Statistical Analysis Plan

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

Sponsored by:

Coherus Biosciences, Inc.

Version: 1.2

Date: 25 October 2017

Table of Contents

List of Tables

1 Study Description

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. The purposes of this open-label safety extension study (OLSES) are to evaluate the longer-term safety and durability of response of CHS-0214 in subjects who completed 48 weeks of evaluations in the confirmatory safety and efficacy studies, CHS-0214-02 (RA population) or CHS-0214-04 (PsO population), and who received CHS-0214 in the OLSES. Subjects will receive study drug for an additional 48 weeks, and any subject discontinuing treatment at any time during the study will undergo follow-up evaluations 28 days after last dose of study drug. Subjects in Japan with RA only, were permitted to continue in the OLSES study beyond Week 48 and receive study drug until marketing approval, beginning at Week 60 with quarterly visits thereafter.

The information contained in this document is based on Protocol Version 4.0 (Amendment 3).

1.1 Objectives

The objective of this study 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 plaque PsO, respectively.

1.2 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. 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 in a prefilled syringe. 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.

To qualify for the study, subjects from study CHS-0214-02 must complete the study through Week 48, and have at least a 20% improvement from baseline according to American College of Rheumatology criteria (ACR20). Subjects from study CHS-0214-04 must complete the study through Week 48 and have at least 50% improvement from baseline in Psoriasis Area and Severity Index (PASI-50).

1.3 Method of Assigning Subjects to Treatment Groups

This study is not randomized. All subjects will receive open-label treatment with CHS-0214 50 mg QW.

1.4 Blinding

This is an open-label study.

1.5 Decision Rules

For this open-label study, no inferential testing will be performed. Descriptive statistics will be used to summarize efficacy and safety parameters.

1.6 Sample Size

No calculation of sample size was performed as this is an extension study. Approximately 400 subjects are expected to be enrolled.

2 Statistical Methods

2.1 Populations Analyzed

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

Japanese Enrolled Subject Population: The Japanese Enrolled Subject Population will include all subjects enrolled from the parent CHS-0214-02 Study from Japanese sites.

Full Analysis Population (FAP): 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. There are three subsets of FAP as described below:

- **Population with Rheumatoid Arthritis (RA Population)**: The RA Population will include all subjects with RA who complete the CHS-0214-02 study, meet the entry criteria for enrollment of CHS-0214-05, receive at least 1 dose of study drug of CHS-0214 and have any efficacy measurements.
- **Japanese Population with Rheumatoid Arthritis (Japanese RA 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 enrollment of CHS-0214-05, receive at least 1 dose of study drug of CHS-0214 and have any efficacy measurements.
- **Population with Plaque Psoriasis (PsO Population)**: The PsO Population will include all subjects with PsO who complete the CHS-0214-04 study, meet the entry criteria for enrollment of CHS-0214-05, receive at least 1 dose of study drug of CHS-0214 and have any efficacy measurements.

Safety Population: The Safety Population is defined the same as the FAP Population. The Safety Population is the safety analysis population. There are three subsets of Safety Population as described below:

- **Safety Rheumatoid Arthritis Population (Safety-RA Population)**: The Safety RA Population will include all subjects with RA who complete the CHS-0214-02 study, meet the entry criteria for enrollment into CHS-0214-05 and receive at least 1 dose of study drug of CHS-0214.
- **Safety Japanese Rheumatoid Arthritis Population (Safety-JRA Population)**: The Safety Japanese RA Population will include all subjects with RA who complete the CHS-0214-02 study at Japanese sites, meet the entry criteria for enrollment into CHS-0214-05 for this study, and receive at least 1 dose of study drug of CHS-0214.

- **Safety Plaque Psoriasis Population (Safety-PsO Population)**: The Safety PsO Population will include all subjects with PsO who complete the CHS-0214-04 study, meet the entry criteria for enrollment of CHS-0214-05, and receive at least 1 dose of study drug of CHS-0214.
- **Pharmacokinetic Concentration Population (PK Population):** All enrolled subjects with serum PK measured due to either adverse events or loss of response.

2.2 Baseline

Baseline values for efficacy assessments:

In this CHS-0214-05 study, the changes in ACR or PASI scores over time are compared to the baseline values measured at Week 0 of the parent study. This is because we are not measuring a novel response but rather the maintenance overtime of a response already obtained in the parent study. Hence, the baseline values used to calculate the maintenance of this response have to be the same between CHS-0214-02 and CHS-0214-05 for subjects with RA or between CHS-0214-04 and CHS-0214-05 for subjects with psoriasis.

Baseline values for safety assessments:

The safety of CHS-0214 in the CHS-0214-05 study is assessed in a traditional manner, i.e. compared to the baseline values at Week 0 in CHS-0214-05; i.e. we are not trying to assess "the maintenance of safety" over time.

2.3 Study Parameters

An overview of study parameters and populations for which they will be analyzed are listed in Table 1 through Table 3. The parameters are further described in the sections below.

Table 1 Baseline and Disposition Parameters

Parameter	Population
Subject Disposition	Enrolled, Japanese Enrolled
Demographics	Enrolled, RA, JRA, PsO (If different populations then: Safety, Safety-RA, Safety-JRA, Safety-PsO)
Baseline Disease Characteristics	Enrolled, RA, JRA, PsO (If different populations then: Safety, Safety-RA, Safety-JRA, Safety-PsO)
Subgroup Analysis	
• Perfusion Medication Dosing (Any Perfusion, No Perfusion)	Enrolled, Japanese Enrolled

Table 2 Efficacy Parameters

Parameters	Time-point[1]	Population
Rheumatoid Arthritis (RA) Parameters		
Primary Endpoint		
Durability of response (Result)	Once per subject	RA, JRA
Secondary Parameters		
DAS28-CRP(4) <3.2 (Result)	Weeks 4, 12, 24, 36, 48	RA, JRA
DAS28-CRP(4) <2.6 (Result)	Once per subject	RA, JRA
Other RA Parameters		
ACR20 (Result)	Weeks 4, 12, 24, 36, 48	RA, JRA
ACR50 (Result)	Weeks 4, 12, 24, 36, 48	RA, JRA
ACR70 (Result)	Weeks 4, 12, 24, 36, 48	RA, JRA
TJC (Result, CFB, pCFB)	Weeks 4, 12, 24, 36, 48	RA, JRA
SJC (Result, CFB, pCFB)	Weeks 4, 12, 24, 36, 48	RA, JRA
Pain VAS (Result, CFB, pCFB)	Weeks 4, 12, 24, 36, 48	RA, JRA
SGA (Result, CFB, pCFB)	Weeks 4, 12, 24, 36, 48	RA, JRA
PGA (Result, CFB, pCFB)	Weeks 4, 12, 24, 36, 48	RA, JRA
HAQ-DI (Result, CFB, pCFB)	Weeks 4, 12, 24, 36, 48	RA, JRA
hs-CRP (Result, CFB, pCFB)	Weeks 4, 12, 24, 36, 48	RA, JRA
DAS28-CRP(4) (Result, CFB)	Weeks 4, 12, 24, 36, 48	RA, JRA
Subgroup analysis for primary endpoint and secondary endpoints: DAS28-CRP(4)		
• Gender (Male, Female)	All (See above)	RA, JRA
• Race (White, Non-white)	All (See above)	RA, JRA
• Age (<65, ≥65 years)	All (See above)	RA, JRA
• Perfusion Medication Dosing (Any, None)	All (See above)	RA, JRA
• ADA Status (Binding Antibodies: Yes, No)	All (See above)	RA, JRA
[1] For subjects in Japan with RA only who continue participation beyond Week 48, visits begin at Week 60, with quarterly visits thereafter (± 7 days)		
Plaque Psoriasis (PsO) Parameters		
Primary Endpoint		
Durability of response (Result)	Once per subject	PsO
Other PsO Parameters		
PASI-50 (Result)	Weeks 4, 12, 24, 36, 48	PsO
PASI-75 (Result)	Weeks 4, 12, 24, 36, 48	PsO
PASI-90 (Result)	Weeks 4, 12, 24, 36, 48	PsO
PASI (Result, CFB, pCFB)	Weeks 4, 12, 24, 36, 48	PsO
PSGA (Result, CFB, pCFB)	Weeks 4, 12, 24, 36, 48	PsO
SGA (Result, CFB, pCFB)	Weeks 4, 12, 24, 36, 48	PsO
Subgroup analysis for primary endpoint		
• Gender (Male, Female)	Once per subject	PsO
• Race (White, Non-white)	Once per subject	PsO
• Age (<65, ≥65 years)	Once per subject	PsO
• Perfusion Medication Dosing (Any, None)	Once per subject	PsO
• ADA Status (Binding Antibodies: Yes, No)	Once per subject	PsO

Note: pCFB=% change from baseline; CFB=change from baseline

Table 3 Safety Parameters

Endpoint	Population
Drug Exposure and compliance	Safety, Safety-RA, Safety-JRA, Safety-PsO
Subject incidence of Treatment-emergent adverse events (TEAEs) overview	Safety, Safety-RA, Safety-JRA, Safety-PsO
Subject incidence and exposure adjusted rate of TEAEs	Safety, Safety-RA, Safety-JRA, Safety-PsO
Subject incidence of Serious TEAEs	Safety, Safety-RA, Safety-JRA, Safety-PsO
Subject incidence of study drug related TEAEs per investigator	Safety, Safety-RA, Safety-JRA, Safety-PsO
Subject incidence of study drug related treatment emergent serious adverse events per investigator	Safety, Safety-RA, Safety-JRA, Safety-PsO
Subject incidence of TEAEs leading to study drug discontinuation	Safety, Safety-RA, Safety-JRA, Safety-PsO
Subject incidence of study drug related TEAEs per investigator leading to study drug discontinuation	Safety, Safety-RA, Safety-JRA, Safety-PsO
Subject incidence of injection site reactions	Safety, Safety-RA, Safety-JRA, Safety-PsO
Laboratory parameters	Safety, Safety-RA, Safety-JRA, Safety-PsO
Subject incidence of Anti-drug antibodies (ADA) including neutralizing (NAB)	Safety, Safety-RA, Safety-JRA, Safety-PsO
Vital signs	Safety, Safety-RA, Safety-JRA, Safety-PsO
QuantiFERON-TB Gold test	Safety, Safety-RA, Safety-JRA, Safety-PsO
Physical examination	Safety, Safety-RA, Safety-JRA, Safety-PsO
Electrocardiogram	Safety, Safety-RA, Safety-JRA, Safety-PsO
Subgroup analysis	
• Gender (Male, Female); • Race (White, Non-White) • Age (<65, ≥65 years) • Perfusion Medication Dosing (Any Perfusion, No Perfusion) • ADA Status (Binding Antibodies: Yes, No)	
Subject incidence of TEAEs	Safety, Safety-RA, Safety-JRA, Safety-PsO
Subject incidence of study drug related TEAEs per investigator	Safety, Safety-RA, Safety-JRA, Safety-PsO
Subject incidence of injection site reactions	Safety, Safety-RA, Safety-JRA, Safety-PsO

2.3.1 Description of Rheumatoid Arthritis Parameters

2.3.1.1 ACR20 and Durability of Response

The primary RA endpoint is the durability of response and 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. ACR20, is a composite endpoint based upon the results from seven parameters: 66/68 SJC or TJC, CRP, HAQ DI, VAS for Pain, SGA and PGA. The baseline value 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).

Subjects will be considered an ACR20 responder at a visit if compared to baseline they achieve:

- At least 20% decrease in swollen joint count (SJC), and

- At least 20% decrease in tender joint count (TJC), and
- At least 20% improvement in at least 3 of the following 5 measures
  - C-reactive protein (CRP)
  - Health assessment questionnaire – disability index (HAQ-DI)
  - Subject's pain assessment (using a visual analog scale [VAS]) for pain
  - Subject's global assessment of disease activity (SGA) (using a VAS)
  - Physician's global assessment of disease activity (PGA) (using a VAS)

In these calculations, the percent change from baseline to endpoint (pCFB) will be used to determine ACR20. For percentage change calculations, results will be rounded to 5 decimal places prior to comparing to the threshold of 20%. Additional details for calculating ACR20 include the following:

1) If the SJC or TJC assessment is not complete then
   a. If the SJC or TJC is completely missing then ACR20 is set to non-response
   b. If the SJC or TJC is partially missing (i.e., not all questions answered) then ACR20 is set to non-response unless when all missing items are set to not swollen/not tender there would be a 20% decrease from baseline
2) For the remaining parameters (CRP, HAQ DI, VAS for Pain, SGA and PGA)
   a. If three of more are missing then the ACR20 is set to non-response.
   b. If one or two are missing then
      i. If, of the non-missing items, less than 3 have a 20% decrease from baseline then the ACR20 is set to non-response,
      ii. If, of the non-missing items, 3 or more have a 20% decrease from baseline then this criteria for the ACR20 is met.

This endpoint will be considered missing if a score is not available as indicated by this algorithm.

2.3.1.2 ACR50 and ACR70

ACR50 and ACR70 are defined similarly to ACR20 but use a cutoff of 50% and 70%, respectively.

2.3.1.3 Swollen Joint Count/Tender Joint Count Assessments

For assessment of the number of tender joints (TJC), 68 joints will be evaluated. The presence of tenderness will be used to determine the TJC. The number of swollen joints (SJC) will be similarly derived but will be limited to 66 joints (excludes hips).

A subset of joints in the 66/68 joint count are used for the 28 joint count used to calculate the DAS28-CRP (4) and other measures as indicated. These joints include the shoulder (2), elbow (2), wrist (2), metacarpophalangeal (10), thumb interphalangeal (2), proximal interphalangeal (8) and knee (2).

Any joint injected prior to a study visit will subsequently be counted as tender and swollen for the remainder of the study.

2.3.1.4 Subject's Pain Assessment (Visual Analog Scale)

The subject will rate the severity of pain at the time of visit using a horizontal 100 mm-cm VAS with the best anchor and lowest score on the left side and worst anchor and highest score on the right side. The question asked of the subject is "How severe is your pain today?"

2.3.1.5 Subject's Global Assessment (SGA) (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 100 mm VAS with the anchors "very well" (low score) and "very poor" (high score).

2.3.1.6 Physician's Global Assessment (PGA) (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 100 mm VAS with the anchors "none" (low score) and "extremely active" (high score).

2.3.1.7 Health Assessment Questionnaire – Disability Index

The HAQ-DI is a 20-item assessment with eight categories: Dressing and Grooming (2 questions), Arising (2 questions), Eating (3 questions), Walking (2 questions), Hygiene (3 questions), Reach (2 questions), Grip (3 questions), and Activities (3 questions). The first step is to score within each category.

The score for each category is the single response within the category with the highest score (greatest difficulty). For example, in the "Eating" category, there are two answers (one for each item). If "Cut your food with a knife or fork" is marked as "3" and "Lift a full cup or glass to your mouth" is marked as "0", then the score for the "Eating" category would be "3" (the response indicating the greatest difficulty within the category). If a component question is left blank or the response is too ambiguous to assign a score, then the score for that category is determined by the remaining completed question(s). However, if any "aids or devices" and/or "help from another person" items are checked, the category to which they apply is adjusted upward to "2". If the basic score is already "2" or "3", the score remains unchanged. The mapping of items on the CRF to the eight categories is provided in Table 4
.

Table 4 HAQ-DI "aids or devices" and "help from another person" Items

Category	aids or devices	help from another person
Dressing and Grooming	Devices used for dressing	Dressing and grooming
Arising	Special or built up chair	Arising
Eating	Built up or special utensils	Eating
Walking	Cane, Walker, Crutches or Wheelchair	Walking
Hygiene	Raised toilet seat, Bathtub seat or Bathtub bar	
Reach	Long-handled appliances in bathroom	
Grip	Long-handled appliances for reach	
Activities	Jar opener	

The overall score for the disability index is the mean of the eight category scores. If more than two of the categories are missing, the HAQ-DI is missing; otherwise the score if the average of the non-missing categories. Only this overall disability index score will be included in summary tables.

2.3.1.8 C-Reactive Protein

CRP (mg/L) results will be based upon blood samples.

2.3.1.9 DAS28-CRP(4)

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

$$0.56\times\sqrt{TJC_{28}}+0.28\times\sqrt{SJC_{28}}+0.36\times\ln(CRP+1)+0.014\times SGA+0.96,$$

where CRP is measured in mg/L. The TJC and SJC measures will be based upon the following joint counts:

- Shoulder (2 pts)
- Elbow (2 pts)
- Wrist (2pts)
- Metacarpophalangeal (10 pts)
- Thumb interphalangeal (2 pts)
- Proximal interphalangeal (8 pts)
- Knee (2 pts)

The DAS28-CRP(4) will be missing if any of the components are missing. For DAS28-CRP(4), scores indicating high disease activity are >5.1; low disease activity, <3.2; and remission, <2.6.

2.3.2 Exploratory Statistical Evaluation of Rheumatoid Arthritis Parameters

No inferential analyses will be performed. Continuous variables will be summarized using descriptive statistics (N, mean, standard deviation, median, minimum, and maximum). Discrete variables will be

summarized using frequency counts and percentages. Additional details are provided in the sections below.

2.3.2.1 Primary Rheumatoid Arthritis Parameter

The percentage of subjects with durability of response will be calculated in the RA Population, 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. If ACR20 is not achieved at one or more visits, including missing data, the subject will not be considered to achieve durability of response.

The number and percentage of subjects with durability of response will be presented for each of the populations specified.

2.3.2.2 Secondary Rheumatoid Arthritis Parameters

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

The number and percentage of subjects achieving DAS28-CRP (4) <3.2 will be presented for each visit for each of the populations specified. The number and percentage of subjects achieving remission will also be presented for each of the populations specified. Subjects with a missing Week 48 assessment will be classified as not in remission. For Japanese RA subjects who continue beyond 48 weeks, subjects with a missing assessment at their last on-treatment study visit will be classified as not in remission.

2.3.2.3 Other Rheumatoid Arthritis Parameters

Summary statistics will be presented for each parameter (ACR20, ACR50, ACR70, SJC, TJC, Pain VAS, SGA, PGA, HAQ-DI, and hs-CRP) for each visit for each of the populations specified. See Table 2 for additional details.

2.3.3 Exploratory Statistical Evaluation of Psoriasis Parameters

No inferential analyses will be performed. Continuous variables will be summarized using descriptive statistics (N, mean, standard deviation, median, minimum, and maximum). Discrete variables will be summarized using frequency counts and percentages. Additional details are provided in the sections below.

2.3.3.1 Psoriasis Area and Severity Index

For the Psoriasis Area and Severity Index (PASI) the PsO lesions are scored on a scale of 0 to 4 for 3 characteristics: erythema, induration, and scale and within 4 anatomical regions: head, trunk, upper extremities, and lower extremities. Within each of these regions, the area of involvement is scored on a scale of 0-6 with the total score being a weighted average with weights defined by the area of involvement. The clinician will assess the subject's PsO lesions according to the PASI and provide this score within the CRF. An example of this instrument is provided in the protocol.

Subjects are classified as having a PASI-50 response based upon 50 percent reduction from baseline. Subjects with a reduction of at least 50% are classified as having a PASI-50 response.

The percentage of subjects with durability of response will be calculated in the 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. If PASI-50 is not achieved at one or more visits, including missing data, the subject will not be considered to achieve durability of response.

The number and percentage of subjects with durability of response will be presented for PsO population.

Summary statistics will be presented for each parameter (percentage of subjects achieving PASI-50, PASI-75, PASI-90; PASI, percent change from baseline in PASI) for each visit for PsO population. See Table 2 for additional details.

2.3.3.2 Physician's Static Global Assessment

The Physician's Static Global Assessment of Psoriasis (PSGA) 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 scores indicating more severe disease. Subjects with a clear (0) or almost clear (1) evaluation will be considered PSGA responders. Summary statistics will be presented for PSGA and change in PSGA for each visit for PsO population. See Table 2 for additional details.

2.3.3.3 Subject's Global Assessment

The Subject's Global Assessment of Psoriasis (SGA) will be assessed on a scale ranging from 0 (good) to 5 (severe). Summary statistics will be presented for SGA and change in SGA for each visit for PsO population. See Table 2 for additional details.

2.4 Study Day and Visit Windows

Study day is defined as

Study Day = Event Date –Date of First Treatment + 1

As defined in the protocol, the day of first treatment will be day 0. However the date of first treatment will be mapped to Study Day 1 based on the guidelines specified in the CDISC SDTM database as CDISC does not allow for a Study Day 0. A schedule of events for subjects with RA can be found in

Table 6 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

Table 6 Schedule of Procedures for Subjects with Rheumatoid Arthritis

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

Table 6 Schedule of Procedures for Subjects with Rheumatoid Arthritis

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 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 **Error! Reference source not found.**).
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.

and a schedule of events for subjects with PsO can be found in **Error! Reference source not found.**. For additional details, please see the protocol.

For the purpose of data displays, subject data will be associated with an analysis window based upon the actual date the assessment took place as outlined in. For post-baseline assessments, study days from the first day of dosing through 14 days after the last day of dosing will be considered. Where multiple measurements for a particular parameter appear within an analysis window the result closest to target day will be used. If equidistant, the later result will be used for the summary measure. Though all measures may not be used in the data summaries (e.g, two lab measures within the same analysis visit window), all measurements appear in the datasets and listings. For subjects where the event date is missing, the study day and analysis window will also be missing.

Table 5 Analysis Windows

Analysis Window	Start Day	End Day	Target Day
Baseline		1	1
Day 1	1	1	1
Week 4	2	42	29
Week 12	43	126	85
Week 24	127	210	169
Week 36	211	294	253
Week 48	295	366	337
Week 52 (Follow-up)	Last dose+15	NA	Last dose + 28
For Subjects with RA in Japan			
Week 60	367	462	421
Week 72	463	546	505
Week 84	547	630	589
Week 96	631	714	673
Week 108	715	786	757
Follow-up	Last dose+15	NA	Last dose + 28

Note: Only observations from Day 1 through 14 days after the last dose of study medication are considered for the Day 1 through Week 48 windows. For RA subjects in Japan who continued dosing with study medication beyond Week 48, observations from Day 1 through 14 days after the last dose of study medication are considered for the Day 1 through Week 108 windows.

The Week 52 (follow-up) time-point will be used for data summaries. This time-point is the post-dose assessment. This time-point will encompass the result that is closest to 28 days after the last dose of study medication. For RA subjects in Japan who continued dosing with study medication beyond Week 48, the post-dose assessment follow-up time point will encompass the result that is closest to 28 days after the last dose of study medication.

Table 6 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]	**[e]	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]	

Table 6 Schedule of Procedures for Subjects with Rheumatoid Arthritis

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.

v Begins with the Week 60 Visit for subjects in Japan who continue participation in OLSES beyond Week 48.
w 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 in the study, and study drug will be dispensed.
x Subjects in Japan will consent on or before their OLSES Week 48 Visit to be able to continue participation in OLSES beyond Week 48.
y 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.
z Weight will be recorded at the Follow-up Visit 28 days after the last dose of study drug.
aa 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.
bb Repeat every 12 months for subjects in Japan who continue participation in OLSES beyond Week 48.
cc Perform ECG at the Follow-up Visit 28 days after the last dose of study drug for those subjects who discontinue study drug
dd 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.
ee Perform every 6 months for subjects in Japan who continue participation in OLSES beyond Week 48.
ff 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.
gg 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.
hh Japan only (see Section **Error! Reference source not found.**).
ii 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.
jj Perform for subjects in Japan who continue participation in OLSES beyond Week 48.
kk Perform PGA (VAS) prior to SGA (VAS).
ll 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.
mm 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.
nn 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.
oo Record ISRs observed by site personnel as AEs.
pp 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 7 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.
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.

2.5 Handling of Missing Data

Summary statistics will be reported based upon observed data without imputation with the following exceptions:

1) Adverse Events with missing severity will be assumed to be severe. Adverse Events with missing or partial dates will be assumed to have occurred on treatment unless the available parts of the date make this impossible.
2) If concomitant medications start or stop dates are partial dates the medication will be considered as concomitant unless the available parts of the date make this impossible.

2.6 Sensitivity Analyses, Subgroups and Covariates

The results for the primary endpoints and secondary efficacy parameters (RA) (See Table 2) will be summarized for the subgroups of the RA, JRA, and PsO populations listed below. These summaries will be descriptive in nature.

- Sex
- Race (White, Non-white)
- Age (<65, ≥65)
- Perfusion Medication Dosing (Any Perfusion vs No Perfusion)
- ADA Status (Binding Antibody Incidence: Yes, No)

2.7 Safety Analyses

Statistical analyses will be descriptive in nature, testing will not be utilized.

Subgroup analyses for select safety parameters (see Table 3) will be summarized for the subgroups of Safety, Safety-RA, Safety-JRA, Safety-PsO below.

- Sex
- Race (White, Non-white)
- Age (<65, ≥65)
- Perfusion Medication Dosing (Any Perfusion vs No Perfusion)
- ADA Status (Binding Antibody Incidence: Yes, No)

2.8 Interim Analysis

Interim analyses are planned to support a Japanese NDA submission, a MAA submission, and supplemental updates after initial regulatory submissions and regulatory filings in other geographic regions. A data-cut occurred to support initial J-NDA and separate data-cuts to support J-NDA and MAA supplemental updates are planned. All interim analyses will be described in the clinical study report.

3 Summary Tables Listings and Figures

3.1 General Conventions

Unless otherwise stated, summary statistics including the number of subjects (n), mean, standard deviation, median, minimum and maximum will be presented for continuous variables. Minimum and maximum values will be presented to the same decimal precision as the raw values, the mean and median values to one more, and the standard deviation, to two more decimal places than the raw values. For categorical variables, per category, the absolute counts (n) and percentages (%) of subjects with data, and where part of the data, the number of subjects with missing data, will be presented. Percentages will be presented to one decimal place.

Please refer to Table 1, Table 2 and Table 3 for the populations for which all analyses will be performed.

3.2 Subject Disposition and Treatment

The number of subjects enrolled, treated, discontinued study drug early, terminated from the study early and in each of the analysis population will be summarized. The reason for early termination of treatment or from the study will be summarized.

3.3 Protocol Deviations

Protocol deviations will be captured in the monitoring reports and stored in a tracking database. These deviations will be discussed (narratives rather than data summaries) in the clinical study report if it is concluded by the sponsor that these deviations may affect the interpretation of the efficacy parameters or the overall safety assessment. All protocol deviations will be included in the data listings.

A summary of major protocol deviations will be provided. The following are considered to be major protocol deviations:

- Subjects who are non-compliant: less than 80% injections during the study
- RA subjects who received prohibited concomitant medication at least consecutively ≥ 1 month with any of the following (extracted from protocol App. 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 DMARDS, other than MTX (Rheumatrex, Trexall) (e.g., hydroxychloroquine [Plaquenil], oral or injectable gold, D-penicillamine, sulfasalazine [Azulfidine], leflunomide [Arava], and iguratimod [Careram, Kolbet]). Any DMARDs to which the subject had an inadequate response should be noted in the eCRF;
    - 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

- PsO subjects who received prohibited concomitant medication at least consecutively ≥ 1 month with any of the following (extracted from protocol App. 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); 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 without exacerbation of psoriasis;
  - Use of topical corticosteroids (class 1-5); and
  - Live vaccines

3.4 Study Treatment and Compliance

Study drug compliance will be assessed based on study drug use recorded by the subject in the eDiary. The following information will be presented:

- duration of treatment in weeks: (last treatment date – first treatment date + 1)/7
- number of injections
- compliance: (100*number of injections received)/integer component of ((last treatment date – first treatment date +7)/7)
- total number of weeks subjects missed doses
- largest number of consecutive weeks subjects missed doses

3.5 Demographics and Baseline Characteristics

Descriptive statistics will be provided for demographic variables including:

1. Gender
2. Race (Asian, American Indian or Alaska Native, Black or African American, Native Hawaiian or Other Pacific Islander, White, Other)
3. Region (Japan/non-Japan)
4. Age
5. Age group (<65, ≥65)
6. Height

7. Weight

3.6 Prior and Concomitant Medications

Concomitant medications will be descriptively summarized based upon the coded values for the Safety, Safety RA, Safety Japanese RA, and Safety PsO populations. Data summaries will be sorted by the overall frequency of recorded use. Prior medications, defined as medications with end dates prior to dosing in CHS-0214-05, will not be included in these summaries but will be provided in the listings, if applicable.

Medications with partial dates will be assumed to have been concomitant unless the available parts of the date exclude this possibility.

3.7 Efficacy Parameters

3.7.1 Rheumatoid Arthritis Parameters

The results for the primary and secondary parameters will be summarized descriptively as indicated in Table 2. Separate tables will be produced for each endpoint and measurement type.

3.7.2 Psoriasis Parameters

The results for the primary and other parameters will be summarized descriptively as indicated in Table 2. Separate tables will be produced for each endpoint and measurement type.

Exploratory analyses may be performed to evaluate the impact of baseline covariates and ADA status on the primary efficacy variables. Such analyses may be described in the clinical study report.

3.8 Safety Parameters

Adverse events will be considered as treatment-emergent (TEAE) for this study if the date of the event is on or after the date of first dose of study medication. The summaries and listings described below will be prepared for TEAEs. All adverse events that start during the parent study and are ongoing upon entry into this study will be defined as Pre-Treatment AEs, will be listed only.

In the event of multiple occurrences of the same TEAE with the same preferred term in one subject, the TEAE will be counted once as the occurrence with the highest severity.

Subgroup analyses of "Any perfusion usage vs. no perfusion usage" will be provided.

Analyses of all safety parameters described in the following will be conducted using the Safety-RA, Safety-JRA and Safety-PsO Populations (see Table 3).

3.8.1 Treatment-emergent Adverse Events

Brief Summary of TEAEs

A brief summary of TEAEs, serious TEAEs, deaths, TEAEs leading to drug discontinuation, study drug related TEAEs per Investigator, study drug related treatment emergent serious adverse events per Investigator, study drug related TEAEs per Investigator leading to drug discontinuation, and a summary

by severity will be presented. The following frequency counts will be included in the brief summary of TEAEs:

- No. of subjects with treatment-emergent adverse event (TEAE)
- No. of subjects with serious TEAE
- No. of deaths
- No. of subjects with TEAE leading to study drug discontinuation
- No. of subjects with study drug related TEAEs per Investigator
- No. of subjects with study drug related treatment emergent serious adverse events per Investigator
- No. of subjects with study drug related TEAEs per Investigator leading to study drug discontinuation

Summary of TEAEs by SOC and Preferred Term

The incidence of TEAEs will be tabulated by SOC and preferred term. TEAEs will be classified by SOC and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA). These summaries of TEAEs will be produced in the following ways

- Overall: by SOC and preferred term
- by severity: by SOC, preferred term and severity
- by relationship to study drug: by SOC, preferred term and relationship to study drug
- by exposure time interval
- by binding antibody incidence at any time-point after first dose of study medication (yes or no)
- by perfusion usage: with or without

For the summaries by exposure time interval, exposure time to study medication will be categorized in four-week intervals, e.g., >0 to ≤4 weeks, >4 to ≤8 weeks, etc. through the first 12 weeks and then 12 week intervals beyond 12 weeks. For each interval, the numbers of subjects who were exposed to study medication for at least the minimum duration for the interval will be considered as the risk set for the interval and the incidence rate will be calculated as the number of subjects with a TEAE with a start date in the specified interval divided by the number of subjects in the risk set for the interval.

An additional summary will be prepared in which the rate of adverse events by SOC and preferred term. The numerator for the rate will be the total number of TEAEs reported and the denominator will be the total number of patient-years of exposure to study drug. Patient-years will be calculated from the date of first dose of study drug to the date of last dose of study drug.

Treatment-emergent Serious AEs and Deaths

Treatment-emergent serious adverse events (TESAEs) will be summarized by SOC and preferred term. This table will be repeated with events classified by relationship to study drug. TESAEs will also be listed. Events with a fatal outcome will be summarized by cause of death.

Premature Discontinuations Due to TEAEs

Treatment discontinuation due to TEAEs will be summarized by the reason for discontinuation. These discontinuations will also be listed.

Injection Site Reactions Adverse Events

A treatment-emergent adverse event listing will be produced for injection site reactions (ISRs) that have been recorded as TEAEs. An ISR recorded in the eDiary will not be listed as an AE unless it is observed by study staff and recorded as such. The intensity for the ISR AE will be the highest intensity of any characteristic observed.

3.8.2 Clinical Laboratory Result Analysis

The clinical laboratory results will be displayed in tabular form. The tabular displays will provide summary information over time, using the defined visit windows, for the observed data as well as the changes from baseline over time. A table of abnormal lab values per parameter per visit will be produced. Plots of mean values and standard errors over time will also be prepared.

Liver Function Parameter Abnormalities

Three categories of liver function abnormalities will be evaluated. The first category will include all subjects with at least one post-CHS-0214 dose alanine aminotransferase (ALT) assessment >3 times upper limit of normal (ULN) or aspartate aminotransferase (AST) >3 times ULN or total bilirubin >1.5 times ULN. The number and percentage of subjects with at least one observation meeting at least one of these criteria will be summarized by analysis category. The second liver function abnormality category will include all subjects with at least one post-CHS-0214 dose assessment of ALT or AST >3 times ULN AND a total bilirubin assessment >1.5xULN at the same visit. The third liver function abnormality category will include all subjects with at least one post-CHS-0214 dose assessment of ALT or AST >3 times ULN AND a creatinine kinase (CK) assessment >2.5 times ULN at the same visit. The number and percentage of subjects meeting these criteria at least once after the first dose of CHS-0214 will be summarized by analysis category.

Liver Function Parameter Shift Tables

Shifts from baseline will be evaluated for alkaline phosphatase, ALT, AST, total bilirubin, and CK based on Common Terminology Criteria for Adverse Events (CTCAE) grade. The baseline and highest post-CHS-0214 results for each of these parameters will be categorized by CTCAE grade. The number and percentage of subjects in each baseline by post-baseline category will be summarized by analysis category. Separate shift tables will be prepared for the highest post-CHS-0214 dose assessment and one for the last post-CHS-0214 dose assessment.

A table displaying the CTCAE grades for the liver function parameters is provided below:

Table 7: Liver Function Parameter CTCAE Grades

Parameter	Normal Range	Grade 1	Grade 2	Grade 3	Grade 4
Alkaline phosphatase	37-116 U/L	>ULN-2.5xULN	>2.5xULN-5xULN	>5xULN-20xULN	20xULN
ALT	6-41 U/L	>ULN-3xULN	>3xULN-5xULN	>5xULN-20xULN	>20xULN
AST	9-34 U/L	>ULN-3xULN	>3xULN-5xULN	>5xULN-20xULN	>20xULN
Total bilirubin	1.7-18.8 µmol/L	>ULN-1.5xULN	>1.5xULN-3xULN	>3xULN-10xULN	>10xULN
CK	25-210 U/L	>ULN-2.5xULN	>2.5xULN-5xULN	>5xULN-10xULN	>10xULN

3.8.3 QuantiFERON-TB Gold Test

The QuantiFERON-TB Gold test results will be summarized for the Safety, Safety RA, Safety Japanese RA, and Safety PsO populations. Listings of positive results will be prepared and compared to the numbers of reported adverse events of tuberculosis.

3.8.4 Immunology Data Analysis and Anti-Drug Antibodies

The immunogenicity of CHS-0214 will be evaluated using a validated ECL assay for the presence of ADA. Samples confirmed positive for ADA in the confirmatory ECL assay will be assessed in the neutralizing antibody (NAB) assay.

The number and percent of subjects with anti-drug antibodies will be summarized overall and by visit.

In the event that retained serum samples are analyzed for subjects who are confirmed positive for ADA or NAB, summaries of pharmacokinetic (PK) results and correlations with positive results may be calculated. Graphical displays or listings may also be produced.

3.8.5 Vital Signs

Listing of vital signs by visit will be presented. The listing will include the results as well as change from baseline.

3.8.6 Physical Examination

Physical exam data will be summarized by visit. The summary will include a summary of the percent of subjects with a clinically significant finding which is qualified as an AE. Listing of clinically significant findings will be provided.

3.8.7 12-Lead Electrocardiogram

A summary of the percent of subjects with a clinically significant ECG finding by visit will be produced.

3.8.8 Subject Reported Injection Site Reactions

In addition to the ISRs observed by site staff and reported as adverse events, subjects will record their own observed ISRs with an eDiary. The subjects will also record the symptoms of the ISRs (redness, swelling, pain, tenderness, or burning sensation). The cumulative frequency of subject reported injection site reactions recorded via the eDiary will be summarized by study week. In addition, ISR symptoms will also be summarized.

4 Protocol and SAP Amendments and Deviations from the Protocol

4.1 Protocol Amendments

4.2 SAP Amendments

The following updates were made for version 1.1 of the SAP:

- The terminology ‘adverse drug reaction’ was replaced with ‘study drug related treatment emergent adverse event’.

The subsections of Section 3.8.2 describing Liver Function Parameter Abnormalities and Liver Function Parameter Shift Tables were added.

The following updates were made for version 1.2 of the SAP:

- Addition of details regarding subjects in Japan with RA only, who were permitted to continue in the OLSES study beyond Week 48 and receive study medication.
- Addition of visit windows beyond Week 48, beginning at Week 60.

4.3 Deviations from the Protocol

Removal of subgroup analysis by Auto-Injector usage (never incorporated in trial).

5 Approval Sheet

Product:	CHS-0214
Protocol Number:	CHS-0214-05
SAP Version:	1.2
Version Date:	25 October 2017

The individuals signing below have reviewed and approve this statistical analysis plan.

Jeff Vest, PhD
Project Biostatistician
Medpace

15-Nov-2017
Date

Barbara Finck, MD
Clinical/Medical Reviewer
Coherus Bioscience, Inc.

15 Nov 2017
Date

Helen Tang, MS
Biometrics Reviewer
Coherus Bioscience, Inc.

15 NOV 2017
Date