessment in the parent study).

8.2.2.1.2 Secondary Endpoints

The secondary endpoints include DAS28-CRP (4) <3.2 (low disease activity) assessed at all visits and DAS28-CRP (4) <2.6 (remission) assessed on all visits after DAS28-CRP (4) <2.6 is achieved for rate calculations.

8.2.2.2 Plaque Psoriasis

8.2.2.2.1 Primary Endpoint

Proportion of subjects with durability of response will be calculated in the PsO Population and Per-Protocol PsO Population. Durability of response is defined as the maintenance of the 50% improvement in Psoriasis Area and Severity Index [PASI-50] (or greater) at Week 4, Week 12 and every 3 months thereafter during the study. The baseline values to assess the PASI-50 during this study will be the same baseline value used to assess the PASI-50 during the parent study (i.e., the Week 0 assessment in the parent study).

8.2.3 Safety Analysis

Safety data will be summarized and listed. No inferential statistical analysis of the safety data is planned. All safety summaries and listings will be generated using the Safety Population.

All AEs will be coded and classified by system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA). Data summaries will be based upon TEAEs. All TEAEs will be listed and summarized. A summary of all drug-related AEs will also be generated. If there are any SAEs or any AEs leading to the discontinuation of study drug, a separate data listing will be generated. Events recorded after enrollment (from the time of informed consent) but before treatment initiation will be listed separately.

Clinical laboratory data will be summarized descriptively. The change from pre-dose to the end of the study will also be summarized. For selected laboratory assessments, the frequency of abnormal values may be tabulated, if appropriate.

Prior and concomitant medications will be coded with the World Health Organization Drug Dictionary (WHO-DD) and listed. All concomitant medication taken after first dosing of study drug will be summarized.

Vital signs and ECG data will be summarized and listed by visit. All other safety data will be listed.

The safety profile of the subgroup of Japanese subjects with RA will be explored.

8.2.4 Immunogenicity Analysis

The immunogenicity of CHS-0214 will be evaluated using a validated ECL assay for the presence of ADA. A cell-based assay may be used to assess whether the confirmed ADAs on ELISA are NABs. Immunogenicity data will be summarized and compared to the literature for immunogenicity of Enbrel.

8.2.5 Pharmacokinetic Analysis

No overall population PK analysis is planned. Serum samples will be obtained at each study visit and may be used to evaluate an AE or loss of response to study drug, to confirm compliance to the dosing regimen, or used for tests required by regulatory agencies or to fulfill a regulatory requirement.

8.2.6 Determination of Sample Size

No formal calculation of sample size is necessary as this is an extension study.

9 DATA SAFETY MONITORING BOARD

A Data Safety Monitoring Board (DSMB) will be convened to review accumulating data and monitor the safety of subjects over the course of the study.

In addition to periodic reviews of the accumulating safety data (including unexpected AE data), the DSMB will review efficacy results. The Sponsor may discontinue the study should the results of the analysis indicate that either parent study (CHS-0214-02 or CHS-0214-04) did not meet its primary efficacy endpoints.- Additional information may be found in the DSMB charter.

10 DATA MANAGEMENT

10.1 Data Handling

Data will be recorded at the site on source documents and entered into eCRFs. The Clinical Research Associate (CRA) assigned to the site will verify data recorded in the eCRF system with source documents. All corrections or changes made to any study data must be appropriately tracked in an audit trail in the eCRF system. The eCRFs will be considered complete when all missing, incorrect, and/or inconsistent data have been accounted for.

10.2 Computer Systems

Data will be processed using a validated computer system conforming to regulatory requirements.

10.3 Data Entry

Data must be recorded using the eCRF system. All study site personnel must log into the system using their secure usernames and passwords in order to enter, review, or correct study data. These procedures must comply with 21 Code of Federal Regulations (CFR) Part 11 and local regulation. All passwords will be strictly confidential.

10.4 Medical Information Coding

For medical information, the following thesauri will be used:

- MedDRA for AEs and
- WHO-DD for concomitant medications.

10.5 Data Validation

Validation checks programmed within the eCRF system, as well as supplemental validation performed via review of the downloaded data, will be applied to the data in order to ensure accurate, consistent, and reliable data. Data identified as erroneous and data that are missing will be referred to the investigative site for resolution through data queries.

11 STUDY ADMINISTRATION

11.1 Regulatory and Ethical Considerations

11.1.1 Regulatory Authority Approval

This study will be conducted in accordance with GCP (an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve human subjects), the protocol, and any other applicable regulatory requirements. Such compliance provides public assurance that the rights, safety, and well-being of study subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical study data are credible.

11.1.2 Ethics Approval

It is the responsibility of the Investigator or the head of the medical institution to ensure that the appropriate IRB or EC has reviewed and approved this protocol prior to initiating the study.

The IRB/EC must also review and approve the investigative site's ICFs and other written information provided to the subject.

If the protocol or the ICFs are amended during the study, per local regulations, the Investigator or the head of the medical institution is responsible for ensuring that the IRB/EC has reviewed and approved these amended documents. In addition, IRB/EC approval of the amended documents must be obtained before implementation and before new subjects are consented to participate in the study using the amended version of an ICF. In Japan, the head of the medical institution must provide the Investigator and Sponsor with the dated IRB approval of the amended documents as soon as available; in the rest of the world, the Investigator is required to provide the Sponsor with the dated IRB/EC approval of the amended documents as soon as available.

11.1.3 Subject Informed Consent

Prior to study entry and, for subjects in Japan with RA (in order to continue participation in OLSES beyond Week 48), on or before their Week 48 Visit, the Investigator, or a qualified person designated by the Investigator, will explain the nature, purpose, benefits, and risks of participation or continued participation in the study to each subject, subject's legally acceptable representative, or impartial witness. Written informed consent must be obtained prior to the subject entering the study (before initiation of any study-related procedure and administration of the study medication) and prior to continuing participation in the study beyond Week 48 using an ICF specific for RA or for PsO as appropriate. Sufficient time will be allowed to discuss any questions raised by the subject. If the consenting process is conducted by an Investigator designee, then the subject is offered the opportunity to discuss any of his/her questions or concerns regarding informed consent with an Investigator. The Investigator or designated staff will document this process in the study records. An ICF must be signed by all subjects. The process of obtaining the informed consent will be in compliance with all federal regulations, International Conference on Harmonisation (ICH) requirements (ICH E6 4.8) and local laws.

If an ICF is amended during the study, the Investigator must follow all applicable regulatory requirements pertaining to approval of the amended ICF by the IRB/EC. The investigative site must use the amended ICF for all new subjects and repeat the consent process with the amended ICF for any ongoing subjects if applicable.

11.1.4 Investigator Reporting Requirements

In accordance with applicable regulatory requirements, the Investigator is solely obligated to inform the IRB/EC of progress of the study and notify the IRB/EC of study closure. The Investigator must also provide the Sponsor with copies of all IRB/EC correspondence that relate to study approvals, updates, or changes. The Investigator must also forward all IRB/EC renewals to the Sponsor or Sponsor's representative.

11.2 Study Monitoring

In accordance with applicable regulations, GCP, and the procedures of the Sponsor and its designees, the CRA will periodically contact the investigative site, including conducting on-site visits.

During these contacts, the monitoring activities will include:

- Checking and assessing the progress of the study;
- Reviewing study data collected to date for completeness and accuracy;
- Conducting source document verifications by reviewing each subject's eCRF against source documents; and
- Identifying any issues and addressing resolutions.

These activities will be done in order to verify that the:

- Data are authentic, accurate, and complete;
- Safety and rights of the subject are being protected; and
- Study is conducted in accordance with the currently approved protocol (and any amendments), GCP, and all applicable regulatory requirements.

In addition to contacts during the study, the CRA will contact the investigative site prior to the start of the study to discuss the protocol and data collection procedures with site personnel.

A Data and Safety Monitoring Board will review safety data (e.g., AEs and SAEs, laboratory data, and ECG assessments) at regular time points while the clinical trial is ongoing.

11.3 Quality Control

Medpace (in Japan, CMIC), as an agent for the Sponsor, will perform quality control and quality assurance checks. Before the enrollment of any subject in this study, Medpace (in Japan, CMIC) personnel will review and provide training as needed to the site Investigator and site personnel regarding the following: protocol, Investigator's Brochure, eCRFs and procedures for their completion, informed consent process, procedures for reporting SAEs, and subject enrollment and drug tracking requirements. Site visits will be performed by the Sponsor and/or Medpace (in Japan, CMIC) CRA periodically throughout the study. During these visits, information recorded on the eCRFs will be verified against source documents, and requests for clarification or correction may be made. The eCRFs will be reviewed by the CRA for safety information, legibility, completeness, accuracy, and logical consistency. Computer programs that identify data inconsistencies may be used to help monitor the clinical study.
If necessary, requests for clarification or correction will be sent to Investigators via data queries.

11.4 Study Initiation

Before the start of this study, the following documents must be on file with Sponsor or a Sponsor representative:

- All regulatory documentation as required by local and national regulations, including United States Food and Drug Administration (FDA) Form 1572 and Financial Disclosure Forms (completed by the Investigator with the assistance of the Sponsor);
- Current curricula vitae and medical licenses (or equivalent) of the Principal Investigator and all Sub-investigators;
- IRB/EC membership list and/or Department of Health and Human Services number, where applicable;

- Written documentation of IRB/EC approval of protocol (identified by Sponsor protocol number or title and date of approval) and ICFs (identified by Sponsor protocol number or title and date of approval);
- A copy of the IRB/EC-approved ICFs. ICFs must be reviewed and approved by Sponsor prior to submission to the IRB/EC;
- Current laboratory certification of the laboratory performing the analysis as well as current normal laboratory ranges for all laboratory tests;
- A signed Clinical Site Agreement.

11.5 Study Termination

Upon completion of the study, the following activities, when applicable, must be conducted by the CRA and the Investigator:

- Return of all electronic and any non-electronic study data (e.g., copies of ECG tracings) to Medpace, Inc. if requested by the Sponsor;
- Data clarifications and/or resolutions;
- Accounting, reconciliation, and final disposition of used and unused study drug; and
- Review of site study records for completeness.

In addition, the Sponsor reserves the right to temporarily suspend or prematurely terminate this study for any reason.

If the study is suspended or terminated for safety reasons, the Sponsor will promptly inform the Investigator or head of the medical institution, and will also inform the regulatory authorities of the suspension or termination of the study and the reasons for the action. The Investigator or head of the medical institution is responsible for promptly informing the IRB/EC and providing the reasons for the suspension or termination of the study.

11.6 Site Termination

The Sponsor has the right to terminate a study site at any time for various reasons. Study termination and follow-up will be performed in compliance with the conditions set forth in 21 CFR Parts 312.50 and 312.56 and local regulation. If the study is prematurely terminated, all study data must be returned if requested by the Sponsor.

11.7 Records Retention

Records of subjects, source documents, monitoring visit logs, inventories of study product, regulatory documents, and other Sponsor correspondence pertaining to the study must be kept in the appropriate study files at the site. Source documents include all recordings and observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical

study. These records will be retained in a secure file for the period required by the institution or site policy but not less than 15 years. Prior to the transfer or destruction of these records, the Sponsor must be notified in writing and be given the opportunity to further store such records.

11.8 Confidentiality of Information

Subjects' names will remain confidential and will not be included in the database. All study findings will be stored in electronic databases. The Investigators will maintain subject identification lists (subject and treatment numbers with the corresponding subject names) to enable records to be identified.

11.9 Publication Policy

The Sponsor is responsible for the final clinical study report prepared according to the ICH guideline on structure and contents of clinical study reports. A final clinical study report will be prepared and include results for any subject who has signed an ICF, regardless of whether the study is completed or prematurely terminated. If appropriate, an abbreviated report may be prepared. The clinical study report will be in compliance with any applicable regulatory requirements and national laws and will be in English.

All unpublished information given to the Investigators by the Sponsor shall not be published or disclosed to a third party without the prior written consent of the Sponsor.

When the Sponsor or designee generates reports from the data collected in this study for presentation to regulatory authorities, drafts may be circulated to the Investigators for comments and suggestions. An endorsement of the final report will be sought from the Investigators when required by local regulatory agencies.

No patent application(s) based on the results of the study may be made by the Investigators nor may assistance be given to any third party to make such an application without the written authorization of Sponsor.

The Principal Investigator or anyone else working on the study may not submit any publications, papers, abstracts, or other written materials or oral presentations related to the study without written permission from the Sponsor.

11.10 Address List

11.10.1 Sponsors

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11.10.2 Contract Research Organization

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Japan Contract Research Organization:

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11.10.3 Global Drug Safety

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Additional safety contact information is provided in Section 7.1.6.

11.10.4 Central Laboratory

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11.10.5 Bioanalytical Laboratory

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APPENDIX A: AMERICAN COLLEGE OF RHEUMATOLOGY/EUROPEAN LEAGUE AGAINST RHEUMATISM CRITERIA FOR RHEUMATOID ARTHRITIS

The American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) criteria for RA (2010) are listed below. These criteria may also be accessed electronically at the following web address: http://www.rheumatology.org/practice/clinical/classification/ra/ra_2010.asp.

	Score
Target population (Who should be tested?): Subjects who 1. have at least 1 joint with definite clinical synovitis (swelling)[†] 2. with the synovitis not better explained by another disease[‡]	
Classification criteria for RA (score-based algorithm: add score of categories A–D; a score of ≥ 6/10 is needed for classification of a subject as having definite RA)[§]	
A. Joint involvement [§]	
1 large joint[¶]	0
2-10 large joints	1
1-3 small joints (with or without involvement of large joints)[#]	2
4-10 small joints (with or without involvement of large joints)	3
> 10 joints (at least 1 small joint)[**]	5
B. Serology (at least 1 test result is needed for classification)[††]	
Negative RF *and* negative ACPA	0
Low-positive RF *or* low-positive ACPA	2
High-positive RF *or* high-positive ACPA	3
C. Acute-phase reactants (at least 1 test result is needed for classification)[‡‡]	
Normal CRP *and* normal ESR	0
Abnormal CRP *or* abnormal ESR	1
D. Duration of symptoms[§§]	
< 6 weeks	0
≥ 6 weeks	1