

CLINICAL STUDY PROTOCOL

PRODUCT: M923

STUDY TITLE: An open-label single-arm multicenter study to evaluate usability of a subcutaneous (SC) autoinjector (AI) for a proposed adalimumab biosimilar (M923) in subjects with moderate to severe rheumatoid arthritis (RA)

STUDY SHORT TITLE: Usability of an AI for M923 in subjects with moderate to severe RA

PROTOCOL IDENTIFIER: 911502

CLINICAL TRIAL PHASE 3

AMENDMENT 1: 2016 AUG 26

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Study Sponsor(s):

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1. STUDY PERSONNEL

1.1 Authorized Representative (Signatory) / Responsible Party

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1.2 Study Organization

The name and contact information of the responsible party and individuals involved with the study (eg, investigator(s), Sponsor's medical expert and study monitor, Sponsor's representative(s), laboratories, steering committees, and oversight committees [including ethics committees (ECs)], as applicable) will be maintained by the Sponsor and provided to the investigator.

2. SERIOUS ADVERSE EVENT REPORTING

The investigator will comply with applicable laws/requirements for reporting serious adverse events (SAEs) to the ECs.

ALL SAEs, INCLUDING SUSARs, ARE TO BE REPORTED ON THE SERIOUS ADVERSE EVENT REPORT (SAER) FORM AND TRANSMITTED TO THE SPONSOR WITHIN 24 HOURS AFTER BECOMING AWARE OF THE EVENT.

**Drug Safety contact information: see SAE Report Form.
Refer to SAE Protocol Sections and the study team roster for further information.**

For definitions and information on the assessment of these events, refer to the following:

- Adverse event (AE), [Section 12.1](#)
 - SAE, [Section 12.1.1.1](#)
 - SUSARs, [Section 12.1.1.2](#)
 - Assessment of AEs, [Section 12.1.2](#)
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3. SYNOPSIS

INVESTIGATIONAL PRODUCT	
Name of Investigational Product (IP)	M923, a proposed adalimumab biosimilar
Name of Active Ingredient	Adalimumab
CLINICAL CONDITION/INDICATION	
<ul style="list-style-type: none">Rheumatoid arthritis (RA)	
PROTOCOL ID	911502
PROTOCOL TITLE	An open-label single-arm multicenter study to evaluate usability of a subcutaneous (SC) autoinjector (AI) for a proposed adalimumab biosimilar (M923) in subjects with moderate to severe rheumatoid arthritis (RA)
Short Title	Usability of an AI for M923 in subjects with moderate to severe RA
STUDY PHASE	Phase 3
PLANNED STUDY PERIOD	
Initiation	2016 Q1
Primary Completion	2016 Q3
Study Completion	2017 Q1
Duration	Up to 32 weeks
STUDY OBJECTIVES AND PURPOSE	
Study Purpose The purpose of this study is to evaluate the usability of an AI for the delivery of M923 in patients with RA.	
Primary Objective Evaluate the usability of the AI as assessed by the subject using the PRE- and POST-Self-Injection Assessment Questionnaire (SIAQ) questionnaire.	
Secondary Objectives <ol style="list-style-type: none">Evaluate the usability of the AI as assessed by observer rating of successful, hazard-free self-injection as assessed by the observer assessment checklistEvaluate the safety (including immunogenicity) and tolerability of M923	
CCI	
STUDY DESIGN	
Study Type/ Classification/ Discipline	Usability, Safety, Immunogenicity
Control Type	No control

Study Indication Type	Treatment
Intervention model	Single group
Blinding/Masking	Open label
Study Design	This study is an open-label, Phase 3, single-arm, multicenter study to evaluate the usability of an AI and safety of M923 targeting a total of 32 subjects with active, moderate to severe RA.
Planned Duration of Subject Participation	Up to 32 weeks (4-week Screening period, 4-week treatment period, 20-week treatment extension period, and 4-week safety follow-up period). Subjects who are inadequate responders, or who withdraw early or choose not to continue to the treatment extension period, will directly enter the 4-week safety follow-up period; all other subjects will enter the safety follow-up period on completion of the treatment extension period.
Primary Outcome Measure Usability of the AI as assessed by the subject ratings captured in the PRE- and POST-SIAQ modules at Week 4	
Secondary Outcome Measures Usability <ol style="list-style-type: none">Observer assessment of usability by the subjects as determined by (i) ability to successfully follow the steps in the Instructions for Use (IFU) to self-administer M923 via the AI and (ii) investigation of the frequency of observed or reported difficulties ('potential hazards') at Week 4 as well as change over timeEvaluations at Baseline and Week 2 for subject and observer assessments, as well as change over time Safety <ol style="list-style-type: none">Clinical safety and tolerability of M923 as assessed by vital signs, clinical laboratory results, electrocardiograms (ECGs), and adverse events (AEs) (including serious adverse events [SAEs], AEs leading to premature withdrawal, and injection site reactions)Immunogenicity of M923 assessed as proportion of subjects with evidence of seroconversion as measured by titer of anti-drug antibody (ADA) levels over time, and proportion of subjects with neutralizing ADAs (nADAs) <p>CCI</p> 	

INVESTIGATIONAL PRODUCT, DOSE AND MODE OF ADMINISTRATION	
Active Product	M923, a proposed adalimumab biosimilar Dosage form: 40 mg (0.8 mL) AI (Treatment Period) Dosage frequency: Every 2 weeks (Q2W) AI: 40 mg Q2W at Baseline/Day 1, Day 15 ±3 days and Day 29 ±3 days (Visits 2 to 4) Mode of Administration: SC
SUBJECT SELECTION	
Targeted Accrual	32 subjects enrolled from sites in the United States (US), to achieve 30 evaluable subjects, CCI [REDACTED]
Number of Groups/Arms/Cohorts	1
Inclusion Criteria	
<ol style="list-style-type: none"> 1. Subjects ≥18 years old at the time of Screening 2. Able to understand and communicate with the investigator and comply with the requirements of the study, and must give a written, signed and dated informed consent before any study related activity is performed. 3. RA diagnosed for at least 6 months before Screening 4. Meets classification criteria for RA by 2010 American College of Rheumatology/European League Against Rheumatism criteria 5. Active disease defined as both DAS28-C-reactive protein (CRP) >3.2 at Screening and 4 swollen and tender joints each on a 66/68 joint count at Screening and Baseline 6. Subjects must have at least 1 documented swollen and/or tender joint in their hand or wrist of the dominant hand as assessed by the investigator or designated assessor 7. Must be willing and able to attempt self-administration of SC injection(s) 8. Male subjects must be willing to abstain from sexual intercourse or be willing to use a condom in addition to having their female partner use another form of contraception such as an intra-uterine device, barrier method (eg, diaphragm or sponge; female condom not permitted) with spermicide, oral contraceptive, injectable progesterone, sub-dermal implant, unless their partners are infertile or surgically sterile from the time of the first administration of IP until 3 months after the last dose, or have been vasectomized with confirmation of sterility 9. Female subjects must have a negative pregnancy test at Screening and on admission to the clinic and must not be lactating. Female subjects must also agree to or be one of the following for the duration of the study until 5 months after the last dose: <ol style="list-style-type: none"> a. Abstain from sexual intercourse –OR– b. Use a method of contraception, as described in Inclusion Criterion 8, and to have their male partner use a condom –OR– c. Of non-childbearing potential, confirmed at Screening by fulfilling one of the following criteria: <ol style="list-style-type: none"> i. Post-menopausal, defined as amenorrhea for at least 12 months following cessation of all exogenous hormonal treatments and with follicle-stimulating hormone (FSH) levels within the laboratory defined post-menopausal range 	

- ii. If they do not meet the previous criterion (c.i.), due to use of exogenous hormonal treatment, they must be over 55 years of age and have had documented amenorrhea for at least 2 years
- iii. Documentation of irreversible surgical sterilization by hysterectomy, bilateral oophorectomy, bilateral tubal ligation (BTL; with no subsequent pregnancy at least 1 year from BTL) or bilateral salpingectomy

Exclusion Criteria

1. Prior use of systemic tumor necrosis factor (TNF) inhibitor therapy, including other investigational or licensed biosimilar TNF inhibitor therapies
2. Prior use of rituximab
3. Prior use of abatacept, tocilizumab, and tofacitinib within 4 weeks prior to Screening
4. Current use of a conventional disease-modifying anti-rheumatic drug (DMARD) other than the following: methotrexate orally (≤ 25 mg/day), hydroxychloroquine (≤ 400 mg/day) or sulfasalazine (≤ 3 g/day) at a stable dose for at least 4 weeks prior to Screening. If discontinued, methotrexate, hydroxychloroquine, and sulfasalazine must have been discontinued at least 4 weeks prior to Baseline. No other conventional DMARDs are permitted and no combination therapy is permitted.
5. Prior use of cytotoxic or alkylating agents such as, but not limited to, chlorambucil, cyclophosphamide or immunosuppressants such as cyclosporine, tacrolimus, mycophenolate, and azathioprine must have been discontinued for at least 90 days prior to Baseline
6. Current use of oral corticosteroids at a dose >10 mg/day prednisone or equivalent or change of dose within 2 weeks prior to Screening
7. Current use of more than 1 nonsteroidal anti-inflammatory drug. Doses used should not be greater than the maximum permitted per product labeling or dosing has been changed within 2 weeks prior to Baseline.
8. Prior use of injectable corticosteroids (intramuscular [IM], intra-articular [IA], or intravenous [IV]) within 6 weeks prior to Baseline
9. Prior or current use of other self-injected drugs, eg, insulin
10. All other prior non-RA concomitant treatments must be on a stable dose for at least 4 weeks before Baseline
11. Meets Class IV Steinbrocker criteria for disability/activities of daily living
12. Laboratory abnormalities at Screening deemed clinically significant by the investigator and/or Sponsor:
 - a. Hemoglobin <8.5 g/dL for women or 9.0 g/dL for men
 - b. White blood cell count $<3 \times 10^9/L$
 - c. Platelet count $<100 \times 10^9/L$
 - d. Aspartate transaminase (AST) or alanine transaminase (ALT) >2 times the upper limit of normal or bilirubin ≥ 3 mg/dL
 - e. Creatinine >1.6 mg/dL if female or >1.8 mg/dL if male
 - f. Proteinuria 3+ by dipstick

13. Presence of fibromyalgia (as a primary disease), another autoimmune rheumatologic illness or inflammatory arthritis, eg, systemic lupus erythematosus, gout. The presence of secondary Sjogren's syndrome is permitted. At the discretion of the investigator, a patient with stable and low-grade fibromyalgia may be included in the study if the fibromyalgia is not a primary disease and will not interfere with the assessment of RA (specifically in the diagnosis, severity classification, monitoring, and outcomes).
14. Joint surgery within the last 8 weeks prior to Screening
15. Severe, progressive, or uncontrolled renal, hepatic, metabolic, hematologic, gastrointestinal, endocrine, pulmonary, cardiac or neurologic disease, including pleural effusions or ascites, which in the opinion of the investigator would preclude the subject from adhering to or completing the study or where participation in the study exposes the subject to unfavorable benefit/risk
16. History or presence of signs and/or symptoms or a diagnosis of a demyelinating disorder
17. History or presence of Class III or IV New York Heart Association congestive heart failure
18. History or presence of symptoms suggestive of lymphoproliferative disorders, lymphoma, leukemia, myeloproliferative disorders, or multiple myeloma
19. Existing malignancy or history of any malignancy except adequately treated or excised non-metastatic basal cell or squamous cell cancer of the skin or cervical carcinoma in situ, with no more than 3 lifetime basal cell or squamous cell carcinomas
20. Chronic infections, recurrent infections (3 or more of the same infection requiring anti-infective treatment in any rolling 12-month period); any recent infection (ie, in the last 30 days) requiring hospitalization or any infection requiring parenteral anti-infective therapy within 30 days or oral infective therapies within 14 days of Baseline; herpes zoster within 6 months of Baseline or more than 2 lifetime episodes of herpes zoster; or history of systemic fungal infection or opportunistic infection (eg, coccidioidomycosis, histoplasmosis, toxoplasmosis).
21. History or presence of human immunodeficiency virus (HIV), Hepatitis B or C virus
22. History of active tuberculosis (TB) or untreated or inadequately treated latent TB. Tuberculosis screening requirements include negative QuantiFERON[®]; or purified protein derivative (PPD) and chest imaging (ie, x-ray) within 3 months of Screening
23. Subject has been exposed to an IP within 30 days (or 5 half-lives) prior to enrollment, whichever is longer, or is scheduled to participate in another clinical study involving an IP or investigational device during the course of this study
24. Subject is a family member or employee of the investigator or Baxalta or its partners

STATISTICAL ANALYSIS

Sample Size Calculation

Based on discussions with the US Food and Drug Administration, a sample size of 30 was judged to be adequate to achieve the objectives of the study. CCI [REDACTED]
[REDACTED]. Patients dropping out of the study will not be replaced.

Planned Statistical Analysis

Usability

The primary analysis of usability will be conducted at Week 4 at the end of the 4-week treatment period once enrollment is completed. This will trigger the planned interim analysis and interim Clinical Study Report, with the database being locked after the last subject completes Week 4. The Clinical Study Report will be supplemented with the data collected after Week 4 once the last subject completes the last visit.

Descriptive statistics for usability measurements will be presented by timepoint. Continuous responses will be summarized using N, mean, SD, median, minimum, and maximum. Categorical responses will be summarized by proportions.

Safety

Adverse events will be summarized by preferred term and system organ class. Laboratory, ECG and vital signs will be summarized by timepoint using N, mean, standard deviation (SD), minimum, median, and maximum.

Efficacy

CCI [REDACTED]

Pharmacokinetics

CCI [REDACTED]
[REDACTED]
[REDACTED]

4. TABLE OF CONTENTS

1. STUDY PERSONNEL	2
1.1 Authorized Representative (Signatory) / Responsible Party	2
1.2 Study Organization.....	2
2. SERIOUS ADVERSE EVENT REPORTING.....	3
3. SYNOPSIS	4
4. TABLE OF CONTENTS	10
5. LIST OF ABBREVIATIONS	14
6. BACKGROUND INFORMATION	18
6.1 Description of Investigational Product	18
6.2 Clinical Condition/Indication	18
6.3 Population to Be Studied.....	19
6.4 Findings from Nonclinical and Clinical Studies.....	19
6.5 Evaluation of Anticipated Risks and Benefits of the Investigational Product(s) to Human Subjects.....	21
6.6 Compliance Statement.....	21
7. STUDY PURPOSE AND OBJECTIVES	22
7.1 Study Purpose	22
7.2 Primary Objective.....	22
7.3 Secondary Objectives	22
7.3.1 Usability	22
7.3.2 Safety.....	22
CCI	
8. STUDY DESIGN.....	23
8.1 Brief Summary	23
8.2 Overall Study Design	23
8.3 Duration of Study Period(s) and Subject Participation	23
8.4 Outcome Measures	23
8.4.1 Primary Outcome Measure	23
8.4.2 Secondary Outcome Measures	24
8.4.2.1 Usability	24

8.4.2.2 Safety.....	24
CCI	
8.5 Randomization and Blinding.....	24
8.6 Investigational Product(s).....	25
8.6.1 Packaging, Labeling, and Storage.....	25
8.6.2 Administration.....	25
8.6.2.1 Injection Training.....	25
8.6.3 Description of Treatment.....	26
8.6.4 Investigational Product Accountability.....	26
8.7 Source Data.....	27
9. SUBJECT SELECTION, WITHDRAWAL, AND DISCONTINUATION.....	28
9.1 Inclusion Criteria.....	28
9.2 Exclusion Criteria.....	29
9.3 Withdrawal and Discontinuation.....	31
10. STUDY PROCEDURES.....	33
10.1 Informed Consent and Enrollment.....	33
10.2 Subject Identification Code.....	33
10.3 Screening and Study Visits.....	33
10.3.1 Screening Assessments.....	33
10.3.2 Baseline Assessments.....	34
10.3.3 Visit 3 (Day 15 ±3 days) Assessments.....	35
10.3.4 Visit 4 (Day 29 ±3 days) Assessments.....	36
10.3.5 Treatment Extension Period Assessments.....	37
10.3.6 Safety follow-up.....	38
10.4 Medications and Non-Drug Therapies.....	38
10.5 Subject Diary and Patient-reported Outcomes.....	40
10.6 Subject Completion/Withdrawal.....	40
10.7 Procedures for Monitoring Subject Compliance.....	41
11. ASSESSMENT OF USABILITY, EFFICACY AND PHARMACOKINETICS.....	42
11.1 Primary Usability Assessment.....	42
11.2 Secondary Usability Assessments.....	42
11.3 Immunogenicity Assessment.....	42
CCI	
12. ASSESSMENT OF SAFETY.....	45

12.1 Adverse Events	45
12.1.1 Definitions	45
12.1.1.1 Serious Adverse Event.....	45
12.1.1.2 Suspected Unexpected Serious Adverse Reaction (SUSAR).....	46
12.1.1.3 Non-Serious Adverse Event	46
12.1.1.4 Unanticipated Adverse Device Effect	46
12.1.1.5 Unexpected Adverse Events.....	46
12.1.1.6 Pre-existing Diseases.....	47
12.1.2 Assessment of Adverse Events	47
12.1.2.1 Severity	48
12.1.2.2 Causality	49
12.1.2.3 Safety Reporting	49
12.1.3 Medical Device Safety reporting	50
12.2 Urgent Safety Measures	51
12.3 Untoward Medical Occurrences	51
12.4 Non-Medical Complaints	52
12.5 Medical, Medication, and Non-Drug Therapy History	52
12.6 Physical Examinations	53
12.7 Clinical Laboratory Parameters	53
12.7.1 Hematology and Clinical Chemistry	54
12.7.2 Urinalysis	54
12.7.3 Assessment of Laboratory Values	54
12.7.3.1 Assessment of Abnormal Laboratory Values.....	54
12.7.4 Biobanking-Study Sample Storage	55
12.8 Vital Signs	55
12.9 Electrocardiograms	56
12.10 Local Injection Site Reaction Evaluation	56
13. STATISTICS	58
13.1 Sample Size and Power Calculations	58
13.2 Datasets and Analysis Cohorts	58
13.3 Handling of Missing, Unused, and Spurious Data.....	58
13.4 Methods of Analysis.....	58
13.4.1 Primary Outcome Measure.....	58
13.4.2 Secondary Outcome Measures	59
CCI	
13.5 Planned Interim Analysis of the Study	60
14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS	60
15. QUALITY CONTROL AND QUALITY ASSURANCE	61
15.1 Investigator’s Responsibility.....	61
15.1.1 Final Clinical Study Report	61

15.2 Training	61
15.3 Monitoring.....	61
15.4 Auditing	61
15.5 Non-Compliance with the Protocol	62
15.6 Laboratory and Reader Standardization	62
16. ETHICS	63
16.1 Subject Privacy	63
16.2 Ethics Committee and Regulatory Authorities	63
16.3 Informed Consent	63
16.4 Data Monitoring Committee.....	64
17. DATA HANDLING AND RECORD KEEPING.....	65
17.1 Confidentiality Policy	65
17.2 Study Documentation and Case Report Forms	65
17.3 Document and Data Retention.....	65
18. FINANCING AND INSURANCE.....	66
19. PUBLICATION POLICY.....	66
20. SUPPLEMENTS.....	67
20.1 Study Flow Chart.....	67
20.2 Schedule of Study Procedures and Assessments.....	68
20.3 Clinical Laboratory Assessments	71
CCI	
20.5 Self-Injection Assessment Checklist.....	74
20.6 Potential Hazards Checklist.....	75
CCI	
21. REFERENCES.....	77
22. SUMMARY OF CHANGES.....	78
INVESTIGATOR ACKNOWLEDGEMENT.....	84

Tables

Table 1 Injection Site Reaction Grading Scheme 57
Table 2 Schedule of Study Procedures and Assessments 68
Table 3 Clinical Laboratory Parameters 71

Figures

Figure 1 Study Design for Baxalta Clinical Study 911502..... 67

5. LIST OF ABBREVIATIONS

Abbreviation	Definition
ACPA	anti-citrullinated protein antibody
ADA	anti-drug antibody
AE	adverse event
AI	autoinjector
ALT	alanine aminotransferase
ANA	anti-nuclear antibody
anti-dsDNA	anti-double-stranded DNA
AST	aspartate aminotransferase
AUC	area under the curve
BTL	bilateral tubal ligation
CI	confidence interval
C _{max}	maximum concentration
CRF	case report form
CRP	C-reactive protein
CTA	Clinical Trial Agreement
DAS28	Disease Activity Score in 28 joints
DMARDs	disease-modifying anti-rheumatic drugs
DMC	data monitoring committee
DNA	deoxyribonucleic acid
EC	ethics committee
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EDV	early discontinuation visit
EU	European Union
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
Hb _{A1c}	glycosylated hemoglobin
<i>Continued on Next Page</i>	

Abbreviation	Definition
<i>Continued</i>	
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
IA	intra-articular
IB	Investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IFU	instructions for use
IgG1	immunoglobulin G subclass 1
IgM	immunoglobulin M
IM	intramuscular
IP	investigational product
IV	intravenous
IVRS	interactive voice response system
IWRS	interactive web response system
LTBI	latent TB infection
MTX	methotrexate
nADA	neutralizing anti-drug antibody
NMC	non-medical complaint
PA	posteroanterior
PGA	Patient Global Assessment
PK	pharmacokinetic
PPD	purified protein derivative
PRO	patient-reported outcome
Q2W	every 2 weeks
RA	rheumatoid arthritis
RF	rheumatoid factor
RSI	Reference Safety Information
<i>Continued on Next Page</i>	

Abbreviation	Definition
<i>Continued</i>	
SAE	serious adverse event
SAER	Serious Adverse Event Report
SC	subcutaneous
SD	standard deviation
SI	serious injuries
SIAQ	Self-injection Assessment Questionnaire
SIC	subject identification code
SUSAR	suspected unexpected serious adverse reaction
TB	Tuberculosis
TEAE	Treatment-emergent adverse event
TNF- α	tumor necrosis factor-alpha
UADE	unanticipated adverse device effect
US	United States
v	version

6. BACKGROUND INFORMATION

6.1 Description of Investigational Product

M923 (BAX2923) is a proposed similar biological medical product (hereafter referred to as “proposed biosimilar”) to HUMIRA[®] (adalimumab, AbbVie, Inc.; hereafter referred to as “Humira”). Adalimumab is a recombinant human immunoglobulin G subclass 1 (IgG1) monoclonal antibody specific for human tumor necrosis factor–alpha (TNF- α). Unlike etanercept, adalimumab does not bind to tumor necrosis factor–beta. Adalimumab was first approved by the United States (US) Food and Drug Administration in 2002 for treatment of rheumatoid arthritis (RA) and, later, for several other inflammatory conditions and has since been used widely, including in many large clinical studies. Hence, its effectiveness, tolerability, and safety are well established.

M923 is produced by recombinant deoxyribonucleic acid (DNA) technology in a CCI

[REDACTED]

[REDACTED]

6.2 Clinical Condition/Indication

The medical need for a biosimilar to Humira (adalimumab) is demonstrated with the approval and use of the originator product Humira and its place in the treatment of several chronic autoimmune or inflammatory diseases, including RA, juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, adult and pediatric Crohn’s disease, ulcerative colitis, hidradenitis suppurativa, and adult and pediatric plaque psoriasis.

Rheumatoid arthritis is a chronic autoimmune disease associated with approximately symmetrical inflammation of the joints of the hands and feet, leading to joint destruction,

and paraproteinemia (“rheumatoid factor”). The condition is associated with increased morbidity and mortality from all causes, and requires long-term treatment.^{2;3;4}

Medication administered via SC injection offers the option of self-administration, providing benefits for the patient and healthcare system.⁵ Patients with chronic diseases, such as RA, who are able to self-inject their medication gain control of their treatment schedule (within the limits of the product label) and treatment setting, thus improving their treatment experience.⁵ However, there are barriers to self-injection, including dexterity problems and injection anxiety, which can prevent self-injection being used successfully and lead to lower treatment adherence.⁵ This study seeks to evaluate usability of a SC AI for M923 in subjects with active, moderate to severe RA.

6.3 Population to Be Studied

The study will enroll 32 subjects with active, moderate to severe RA. Adult (≥ 18 years) male and female subjects will be considered to be eligible provided that they satisfy all of the eligibility criteria listed in [Section 9.1](#) and [Section 9.2](#).

6.4 Findings from Nonclinical and Clinical Studies

M923 has been characterized and compared with US- and European Union (EU)-sourced Humira using a battery of nonclinical in vitro assays, as well as an in vivo pharmacokinetics (PK) study in mice, and a PK and immunogenicity study in cynomolgus monkeys. The results of the pharmacology, PK, and immunogenicity assessments demonstrated similar biological activity of M923 and Humira. Specifically, the results indicated that M923 was similar to Humira in terms of binding activity for soluble human TNF- α , the human Fc γ receptor, human C1q complex, and the human neonatal Fc receptor; activity in the antibody-dependent cell-mediated cytotoxicity and complement-dependent cytotoxicity assays; potency in the L929 mouse fibroblast cell line assay; in vivo single-dose PK profile in mice and cynomolgus monkeys; and immunogenicity (in vivo in cynomolgus monkeys and ex vivo T-cell proliferation in human dendritic cells).

The PK profiles, safety, tolerability, and immunogenicity of M923, US Humira and EU Humira PK of M923 were evaluated in healthy volunteers in a Phase 1, randomized, double-blind, 3-arm, parallel-group, single-dose clinical study (Study #911301). Subjects received a single dose (40 mg) of M923 or Humira (US Reference Product or EU Reference Protein Product) and were followed-up for 71 days. Overall 324 healthy subjects were randomized and treated. All randomized subjects completed the study.

Mean serum concentration-time profiles for M923 (n=107), EU Humira (n=103), and US Humira (n=105) were similar in the primary PK analysis set of subjects. Median time to maximum concentration was 144.000 hours for M923 and EU Humira and 141.780 hours for US Humira. Geometric mean half-life was 311, 319, and 313 hours for M923, EU Humira, and US Humira, respectively. The geometric least-squares mean ratios for the primary PK parameters [C_{max} (maximum concentration), AUC(area under the curve)_(0-inf), and AUC₍₀₋₃₃₆₎] and secondary PK parameters [AUC₍₀₋₆₇₂₎, AUC₍₀₋₈₄₀₎, AUC₍₀₋₁₀₀₈₎, AUC₍₀₋₁₃₄₄₎, and AUC_(0-last)] were fully contained within the 90% confidence interval (CI) bounds of 80.00% to 125.00% for all treatment pairings. The secondary analyses performed utilizing PK analysis subsets based on immunogenicity designations (anti-drug antibody [ADA] PK analysis set and non-ADA PK analysis set; neutralizing ADA [nADA] PK analysis set and non-nADA PK analysis set) supported the primary analysis results.

Adalimumab exposure was weakly correlated with formation of confirmed ADAs and/or nADAs in subjects with low confirmed ADA titers. Review of individual adalimumab versus concentration time profiles did not reveal a consistent relationship between time of appearance of ADA or nADAs and time of last quantifiable adalimumab concentrations or with shape of the terminal phase in subjects with low titers at low titers (<1:8). ADAs with higher titers which appeared earlier after administration tended to be associated with a shorter time to last quantifiable concentration and elimination half-life. These observations appeared to be independent of treatment.

There appeared to be a relationship of lower overall exposure (AUC) and half-life and higher apparent clearance (CL/F) in the presence of ADAs compared to absence of ADAs (ADA versus non-ADA population) and in the presence of nADAs compared to absence of nADAs (nADA versus non-nADA population). It should be noted that these apparent ADA-correlated differences were independent of treatment (M923, US Humira, or EU Humira).

The overall incidence of ADA and nADA was comparable in each group (78.0% and 16.5%, respectively, for subjects on M923; 78.5% and 20.6% for EU Humira and 80.6% and 27.8% for US Humira).

In this study (Study #911301), M923, US Humira, and EU Humira were safe and well tolerated in the healthy subjects. No subjects died or withdrew from the study due to an AE. One subject reported SAEs of foot fracture, wound infection, and laceration as a result of trauma. All 3 events were assessed by the investigator as not related to study treatment. The percentage of subjects with at least 1 AE was comparable among the

3 treatment arms, ranging from 47.7% to 53.3%. Most of the AEs were considered mild and unrelated to treatment by the investigators. The number of subjects with severe AEs was low. Injection site reactions were mostly mild. No clinically significant trends over time or between the 3 treatment arms were observed in mean and median laboratory variables, vital signs measurements, and 12-lead electrocardiogram (ECG) results.

Thus, bioequivalence was demonstrated for all primary treatment comparisons (M923/US Humira; M923/EU Humira; EU Humira/US Humira) in Study# 911301. M923 was demonstrated to be well-tolerated and to have a safety profile comparable with those of EU Humira and US Humira after a single dose.

6.5 Evaluation of Anticipated Risks and Benefits of the Investigational Product(s) to Human Subjects

All risks, contraindications, precautions, dosage and administration considerations, drug interactions and overdose considerations that have been described for Humira apply to M923 (see Section 9.2 of the Investigator's Brochure [IB] for M923). The safety profile of M923 is anticipated to be similar to that of Humira; however, investigators should carefully monitor for all AEs, including AEs not described as associated with Humira.

6.6 Compliance Statement

This study will be conducted in accordance with this protocol, the International Council for Harmonisation Guideline for Good Clinical Practice E6 (ICH GCP, April 1996), Title 21 of the US Code of Federal Regulations, the European Clinical Trial Directive (2001/20/EC and 2005/28/EC), and applicable national and local regulatory requirements.

7. STUDY PURPOSE AND OBJECTIVES

7.1 Study Purpose

The purpose of this study is to evaluate the usability of an AI for the delivery of M923 in patients with RA.

7.2 Primary Objective

The primary objective of the study is to evaluate the usability of the AI as assessed by the subject.

7.3 Secondary Objectives

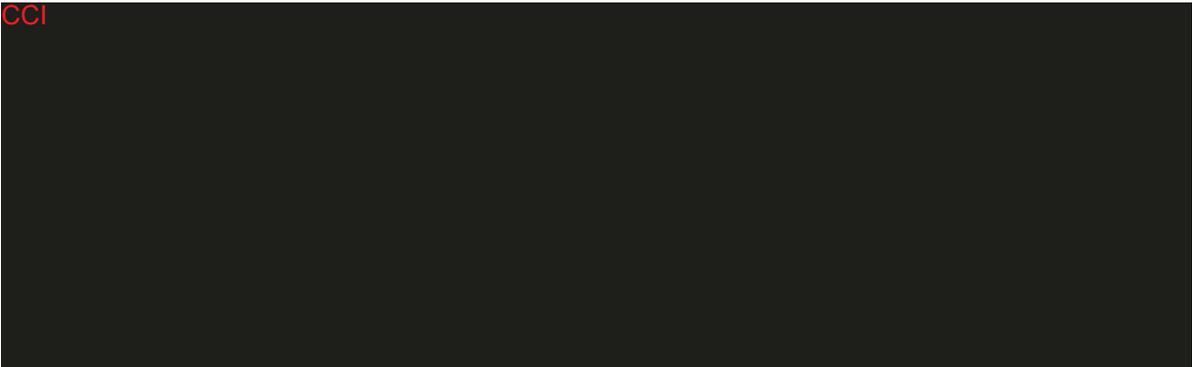
7.3.1 Usability

- Evaluate the usability of the AI as assessed by observer rating of successful, hazard-free self-injection as assessed by the observer assessment checklist

7.3.2 Safety

- Evaluate the safety (including immunogenicity) and tolerability of M923

CCI



8. STUDY DESIGN

8.1 Brief Summary

The proposed biosimilar M923 will be provided in a form for administration via an AI for SC self-injection in subjects with active, moderate to severe RA. The study purpose is to demonstrate that the AI demonstrates adequate usability.

8.2 Overall Study Design

This study is an open-label, Phase 3, single-arm, multicenter study to evaluate the usability of an AI and safety of M923 targeting a total of 32 subjects with active, moderate to severe RA. The overall study design is illustrated in [Figure 1](#).

8.3 Duration of Study Period(s) and Subject Participation

The overall duration of the study is up to 10 months from study initiation (ie, first subject enrolled) to study completion (ie, last subject last visit). The recruitment period is expected to be 4 months.

The planned duration of subject participation from enrollment to study completion for each subject (ie, last study visit), is up to 32 weeks (4-week Screening period, 4-week treatment period, 20-week treatment extension period, and 4-week safety follow-up period). Subjects who are considered inadequate responders, or who withdraw early or choose not to continue to the treatment extension period will continue for a 4-week safety follow-up period. All other subjects will enter the safety follow-up period on completion of the treatment extension period. An inadequate response is defined as a <20% improvement in the swollen joint count and tender joint count from Baseline to Week 12. Subjects with an inadequate response will be counseled about their treatment options and discontinue treatment at the Week 14 Visit.

8.4 Outcome Measures

8.4.1 Primary Outcome Measure

The primary outcome measure is usability of the AI as assessed by the subject ratings captured in the PRE- and POST-Self-injection Assessment Questionnaire (SIAQ) modules at Week 4 (see Section 20.4).

8.4.2 Secondary Outcome Measures

8.4.2.1 Usability

1. Observer assessment of usability by the subjects as determined by (i) ability to successfully follow the steps in the Instructions for Use (IFU) to self-administer M923 via the AI and (ii) investigation of the frequency of observed or reported difficulties ('potential hazards') at Week 4 as well as change over time (see Sections 20.4 and 20.6).
2. Evaluations at Baseline and Week 2 for subject and observer assessments, as well as change over time

8.4.2.2 Safety

1. Clinical safety and tolerability of M923 as assessed by vital signs, clinical laboratory results, ECGs, and AEs (including SAEs, AEs leading to premature withdrawal, and injection site reactions)
2. Immunogenicity of M923 assessed as proportion of subjects with evidence of seroconversion as measured by titer of ADA levels over time, and proportion of subjects with nADAs

CCI



8.5 Randomization and Blinding

This is a non-randomized, open-label, single-arm clinical study.

8.6 Investigational Product(s)

8.6.1 Packaging, Labeling, and Storage

The investigational product (IP) for this study is M923, which is a clear, colorless, sterile solution for SC injection. M923 is supplied as an AI dosage form. This dosage form is a single-use with a 1 mL capacity, which delivers 40 mg (0.8 mL) of M923 drug substance (proposed biosimilar adalimumab). CCI [REDACTED]

[REDACTED] M923 for injection will be supplied by Baxalta or representative, and stored in compliance with Good Manufacturing Practice conditions and labeled in accordance with local regulations.

A sufficient quantity of 1.0 mL AIs (containing 0.8 mL as described above) containing 40 mg M923 will be supplied to each study site by Fisher Clinical Services. Fisher will package and label the M923 AIs, which will be released by a Qualified Person at Fisher to each study site.

Individual subject treatment will be dispensed at each study site labeled in accordance with Good Manufacturing Practice Annex 13 requirements.

All IP should be stored in a refrigerator at 2°C to 8°C in the original container, protected from light, in a secure, temperature-controlled, locked environment with restricted access. Do not freeze and do not use if frozen, even if it has been thawed.

The Sponsor will be permitted upon request to audit the supplies, storage, dispensing procedures, and records provided that the blind of the study is not compromised.

8.6.2 Administration

M923 in AI (as supplied) will be administered via SC injection to the lower abdomen or thigh. There are no special requirements regarding food with respect to dosing. Administration is recommended to be on the same day Q2W (± 3 days at Visits 2 to 4 and ± 3 days at Visits 5 to 14) and at the same time of day. Directions for use materials will be provided.

8.6.2.1 Injection Training

Study staff will train subjects on the SC injection procedure for the AI dosage form. Self-injection training should be provided at Baseline (Week 0, Visit 2) prior to the first injection. Site staff will show the subject how to self-administer IP using the AI and subjects will perform their first injection under observation in the clinic. The training and performance of self-injection will be documented in the subject's source documents.

If the subject requests it, additional training can be provided at Visit 3 (Week 2) prior to the second injection. The subject should perform the injection at Weeks 2 and 4 (Visits 3 and 4) under observation in the clinic. Site staff should observe the injection at Weeks 0, 2 and 4 (Visits 2 to 4) to ensure it is being performed correctly and provide re-training as necessary, indicated by a subject request for additional training.

Subjects are to be instructed that used AIs must be placed in a safety container provided by the Sponsor. This safety container should be returned to the investigational site for disposal once full or at the end of the study.

8.6.3 Description of Treatment

Subjects will self-administer 40 mg of M923 Q2W starting at the Baseline Visit 2. Self-injection should occur on the same day each treatment week (± 3 days at Visits 3 and 4 and could be ± 3 days at Visits 5 to 14) targeting the same time of day. At Baseline and Weeks 2 and 4 (Visits 2 to 4), injections will be administered by the subject using the AI under the observation of the study site staff in the clinic after all required assessments and blood sample collections have been completed. Subjects should be observed for 2 hours post-injection at Baseline and Week 2 and for 30 minutes post-injection at Week 4.

At any time during the study, the IP may be interrupted or discontinued at the discretion of the investigator based on his/her evaluation of the subject's condition or safety. No dose modification is permitted for this study.

Any injection site reactions, regardless of causality, will be recorded on the AE case report form (CRF). Any concomitant medications, including those used to treat AE(s), will be recorded on the appropriate CRF.

8.6.4 Investigational Product Accountability

The investigator will ensure that the IP is stored as specified in the protocol and that the storage area is secured, with access limited to authorized study personnel. The investigator will maintain records that the IP was received, including the date received, drug identity code, date of manufacture or expiration date, amount received, and disposition. Investigational Product must be dispensed only at the study site. Records will be maintained that include the subject identification code (SIC), dispensation date, and amount dispensed. All remaining partially used and/or unused IP will be returned to the Sponsor or Sponsor's representative after study completion/termination, or destroyed with the permission of the Sponsor in accordance with applicable laws and study site procedures. If IP is to be destroyed, the investigator will provide documentation in accordance with Sponsor's specifications.

8.7 Source Data

Per ICH GCP, source data are defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study that are necessary for the reconstruction and evaluation of the study. Source data are contained in source documents (original records or certified copies), which may be in paper and/or electronic format. Source data for this study comprise the following: hospital records, medical records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, outcomes reported by subjects, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical study.

For additional information on study documentation and CRFs, see [Section 17.2](#). The use of subject diaries is described in [Section 10.5](#).

9. SUBJECT SELECTION, WITHDRAWAL, AND DISCONTINUATION

9.1 Inclusion Criteria

Subjects who meet **ALL** of the following criteria are eligible for this study:

1. Subjects ≥ 18 years old at the time of Screening
 2. Able to understand and communicate with the investigator and comply with the requirements of the study, and must give a written, signed and dated informed consent before any study related activity is performed
 3. RA diagnosed for at least 6 months before Screening
 4. Meets classification criteria for RA by 2010 American College of Rheumatology/European League Against Rheumatism criteria
 5. Active disease defined as both DAS28-CRP > 3.2 at Screening and 4 swollen and tender joints each on a 66/68 joint count at Screening and Baseline
 6. Subjects must have at least 1 documented swollen and/or tender joint in their hand or wrist of the dominant hand as assessed by the investigator or designated assessor
 7. Must be willing and able to attempt self-administration of SC injection(s)
 8. Male subjects must be willing to abstain from sexual intercourse or be willing to use a condom in addition to having their female partner use another form of contraception such as an intra-uterine device, barrier method (eg, diaphragm or sponge; female condom not permitted) with spermicide, oral contraceptive, injectable progesterone, sub-dermal implant, unless their partners are infertile or surgically sterile from the time of the first administration of IP until 3 months after the last dose, or have been vasectomized with confirmation of sterility
 9. Female subjects must have a negative pregnancy test at Screening and on admission to the clinic and must not be lactating. Female subjects must also agree to or be one of the following for the duration of the study until 5 months after the last dose:
 - a. Abstain from sexual intercourse –OR–
 - b. Use a method of contraception, as described in Inclusion Criterion 8, and to have their male partner use a condom –OR–
 - c. Of non-childbearing potential, confirmed at Screening by fulfilling one of the following criteria:
 - i. Post-menopausal, defined as amenorrhea for at least 12 months following cessation of all exogenous hormonal treatments and with
-

follicle-stimulating hormone (FSH) levels within the laboratory defined post-menopausal range

- ii. If they do not meet the previous criterion (c.i.), due to use of exogenous hormonal treatment, they must be over 55 years of age and have had documented amenorrhea for at least 2 years
- iii. Documentation of irreversible surgical sterilization by hysterectomy, bilateral oophorectomy, bilateral tubal ligation (BTL; with no subsequent pregnancy at least 1 year from BTL) or bilateral salpingectomy

9.2 Exclusion Criteria

Subjects who meet **ANY** of the following criteria are not eligible for this study:

1. Prior use of systemic TNF inhibitor therapy, including other investigational or licensed biosimilar TNF inhibitor therapies
 2. Prior use of rituximab
 3. Prior use of abatacept, tocilizumab and tofacitinib within 4 weeks prior to Screening
 4. Current use of a conventional disease modifying anti-rheumatic drugs (DMARD) other than the following: methotrexate orally (≤ 25 mg/day), hydroxychloroquine (≤ 400 mg/day) or sulfasalazine (≤ 3 g/day) at a stable dose for at least 4 weeks prior to Screening. If discontinued, methotrexate, hydroxychloroquine, and sulfasalazine must have been discontinued at least 4 weeks prior to Baseline. No other conventional DMARDs are permitted and no combination therapy is permitted.
 5. Prior use of cytotoxic or alkylating agents such as, but not limited to, chlorambucil, cyclophosphamide, or immunosuppressants such as cyclosporine, tacrolimus, mycophenolate, and azathioprine must have been discontinued for at least 90 days prior to Baseline
 6. Current use of oral corticosteroids at a dose >10 mg/day prednisone or equivalent or change of dose within 2 weeks prior to Screening
 7. Current use of more than 1 nonsteroidal anti-inflammatory drug. Doses used should not be greater than the maximum permitted per product labeling or dosing has been changed within 2 weeks prior to Baseline
 8. Prior use of injectable corticosteroids (intramuscular [IM], intra-articular [IA], or intravenous [IV]) within 6 weeks prior to Baseline
 9. Prior or current use of other self-injected drugs, eg, insulin
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10. All other prior non-RA concomitant treatments must be on a stable dose for at least 4 weeks before Baseline
 11. Meets Class IV Steinbrocker criteria for disability/activities of daily living
 12. Laboratory abnormalities at Screening deemed clinically significant by the investigator and/or Sponsor:
 - a. Hemoglobin <8.5 g/dL for women or 9.0 g/dL for men
 - b. White blood cell count < 3×10^9 /L
 - c. Platelet count < 100×10^9 /L
 - d. Aspartate transaminase (AST) or alanine transaminase (ALT) >2 times the upper limit of normal or bilirubin ≥ 3 mg/dL
 - e. Creatinine >1.6 mg/dL if female or >1.8 mg/dL if male
 - f. Proteinuria 3+ by dipstick
 13. Presence of fibromyalgia (as a primary disease), another autoimmune rheumatologic illness or inflammatory arthritis, eg, systemic lupus erythematosus, gout. The presence of secondary Sjogren's syndrome is permitted. At the discretion of the investigator, a patient with stable and low-grade fibromyalgia may be included in the study if the fibromyalgia is not a primary disease and will not interfere with the assessment of RA (specifically in the diagnosis, severity classification, monitoring, and outcomes).
 14. Joint surgery within the last 8 weeks prior to Screening
 15. Severe, progressive, or uncontrolled renal, hepatic, metabolic, hematologic, gastrointestinal, endocrine, pulmonary, cardiac or neurologic disease, including pleural effusions or ascites, which in the opinion of the investigator would preclude the subject from adhering to or completing the study or where participation in the study exposes the subject to unfavorable benefit/risk
 16. History or presence of signs and/or symptoms or a diagnosis of a demyelinating disorder
 17. History or presence of Class III or IV New York Heart Association congestive heart failure
 18. History or presence of symptoms suggestive of lymphoproliferative disorders, lymphoma, leukemia, myeloproliferative disorders, or multiple myeloma
 19. Existing malignancy or history of any malignancy except adequately treated or excised non-metastatic basal cell or squamous cell cancer of the skin or cervical carcinoma in situ, with no more than 3 lifetime basal cell or squamous cell carcinomas
-

20. Chronic infections, recurrent infections (3 or more of the same infection requiring anti-infective treatment in any rolling 12-month period); any recent infection (ie, in the last 30 days) requiring hospitalization or any infection requiring parenteral anti-infective therapy within 30 days or oral infective therapies within 14 days of Baseline; herpes zoster within 6 months of Baseline or more than 2 lifetime episodes of herpes zoster; or history of systemic fungal infection or opportunistic infection (eg, coccidioidomycosis, histoplasmosis, toxoplasmosis)
21. History or presence of human immunodeficiency virus (HIV), Hepatitis B or C virus
22. History of active tuberculosis (TB) or untreated or inadequately treated latent TB. Tuberculosis screening requirements include negative QuantiFERON[®]; or purified protein derivative (PPD) and chest imaging (ie, x-ray) within 3 months of Screening
23. Subject has been exposed to an IP within 30 days (or 5 half-lives) prior to enrollment, whichever is longer, or is scheduled to participate in another clinical study involving an IP or investigational device during the course of this study
24. Subject is a family member or employee of the investigator or Baxalta or its partners

9.3 Withdrawal and Discontinuation

Any subject may voluntarily withdraw consent for continued participation in the study. This includes collection of their data. The reason for withdrawal will be recorded on the End of Study CRF. Assessments to be performed at the withdrawal visit are described in [Section 10.6](#) and [Section 20.2](#).

Additionally, the investigator and Sponsor have the discretion to discontinue any subject from the study if, in their judgment, continued participation would pose an unacceptable risk for the subject.

Subjects also will be discontinued from treatment or withdrawn from further study participation for the following reasons:

- The subject becomes pregnant. IP exposure will be discontinued. Attempts will be made to follow the subject through completion of the pregnancy and up to 1 year post-delivery, if feasible. The investigator will record a narrative description of the course of the pregnancy and its outcome.
 - The subject misses 3 consecutive administrations after Week 4 or more than 5 total administrations of IP overall. The subject will be discontinued from treatment.
-

- Subjects considered to have an inadequate response, defined as a <20% improvement in the swollen joint count and tender joint count from Baseline to Week 12, will be withdrawn at Week 14
 - AEs/SAEs that, in the investigator's or Sponsor's opinion, pose an unacceptable risk for continued dosing in the subject
 - The subject is determined by the Sponsor or investigator to be noncompliant with administration of IP, or despite evidence of retraining of the subject. The subject will be withdrawn from further participation in the study.
 - Participation in another clinical study involving an IP during the course of the study
-

10. STUDY PROCEDURES

10.1 Informed Consent and Enrollment

Any patient who provides informed consent (ie, signs and dates the informed consent form [ICF] and assent form, if applicable) is considered a study subject and enrolled in the study.

10.2 Subject Identification Code

PPD

All study documents (eg, CRFs, clinical documentation, sample containers, drug accountability logs, etc.) will be identified with the SIC. Additionally, a uniquely coded SIC(s) is permitted as long as it does not contain a combination of information that allows identification of a subject (eg, collection of a subject's initials and birth date would not be permitted), in compliance with laws governing data privacy.

10.3 Screening and Study Visits

The study site is responsible for maintaining an enrollment/screening log that includes all subjects enrolled. The log also will serve to document the reason for screening failure. All screening data will be collected and reported in CRFs, regardless of screening outcome. If a subject is re-screened with the approval of the medical advisor or sponsor study physician, the End of Study CRF should be completed, and a new ICF, new SIC and new CRF are required for that subject.

The overall study design is illustrated in the [Figure 1](#). Details on the procedures to be performed at each study visit, including Screening, can be found in [Section 20.2](#) Schedule of Study Procedures and Assessments and [Section 20.3](#) Clinical Laboratory Assessments.

10.3.1 Screening Assessments

After informed consent has been obtained, subjects will be screened on-site for eligibility based on the inclusion and exclusion criteria defined in [Section 9.1](#) and [Section 9.2](#), respectively. Screening must be performed within 28 days of Baseline, allowing enough time from Screening (Visit 1, Days -28 to Baseline) to Baseline (Visit 2, Day 1) in order to ensure eligibility requirements for Screening are met.

Screening assessments conducted at Visit 1 (Days -28 to Day 0) will include the following:

- Informed consent process
- Relevant medical history including prior RA therapy
- Eligibility evaluation (review of eligibility criteria)
- Contact interactive web response system/interactive voice response system (IWRS/IVRS) to enroll subject
- Review of concomitant medications, including pharmacologic and non-pharmacologic therapies
- TB screening (see [Section 12.5](#))
- Joint count (see [Section 20.2](#))
- Viral serology tests for HIV, Hepatitis B virus (HBV), and Hepatitis C virus (HCV) (see [Section 12.5](#))
- AE monitoring (see [Section 12.1](#))
- Complete physical examination (see [Section 12.6](#))
- 12-lead ECG, performed prior to blood sampling (see [Section 12.9](#))
- Vital signs, performed prior to blood sampling (see [Section 12.8](#))
- Clinical laboratory assessments (hematology and clinical chemistry; see [Section 12.7.1](#))
- Serology tests for rheumatoid factor (RF) and anti-citrullinated protein antibody (ACPA) (see [Section 12.5](#))
- Urinalysis (see [Section 12.7.2](#))
- Serum pregnancy test (female subjects of childbearing potential only)

10.3.2 Baseline Assessments

Baseline assessments conducted at Visit 2 (Day 1) will include the following:

- Eligibility evaluation reviewed (inclusion/exclusion criteria)
 - Contact IWRS/IVRS to assign subject to treatment
 - Review of concomitant medications, including pharmacologic and non-pharmacologic therapies
 - Joint count (see [Section 20.2](#))
-

- AE collection (see [Section 12.1](#))
- Focused physical examination (see [Section 12.6](#))
- Vital signs, performed prior to blood sampling, within 30 minutes before and after administration of IP (see [Section 12.8](#))
- PK and immunogenicity, with blood samples collected prior to clinical laboratory assessments (hematology/clinical chemistry) and self-administration of IP (see [Sections 11.3](#) and [11.5](#))
- Clinical laboratory assessments (hematology and clinical chemistry; see [Section 12.7.1](#)), performed prior to self-administration of IP
- Serology tests for the following ADAs: anti-nuclear antibody (ANA) and anti-double-stranded DNA (anti-dsDNA) (see [Section 11.3](#))
- Urinalysis (see [Section 12.7.2](#))
- Urine pregnancy test (female subjects of childbearing potential only)
- Patient-reported outcomes (PROs): PRE- and POST-SIAQ questionnaires to be completed by the subject prior to and after self-administration of IP, respectively (see [Section 11.1](#))
- Patient global assessments (see [Section 11.4.2](#))
- Self-injection training provided by study staff at the site (see [Section 8.6.2.1](#))
- Self-administration of IP following completion of all required assessments and blood sample collections. Subjects should be observed for 2 hours post-injection.
- Injection site evaluation performed by investigator (or qualified designee) before IP administration (see [Section 12.10](#)) and 30 minutes after self-administration of IP
- Observer-reported questionnaire: assessment of subject self-injection completed by observer. Re-training of subject provided after observation of full injection completed as necessary (see [Section 11.2](#)).

10.3.3 Visit 3 (Day 15 ±3 days) Assessments

- Review of concomitant medications, including pharmacologic and non-pharmacologic therapies
 - 28 joint count (see [Section 11.4.1](#))
 - AE collection (see [Section 12.1](#))
-

- Vital signs, performed within 30 minutes before and after administration of IP (see [Section 12.8](#))
- PROs: PRE- and POST-SIAQ questionnaires to be completed by the subject prior to and after self-administration of IP, respectively (see [Section 11.1](#))
- Self-injection training provided by study staff at the site (see [Section 8.6.2.1](#))
- Self-administration of IP following completion of all required assessments. Subjects should be observed for 2 hours post-injection.
- Injection site evaluation performed by investigator (or qualified designee) before IP administration (see [Section 12.10](#)) and 30 minutes after self-administration of IP
- Observer-reported questionnaire: assessment of subject self-injection completed by observer. Re-training of subject provided after observation of full injection completed as necessary (see [Section 11.2](#)).

10.3.4 Visit 4 (Day 29 ±3 days) Assessments

- Review of concomitant medications, including pharmacologic and non-pharmacologic therapies
 - 28 joint count (see [Section 11.4.1](#))
 - AE collection (see [Section 12.1](#))
 - Focused physical examination (see [Section 12.6](#))
 - Vital signs, performed prior to blood sampling, within 30 minutes before and after administration of IP (see [Section 12.8](#))
 - PK and immunogenicity, with blood samples collected prior to clinical laboratory assessments (hematology/clinical chemistry) and self-administration of IP (see [Sections 11.3](#) and [11.5](#))
 - Clinical laboratory assessments (hematology and clinical chemistry; see [Section 12.7.1](#)), performed prior to self-administration of IP
 - Urinalysis (see [Section 12.7.2](#))
 - Patient global assessments (see [Section 11.4.2](#))
 - Urine pregnancy test (female subjects of childbearing potential only)
 - PROs: PRE- and POST-SIAQ questionnaires to be completed by the subject prior to and after self-administration of IP, respectively (see [Section 11.1](#))
-

- Self-administration of IP following completion of all required assessments and blood sample collections. Subjects should be observed for 30 minutes post-injection.
- Injection site evaluation performed by investigator (or qualified designee) before IP administration (see [Section 12.10](#)) and 30 minutes after self-administration of IP
- Observer-reported questionnaire: assessment of subject self-injection completed by observer. Re-training of subject provided after observation of full injection completed as necessary (see [Section 11.2](#)).
- Drug dispensing (4 weeks' supplies of M923 AIs)

10.3.5 Treatment Extension Period Assessments

Following Visit 4, subjects will self-administer IP at home, except at Visits 8 and 14. Visits will be conducted at the following timepoints (± 3 days targeted) during the treatment extension period: Visit 5 (Week 6), Visit 6 (Week 8), Visit 7 (Week 10), Visit 8 (Week 12), Visit 9 (Week 14), Visit 10 (Week 16), Visit 11 (Week 18), Visit 12 (Week 20), Visit 13 (Week 22), and Visit 14 (Week 24). Assessments performed at each study visit during the treatment extension period (except where indicated below) will include the following:

- Contact IWRS/IVRS to confirm continuation of treatment (Visit 9 only)
 - Review of concomitant medications, including pharmacologic and non-pharmacologic therapies
 - 28 joint count at Visits 8 and 14/EDV (see [Section 11.4.1](#))
 - AE collection (see [Section 12.1](#))
 - Focused physical examination at Visits 8 and 14/early discontinuation visit (EDV) (see [Section 12.6](#))
 - Vital signs at Visits 8 and 14/EDV, performed prior to blood sampling (when taken at Visits 8 and 14/EDV), within 30 minutes before and after administration of IP (see [Section 12.8](#))
 - PK and immunogenicity at Visits 8 and 14/EDV, with blood samples collected prior to clinical laboratory assessments (hematology/clinical chemistry) and self-administration of IP (see [Sections 11.3](#) and [11.5](#))
 - Clinical laboratory assessments at Visits 8 and 14/EDV (hematology and clinical chemistry; see [Section 12.7.1](#)), performed prior to self-administration of IP
-

- Urinalysis at Visits 8 and 14/EDV (see [Section 12.7.2](#))
- Patient global assessment at Visits 8 and 14 (see [Section 11.4.2](#))
- Urine pregnancy test at Visits 8 and 14 (female subjects of childbearing potential only)
- Drug dispensing at Visit 8 (6 weeks' supplies of M923 AIs)

10.3.6 Safety follow-up

On completion of the treatment extension period or at premature withdrawal, the following assessments will be performed during the 4-week safety follow-up period:

- Contact IWRS/IVRS to record end of treatment
- Review of concomitant medications, including pharmacologic and non-pharmacologic therapies
- AE collection (see [Section 12.1](#))
- Focused physical examination (see [Section 12.6](#))
- Vital signs performed prior to blood sampling (see [Section 12.8](#))
- PK and immunogenicity, with blood samples collected prior to clinical laboratory assessments (hematology/clinical chemistry) (see [Sections 11.3](#) and [11.5](#))
- Clinical laboratory assessments (hematology and clinical chemistry; see [Section 12.7.1](#))
- Serology tests for ADAs (ANA and anti-dsDNA) (see [Section 11.3](#))

10.4 Medications and Non-Drug Therapies

During the study, subjects are expected to be on concomitant medication(s) if they are being treated or receiving prophylaxis for any underlying medical conditions, provided the medications are not considered RA therapies and subjects have been on a stable dose for at least 4 weeks before Baseline. Subjects may take permitted additional concomitant medication(s) as required for medical management during this study. All medications taken 4 weeks prior to Screening and concomitant medication use should be recorded in the appropriate CRF. Exposure to all biologic medications at any time should be collected.

The following medications and non-drug therapies are **not** permitted before study entry and/or during the course of the study:

- Medications:
-

- Use of systemic TNF inhibitor therapy, including other investigational or licensed biosimilar TNF inhibitor therapies, is not permitted
- Use of rituximab is not permitted
- Abatacept, tocilizumab and tofacitinib should have been discontinued at least 4 weeks prior to Screening
- With the exception of methotrexate (MTX) orally (≤ 25 mg), hydroxychloroquine (≤ 400 mg/day) or sulfasalazine (≤ 3 g/day) at a stable dose for at least 4 weeks prior to Screening, no other conventional DMARDs are permitted and no combination therapy is permitted. If discontinued, MTX, hydroxychloroquine, and sulfasalazine must have been discontinued at least 4 weeks prior to Baseline.
- Cytotoxic or alkylating agents such as, but not limited to, chlorambucil, cyclophosphamide or immunosuppressants such as cyclosporine, tacrolimus, mycophenolate, and azathioprine must have been discontinued for at least 90 days prior to Baseline
- Injectable corticosteroids (eg, IM, IA, or IV) are not permitted within 6 weeks prior to Baseline
- Prior or current use of other self-injected drugs, eg, insulin, is not permitted
- Non-drug therapies:
 - Joint surgery within 8 weeks of Screening

A subject who has taken any of these medications or received any of these non-drug therapies will be withdrawn. The subject will then enter the 4-week safety follow-up period as described in [Section 10.3.6](#).

The following medications and non-drug therapies are permitted before study entry and during the course of the study:

- Medications:
 - Subjects on the following conventional DMARDs should be on a stable dose for at least 4 weeks prior to Screening: MTX orally (≤ 25 mg/day), hydroxychloroquine (≤ 400 mg/day) or sulfasalazine (≤ 3 g/day)
 - Oral corticosteroids are permitted at a dose of ≤ 10 mg/day prednisone or equivalent if the subject has been stable for at least 2 weeks prior to Screening
-

- Use of 1 nonsteroidal anti-inflammatory drug is permitted up to the maximum doses permitted per labeling, provided the dose is stable for at least 2 weeks prior to Screening

All other prior non-RA concomitant treatments must be on a stable dose for at least 4 weeks before Baseline.

10.5 Subject Diary and Patient-reported Outcomes

A paper subject diary will be provided to each subject at Baseline to record the following information:

1. Time, date, and location of IP administration, including whether the full dose was administered and, if not, the reason why the full dose was not administered (eg, device malfunction)
2. IP administrator (self)
3. AEs, including injection site reactions
4. PROs: PRE- and POST-SIAQ questionnaires to be completed by the subject prior to and after self-administration of IP, respectively

Subjects will be trained on use of the diary. The diary will be provided in paper format and remain with the subject for the duration of the study. The investigator will review the diary for completeness and request missing information periodically and in a timely manner. Untoward events recorded in the diary will be reported as AEs according to the investigator's discretion and clinical judgment.

The subject diary will serve as a source record and remain at the study site. Entries in the subject diary will be transferred into the appropriate collection device. Any entry in the collection device that does not correspond with an entry in the subject diary will be explained by the investigator in source documentation.

10.6 Subject Completion/Withdrawal

A subject is considered to have completed the study when he/she ceases active participation in the study because the subject has, or is presumed to have, completed all study procedures in accordance with the protocol (with or without protocol deviations).

Reasons for completion/discontinuation will be reported on the Completion/Discontinuation CRF, including: completed, screen failure, AE (eg, death), discontinuation by subject (eg, lost to follow-up [defined as 3 documented unsuccessful attempts to contact the subject], dropout), physician decision (eg, pregnancy, progressive

disease, non-compliance with IP/protocol violation[s], recovery), study terminated by Sponsor, or other (reason to be specified by the investigator, eg, technical problems). Regardless of the reason, all data available for the subject up to the time of completion/discontinuation should be recorded on the appropriate CRF.

Every effort will be made to have discontinued subjects complete the study completion/termination visit. If the completion/termination visit is done as an additional, unscheduled visit, the assessment results shall be recorded with the completion/termination visit. If a subject terminates participation in the study and does not return for the completion/termination visit, their last recorded assessments shall remain recorded with their last visit. The reason for discontinuation will be recorded, and the data collected up to the time of discontinuation will be used in the analysis and included in the clinical study report. If additional assessments are required, the assessments shall be recorded separately. Assessments to be performed at the termination visit (including in cases of withdrawal or discontinuation) can be found in [Sections 20.2](#) and [20.3](#).

In the event of subject discontinuation due to an AE, clinical and/or laboratory investigations that are beyond the scope of the required study observations/assessments may be performed as part of the evaluation of the event. These investigations will take place under the direction of the investigator in consultation with the Sponsor, and the details of the outcome may be reported to the appropriate regulatory authorities by the Sponsor.

10.7 Procedures for Monitoring Subject Compliance

Subject compliance with the treatment regimen will be monitored by completion of a subject diary detailing the time and date of self-administration/home treatment of M923.

11. ASSESSMENT OF USABILITY, EFFICACY AND PHARMACOKINETICS

11.1 Primary Usability Assessment

The primary outcome measure is the usability of the M923 AI as assessed by the subject rating on the PRE- and POST-SIAQ modules at Week 4 of the treatment period.

Usability will be assessed using the SIAQ tool (version [v] 2.1), which is a valid, reliable PRO instrument in patients with RA.⁵

The PRE-SIAQ module (v2.1) is a 7-item questionnaire that investigates feelings about injections, self-confidence (regarding self-administration), and satisfaction with self-injection (each item graded on a 5-point scale).⁵ The POST-SIAQ module (v2.1) is a 27 item questionnaire that assesses feelings about injections, self-image, self-confidence (regarding self-administration), pain and skin reactions during or after the injection (injection-site reactions), ease of use of the self-injection device, and satisfaction with self-injection. Each item graded on either a 5-point or 6-point scale (see Section 20.4). Subjects will complete the PRE- and POST-SIAQ questionnaires prior to and after self-administration of IP, respectively, Q2W during the initial 4-week treatment period (see [Section 20.2](#)). This assessment should be recorded in the eCRF.

11.2 Secondary Usability Assessments

Secondary usability measures are observer assessment of usability by subjects as determined by (i) ability to successfully follow the steps in the IFU to self-administer M923 via the AI and (ii) investigation of the frequency of observed or reported difficulties ('potential hazards') at Week 4, as well as change over time. At Weeks 0, 2, and 4 (Visits 2 to 4), the observer should observe the subject perform self-injection and complete the observer questionnaire (see Sections 20.4 and [20.6](#)). In addition, usability evaluations at Baseline and Week 2 will be performed for subject (completion of PRE- and POST-SIAQ instruments as described in [Section 11.1](#)) and observer assessments, as well as change over time. This assessment should be recorded in the eCRF.

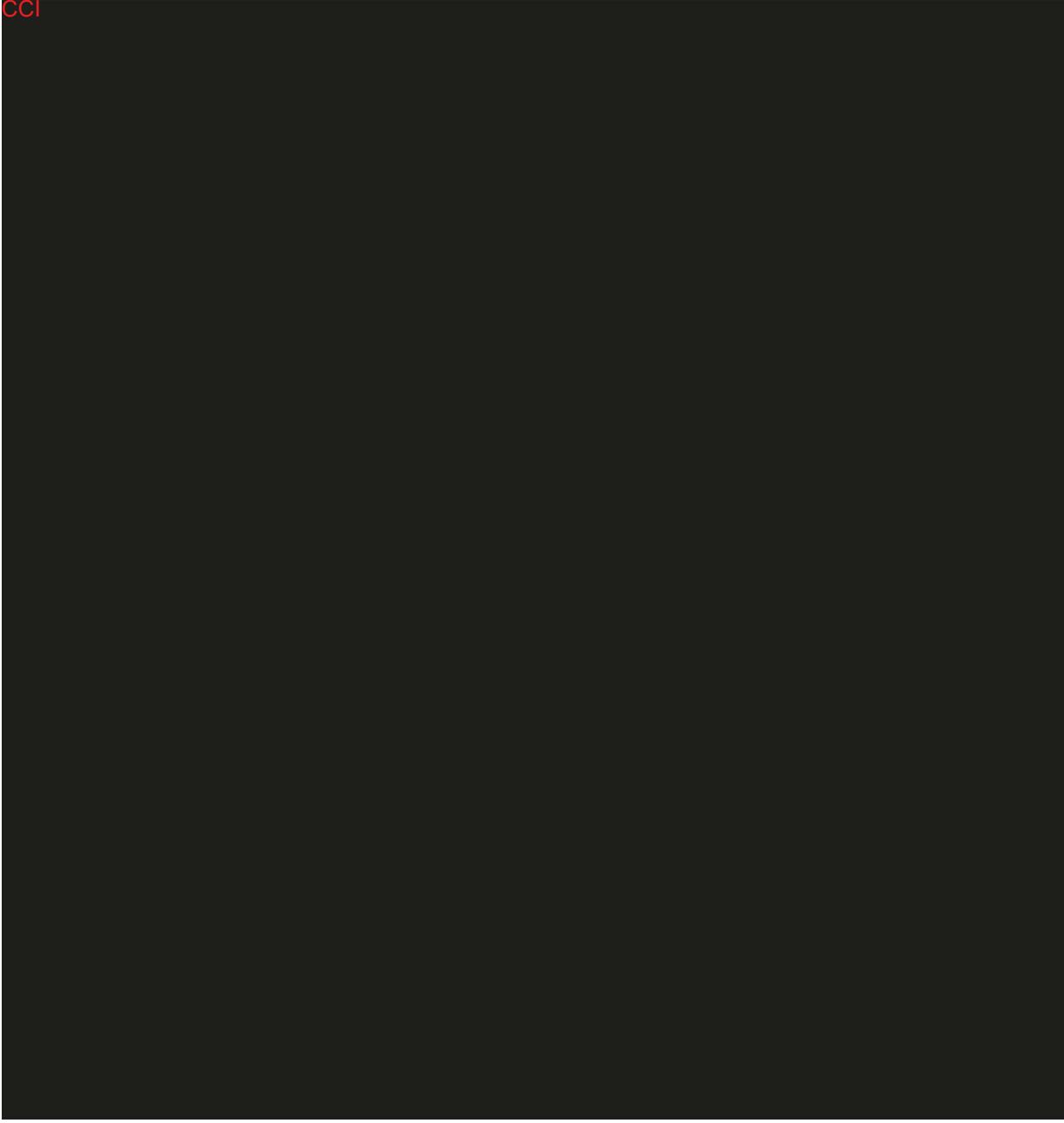
11.3 Immunogenicity Assessment

Immunogenicity of M923 is a secondary safety outcome measure, which will be examined at Baseline and Weeks 4, 12 and 24 (Visits 2, 4, 8 and 14/EDV, respectively) and the Safety Follow-up Visit, assessed as the proportion of all subjects with evidence of seroconversion as measured by titer of ADAs (ANA and anti-dsDNA) levels over time, and proportion of subjects with nADAs. Anti-drug antibody analysis will be conducted using a screening assay based on M923 to identify potentially positive ADA samples. Confirmatory assays based on Humira and M923 will be used to confirm the positive

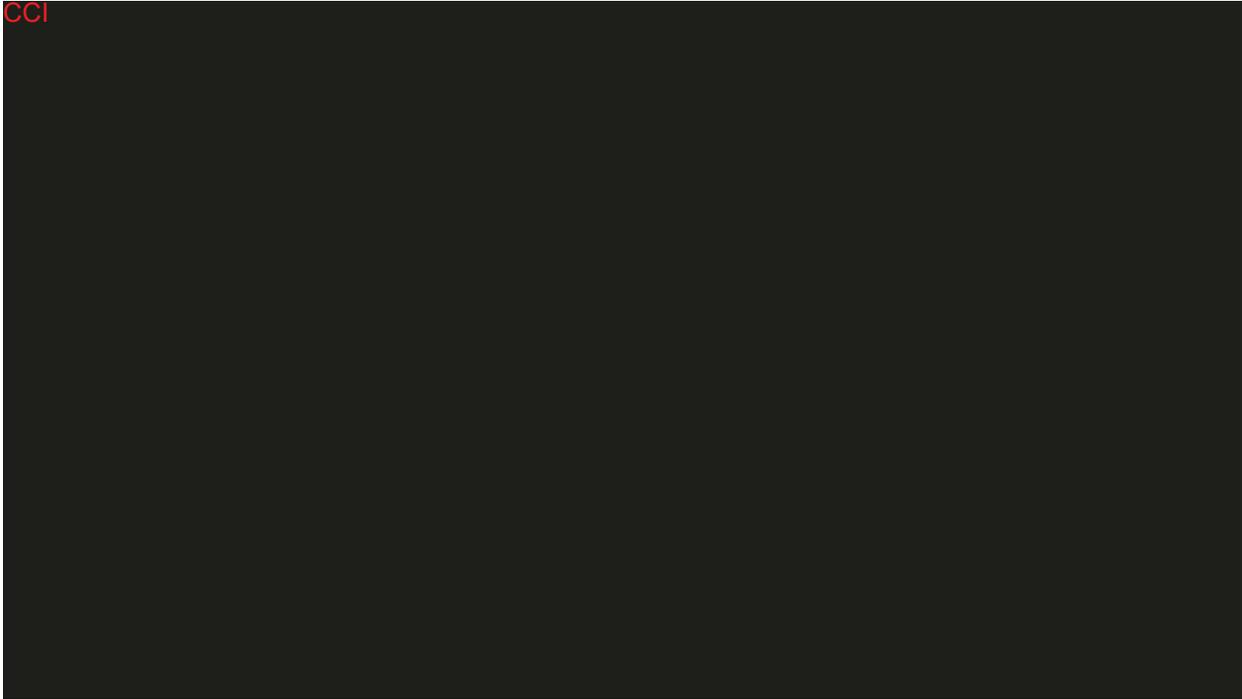
status of the samples. In confirmed positive samples, a third assay will be used to determine the relative titer of the ADA; a subsequent neutralizing antibodies assay will be used to determine the presence of neutralizing antibodies and an isotyping assay will be performed. Blood sample processing and handling details will be presented in a separate laboratory manual. Serum samples will be analyzed by Quintiles BioSciences using validated assays.

Blood samples for immunogenicity analyses will be collected at the times and visits shown in the schedule of assessments in [Section 20.2](#).

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12. ASSESSMENT OF SAFETY

12.1 Adverse Events

12.1.1 Definitions

An AE is defined as any untoward medical occurrence in a subject administered an IP that does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (eg, an abnormal laboratory finding), symptom (eg, rash, pain, discomfort, fever, dizziness, etc.), conditions (eg, peritonitis, bacteremia, etc.), or outcome of death temporally associated with the use of an IP, whether or not considered causally related to the IP.

A treatment-emergent adverse event (TEAE) is defined as any event not present prior to the initiation of the treatments or any event already present that worsens in either intensity or frequency following exposure to the treatments.

12.1.1.1 Serious Adverse Event

An SAE is defined as an untoward medical occurrence that at any dose meets one or more of the following criteria:

1. Outcome is fatal/results in death (including fetal death)
 2. Is life-threatening – defined as an event in which the subject was, in the judgment of the investigator, at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death had it been more severe.
 3. Requires inpatient hospitalization or results in prolongation of an existing hospitalization – inpatient hospitalization refers to any inpatient admission, regardless of length of stay
 4. Results in persistent or significant disability/incapacity (ie, a substantial disruption of a person's ability to conduct normal life functions)
 5. Is a congenital anomaly/birth defect
 6. Is a medically important event – a medical event that may not be immediately life-threatening or result in death or require hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the definitions above. Examples of such events are:
 - Intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependence or drug abuse
 - Reviewed and confirmed seroconversion for HIV, HBV, or HCV
-

Uncomplicated pregnancies, following maternal or paternal exposure to IP are not considered an (S)AE; however, any pregnancy complication or pregnancy termination by therapeutic, elective, or spontaneous abortion shall be considered an SAE.

12.1.1.2 Suspected Unexpected Serious Adverse Reaction (SUSAR)

Any suspected adverse reaction to study treatment (ie, including active comparators) that is both serious and unexpected.

The event(s) must meet all of the following

- Suspected adverse reaction
- Serious
- Unexpected
- Assessed as related to study treatment (see [Section 12.1.2.2](#))

Once determined to meet the criteria for a SUSAR, a serious adverse event should be submitted to regulatory agencies expeditiously.

12.1.1.3 Non-Serious Adverse Event

A **non-serious** AE is an AE that does not meet the criteria of an SAE.

12.1.1.4 Unanticipated Adverse Device Effect

An **unanticipated adverse device effect** (UADE) is defined as any **serious** adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the study protocol or product labeling, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

12.1.1.5 Unexpected Adverse Events

An unexpected adverse event is an AE whose nature, severity, specificity, or outcome is not consistent with the term, representation, or description used in the Reference Safety Information (RSI). “Unexpected” also refers to the AEs that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the product, but are not specifically mentioned as occurring with the particular product under investigation. The expectedness of AEs will be determined by the sponsor using the IB as the RSI. This determination will include considerations such as the number of AEs previously observed, but not on the basis of what might be anticipated from the pharmacological properties of a product.

12.1.1.6 Pre-existing Diseases

Pre-existing diseases that are present before entry in to the study are described in the medical history, and those that manifest with the same severity, frequency, or duration after IP exposure, will not be recorded as AEs. However, when there is an increase in the severity, duration, or frequency of a pre-existing disease, the event must be described on the AE CRF.

12.1.2 Assessment of Adverse Events

For the purposes of this study, each non-serious untoward medical occurrence reported by a subject undergoing study-related procedure(s) before the first M923 treatment will be recorded on the AE CRF; for SAEs the SAE Report (SAER) form is to be used, in addition; however, these events will not be included in the analysis of AEs.

Each treatment-emergent AE (non-serious AE or SAE) from the first M923 exposure until study completion/discontinuation or 4 weeks following the last M923 treatment will be described on the AE CRF using the medical diagnosis (preferred), or, if no diagnosis could be established at the time of reporting the AE, a symptom or sign, in standard medical terminology in order to avoid the use of vague, ambiguous, or colloquial expressions (see definition in [Section 12.1](#)). Each AE will be evaluated by the investigator for:

1. Seriousness as defined in [Section 12.1.1.1](#)
2. Severity as defined in [Section 12.1.2.1](#)
3. Causal relationship to IP exposure, study procedure, or device as defined in [Section 12.1.2.2](#)

For each AE, the outcome (ie, recovering/resolving, recovered/resolved, recovered/resolved with sequelae, not recovered/not resolved, fatal, unknown) and if applicable action taken (ie, dose increased, dose not changed, dose reduced, drug interrupted, drug discontinued, not applicable, or unknown) will also be recorded on the AE CRF. Recovering/resolving AEs will be followed until resolution, medically stabilized, or 4 weeks after the study completion/termination visit, whichever comes first. If the severity rating for an ongoing AE changes before the event resolves, the original AE report will be revised (ie, the event will not be reported as separate AE). During the course of any AE, the highest severity rating will be reported.

Treatment errors (including incorrect route of administration, use of an incorrect product, and deviations from the protocol-defined dosing schedule), failures of expected pharmacological actions, and unexpected therapeutic or clinical benefits will be followed

with regard to occurrence of AEs, lack of efficacy, and/or other observations because these events may be reportable to regulatory authorities.

Any pregnancy that occurs after administration of M923 will be reported on a Pregnancy Report Form and followed-up at estimated date of delivery and 1 year post-delivery, if feasible.

If an investigator becomes aware of an SAE occurring in a subject after study completion, the SAE must be reported on the provided SAER Form **within 24 hours after becoming aware**; no additional reporting on CRFs is necessary.

12.1.2.1 Severity

The investigator will assess the severity of each AE using his/her clinical expertise and judgment based on the most appropriate description below:

1. Mild
 - The AE is a transient discomfort and does not interfere in a significant manner with the subject's normal functioning level
 - The AE resolves spontaneously or may require minimal therapeutic intervention
2. Moderate
 - The AE produces limited impairment of function and may require therapeutic intervention
 - The AE produces no sequela/sequelae
3. Severe
 - The AE results in a marked impairment of function and may lead to temporary inability to resume usual life pattern
 - The AE produces sequela/sequelae, which require (prolonged) therapeutic intervention

These severity definitions will also be used to assess the severity of an AE with a study-related procedure(s), if necessary.

12.1.2.2 Causality

Causality is a determination of whether there is a reasonable possibility that the IP is etiologically related to/associated with the AE. Causality assessment includes, eg, assessment of temporal relationships, de-challenge/re-challenge information, association (or lack of association) with underlying disease, presence (or absence) of a more likely cause, and physiological plausibility. For each AE, the investigator will assess the causal relationship between the IP and the AE using his/her clinical expertise and judgment according to the following most appropriate algorithm for the circumstances of the AE:

1. Not related (either 1 or both circumstances are met)
 - Has little or no temporal relationship to the IP
 - A more likely alternative etiology exists
2. Related (both circumstances must be met)
 - Follows a strong temporal relationship to the administration of IP, which may include but is not limited to the following:
 - Reappearance of a similar reaction upon re-administration of IP (positive re-challenge)
 - Positive results in a drug sensitivity test (skin test, etc.)
 - Toxic level of the IP as evidenced by measurement of the IP concentrations in the blood or other bodily fluid
 - Another etiology is unlikely or significantly less likely

For events assessed as not related or unlikely related and occurring within 72 hours, the investigator shall provide the alternative etiology. These causality definitions will also be used to assess the relationship of an AE with a study-related procedure(s), if necessary.

12.1.2.3 Safety Reporting

Adverse events/SAEs will be assessed at all study visits as outlined in [Table 2](#) and [Section 12.1](#) above.

Adverse Events/SAEs are to be recorded on the AE page of the eCRF. Each event should be recorded separately.

Any SAE, including death due to any cause, which occurs during this study, whether or not related to the IP, must be reported immediately (within 24 hours of the study site's first knowledge of the event). All SAEs must be reported via the Electronic Data Capture (EDC) system by completing the relevant eCRF page(s) in English. Once the SAE has

been recorded in the EDC system, the Sponsor and other designated recipients will be informed of the event automatically. For instances in which the EDC may become unavailable, SAEs must be reported using the back-up paper SAER Form to meet the 24 hour timeline requirement (for contacts and instructions refer to the SAER Form). Once the EDC becomes available, the site must enter all SAE data as reported on the back-up paper SAER Form on the applicable eCRF pages.

The initial SAE information reported on the applicable eCRF pages (or back-up SAER Form, if applicable) must at least include the following:

1. Protocol Number
2. Subject identification number and demographics (gender, age at onset of event and/or date of birth)
3. IP exposure
4. Medical Term for Event (Diagnosis preferably)
5. Description of the (S)AE, including:
 - Date of onset
 - (S)AE treatment (drug, dose, route of administration)
 - Causal relationship by the investigator
 - Measures taken (ie, action taken regarding IP in direct relationship to the AE)
6. Seriousness criteria (ie, death, life-threatening, or other criterion)
7. Cause of death
8. Autopsy findings (if available)
9. Name, address, fax number, email, and telephone number of the reporting investigator (for paper SAER Forms)

12.1.3 Medical Device Safety reporting

The IP kit contains the AI device. All Serious Injuries (SI) and UADE must be reported to the Sponsor as an SAE in the same process as described above.

Serious injury is defined as:

1. Life-threatening injury or illness results in permanent impairment/ damage to body function/ structure
 2. Requires medical or surgical intervention to preclude permanent impairment/ damage to body function/ structure
-

12.2 Urgent Safety Measures

An urgent safety measure is an immediate action taken, which is not defined by the protocol, in order to protect subjects participating in a clinical study from immediate harm. Urgent safety measures may be taken by the Sponsor or clinical investigator, and may include any of the following:

1. Immediate change in study design or study procedures
2. Temporary or permanent halt of a given clinical study or studies
3. Any other immediate action taken in order to protect clinical study participants from immediate hazard to their health and safety

The investigator may take appropriate urgent safety measures in order to protect subjects against any immediate hazard to their health or safety. The measures should be taken immediately and may be taken without prior authorization from the Sponsor. In the event(s) of an apparent immediate hazard to the subject, the investigator will notify the Sponsor immediately by phone and confirm notification to the Sponsor in writing as soon as possible, but within 1 calendar day after the change is implemented. The Sponsor will also ensure the responsible Ethics Committee (EC) is notified of the urgent measures taken in such cases according to local regulations.

12.3 Untoward Medical Occurrences

Untoward medical occurrences that occur before the first exposure to M923 and are not related to study procedures are not considered AEs (according to the definition of AE, see [Section 12.1](#)). However, each **serious** untoward medical occurrence that is experienced before the first M923 exposure (ie, from the time of signed informed consent up to but not including the first M923 exposure) and is not related to study procedures will be described on the AE CRF and on the SAER Form. These events will not be considered as SAEs and will not be included in the analysis of SAEs.

For the purposes of this study, each non-serious untoward medical occurrence experienced by a subject undergoing Screening study-related procedure(s) before the first M923 exposure will be recorded on the AE CRF (see [Section 12.1](#)); these events will not be included in the analysis of AEs. Serious untoward medical occurrences reported before the first administration of M923 (ie, from the time of signed informed consent up to but not including the first administration of M923) will be reported as an SAE.

12.4 Non-Medical Complaints

A non-medical complaint (NMC) is any alleged product deficiency that relates to identity, quality, durability, reliability, safety and performance of the product but **did not result in an AE**. Non-medical complaints include but are not limited to the following:

1. A failure of a product to exhibit its expected pharmacological activity and/or design function, eg, reconstitution difficulty
2. Missing components
3. Damage to the product or unit carton
4. A mislabeled product (eg, potential counterfeiting/tampering)
5. A bacteriological, chemical, or physical change or deterioration of the product causing it to malfunction or to present a hazard or fail to meet label claims

Any NMCs of the product will be documented on an NMC form and reported to the Sponsor within 1 business day. If requested, defective product(s) will be returned to the Sponsor for inspection and analysis according to procedures.

12.5 Medical, Medication, and Non-Drug Therapy History

At Screening (as described in [Table 2](#)), the subject's medical history will be described for the following body systems including severity (defined in [Section 12.1.2.1](#)) or surgery and start and end dates, if known: general; head and neck; eyes, ears, nose, and throat; chest/respiratory; heart/cardiovascular; gastrointestinal/liver; musculoskeletal/extremities; neurological/psychiatric; endocrine/metabolic; hematologic/hematopoietic/lymphatic; dermatological; genitourinary; allergies/drug sensitivities; past surgeries; substance abuse; or any other diseases or disorders.

Subjects' history of TB or exposure thereof will be reviewed at Screening. Subjects will be tested in absence of a TB test within previous 3 months and/or absence of a documented history of prior positive TB test result or active TB infection. Testing methods include QuantiFERON[®]; or PPD and chest x-ray (posteroanterior [PA] or PA and lateral view).

History of or current diagnosis of active TB, or untreated latent TB infection (LTBI), determined by a TB skin test with PPD as evidenced by induration ≥ 5 mm or a positive QuantiFERON[®] test performed locally, either at Screening, or documented with results within 3 months of Screening will be documented. Subjects who have previously completed appropriate and documented LTBI treatment or who are undergoing current treatment for LTBI will not be required to be tested.

Clinically significant chest x-ray report per investigator opinion or evidence of active TB on chest x-ray will be documented. Chest x-ray must have been performed in 3 months prior to the Screening visit or during the Screening period.

At Screening (as described in [Table 2](#)), viral serology assessments will be performed including the following parameters: HIV-I and -II, hepatitis B surface antigen, hepatitis B core antibodies, IgG and/or immunoglobulin M antibodies), and hepatitis C antibody.

Serology tests for RA-specific auto-antibodies (RF and ACPA) will also be performed at Screening (as described in [Table 2](#)).

All medications taken and non-drug therapies received from enrollment (up to 4 weeks prior to Baseline) until completion/termination will be recorded on the concomitant medications and non-drug therapies CRFs.

12.6 Physical Examinations

At Screening, a complete physical examination will be done that is limited to the following body systems: general appearance, head and neck, eyes and ears, nose and throat, chest, lungs, heart, abdomen, extremities and joints, lymph nodes, skin, and neurological. At subsequent study visits (as described in [Table 2](#)), a focused physical examination will be conducted, limited to include the following body systems: heart, lungs, abdomen, extremities, and skin, and any other assessments required to evaluate AEs.

At Screening, if an abnormal condition is detected, the condition will be described on the medical history CRF. At study visits, if a new abnormal or worsened abnormal pre-existing condition is detected, the condition will be described on the AE CRF. If the abnormal value was not deemed an AE because it was due to an error, due to a pre-existing disease (described in [Section 12.1.1.6](#)), not clinically significant, a symptom of a new/worsened condition already recorded as an AE, or due to another issue that will be specified, the investigator will record the justification on the source record.

12.7 Clinical Laboratory Parameters

Clinical laboratory parameters, including hematology, clinical chemistry and urinalysis, will be assessed at Screening (Visit 1), Baseline (Visit 2), Week 4 (Visit 4), Week 12 (Visit 8), Week 24 (Visit 14/EDV), and the Safety Follow-up Visit (hematology and clinical chemistry only) (see [Table 2](#)). Blood samples for these assessments will be taken after ECG and vital signs assessments, after samples have been collected for PK and immunogenicity assessments (if applicable at a given study visit), but before self-administration of M923.

12.7.1 Hematology and Clinical Chemistry

The hematology panel will consist of complete blood count (erythrocytes [ie, red blood cell count], hemoglobin, hematocrit, mean cell volume, and total leukocytes [ie, white blood cell count]) with differentials (ie, neutrophils, lymphocytes, monocytes, eosinophils, and basophils) and platelet counts.

The clinical chemistry panel will consist of AST, ALT, alkaline phosphatase, gamma-glutamyl transferase, total bilirubin, lactate dehydrogenase, creatine kinase, CRP, cholesterol, triglycerides, total protein, sodium, potassium, chloride, blood urea nitrogen, creatinine, albumin, calcium, phosphate, glucose, glycosylated hemoglobin, uric acid, and bicarbonate.

Blood will be obtained for assessment of hematology, clinical chemistry, immunogenicity (see [Section 11.3](#)), PK (see [Section 11.5](#)), viral serology and serology (see [Section 12.5](#)) parameters at study visits as described in [Table 2](#). A serum pregnancy test will also be performed at Screening in females of childbearing potential only. Hematology and clinical chemistry assessments will be performed on EDTA-anticoagulated whole blood and serum, respectively, at the central laboratory.

12.7.2 Urinalysis

The urinalysis panel will consist of leucocytes, protein, bilirubin, urobilinogen, glucose, ketones, blood pH, nitrite, and specific gravity. Urine microscopy will be performed only when clinically indicated. Urine will be obtained for assessment of urinalysis parameters and urine pregnancy testing (females of childbearing potential only) at study visits as described in [Table 2](#). Urinalysis assessments will be performed at the central laboratory.

12.7.3 Assessment of Laboratory Values

12.7.3.1 Assessment of Abnormal Laboratory Values

The investigator's assessment of each laboratory value will be recorded on the CRF. For each abnormal laboratory value, the investigator will determine whether the value is considered clinically significant or not. For clinically significant values, the investigator will indicate if the value constitutes a new AE (see definition in [Section 12.1](#), and record the sign, symptom, or medical diagnosis on the AE CRF), is a symptom or related to a previously recorded AE, is due to a pre-existing disease (described in [Section 12.1.1.6](#)), or is due to another issue that will be specified. If the abnormal value was not clinically significant, the investigator will indicate the reason, ie, because it is due to a pre-existing disease, due to a laboratory error, or due to another issue that will be specified.

Additional tests and other evaluations required to establish the significance or etiology of

an abnormal value, or to monitor the course of an AE should be obtained when clinically indicated. Any abnormal value that persists should be followed at the discretion of the investigator.

Any seroconversion result for HIV, HBV, HCV, or ADAs (ANA and anti-dsDNA) shall be re-tested.

12.7.4 Biobanking-Study Sample Storage

Study samples and backup samples should be taken and stored appropriately for analysis as needed. These samples may be used for re-testing, further evaluation of an AE, or follow-up of other test results. The following samples are planned as per [Table 2](#):

1. Pharmacokinetic samples (see Section 11.5)
2. Immunogenicity samples (see [Section 11.3](#))
3. Hematology and clinical chemistry samples (see [Section 12.7](#) and [12.7.1](#))
4. Antinuclear antibody and anti-dsDNA samples
5. Rheumatoid factor and ACPA samples (see [Section 12.5](#))
6. Urinalysis samples (see [Section 12.7](#) and [12.7.2](#))

Samples will be stored in a coded form until completion of the study and then the samples will subsequently be destroyed.

12.8 Vital Signs

Vital signs will include body temperature (°C or °F), respiratory rate (breaths/min), pulse rate (beats/min), and systolic and diastolic blood pressure (mmHg). Height (in or cm) and weight (lb or kg) will also be collected.

Vital signs will be measured at Screening and within 30 minutes before and after administration of IP at each study visit, and at study completion/termination (see [Table 2](#)). Blood pressure will be measured when subjects are resting in a supine position for at least 5 minutes. Height will be measured at Screening only.

Vital sign values are to be recorded on the CRF. For each abnormal vital sign value, the investigator will determine whether or not to report an AE (see definition in [Section 12.1](#) and record the medical diagnosis [preferably], symptom, or sign on the AE CRF).

Additional tests and other evaluations required to establish the significance or etiology of an abnormal value, or to monitor the course of an AE should be obtained when clinically indicated. Any abnormal value that persists should be followed at the discretion of the investigator.

12.9 Electrocardiograms

A 12-lead ECG assessment will be done at Screening, performed prior to drawing blood at these study visits (see [Table 2](#)).

The 12-lead ECG values are to be recorded on the CRF. For each abnormal ECG value, the investigator will determine whether the value is considered an AE (see definition in [Section 12.1](#) and record the sign, symptom, or medical diagnosis will be recorded on the AE CRF). Additional tests and other evaluations required to establish the significance or etiology of an abnormal result, or to monitor the course of an AE should be obtained when clinically indicated. Any abnormal value that persists should be followed at the discretion of the investigator.

12.10 Local Injection Site Reaction Evaluation

Assessment for local injection site reactions site of SC injections of M923 will be performed prior to M923 administration at these study visits (see [Table 2](#)).

Injection site evaluations will be made by clinical staff as described below; if an injection site reaction is observed, a physician will characterize and document the reaction as an AE. Injection sites will continue to be reviewed at the time points indicated in [Table 2](#), or until the AE is resolved.

Injection sites will be monitored for pain, tenderness, erythema, and swelling. Each injection site reaction will be categorized using the intensity grading scheme presented in [Table 1](#); the intensity of each resulting AE will be categorized as described in [Section 12.1.2.1](#) (eg, a moderate intensity injection site reaction may be recorded as a mild AE if considered appropriate according to the Investigator's judgement, based on the AE grading schemes presented in [Section 12.1.2.1](#)).

Table 1
Injection Site Reaction Grading Scheme

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13. STATISTICS

13.1 Sample Size and Power Calculations

Based on discussions with the US Food and Drug Administration, a sample size of 30 was judged to be adequate to achieve the objectives of the study. CCI

Patients dropping out of the study will not be replaced.

13.2 Datasets and Analysis Cohorts

All subjects who received IP will be included in the Safety Analysis Set.

All subjects in the Safety Analysis set who have usability measurements at Week 4 will be included in the Usability Analysis Set.

All subjects in the Safety Analysis Set who has at least 1 post-dosing efficacy measurement will be included in the Efficacy Analysis Set.

Subjects in the Safety Analysis Set who have at least 1 trough serum measurement will be included in the PK Analysis Set.

13.3 Handling of Missing, Unused, and Spurious Data

Multiple imputation methods may be used for imputation of the continuous endpoints (ie, DAS28-CRP and PGA) after non-responders discontinue treatment at Week 14, including last observation carried forward or mixed-effect modeling. Details will be provided in the statistical analysis plan.

13.4 Methods of Analysis

Baseline will be defined as the last scheduled visit before dosing of IP. Continuous Baseline and demographic characteristics will be summarized by sample size, mean, standard deviation (SD), minimum, median, and maximum. Categorical Baseline data will be summarized by number and proportions in each category.

The number of dropouts will be reported by scheduled timepoint, and reasons for discontinuation will be summarized by number and proportions of each reason.

13.4.1 Primary Outcome Measure

The methods of analysis for the primary outcome measure (see [Section 8.4.1](#)) are summarized using the Usability Analysis Set. At each scheduled time point, raw and change from Baseline of SIAQ will be summarized using number, mean, SD, median, minimum, and maximum.

13.4.2 Secondary Outcome Measures

The methods of analysis for the secondary safety outcome measures (see [Section 8.4.2.2](#)) are performed using the Safety Analysis Set.

The self-injection assessment will be coded as successful if P7, P10, and P11 of the self-injection assessment checklist (Section 20.4) are checked as Yes. The proportion of subjects with a successful self-injection will be summarized by scheduled timepoint as the number and proportion of successful injections; additionally, the 95% CI for the proportion will be constructed using Wilson's score method. Similarly, the number and proportion of subjects who successfully completed all 14 instructions will be summarized, along with 95% CI for the proportion using Wilson's score method.

For each potential hazard ([Section 20.6](#)) listed in the potential hazards checklist, the number and proportion will be summarized by scheduled timepoint.

For the purpose of summaries and listings, the durations of AEs will be calculated as follows: (stop day – start day) + 1 day, which yields the number of days on which the AE was present.

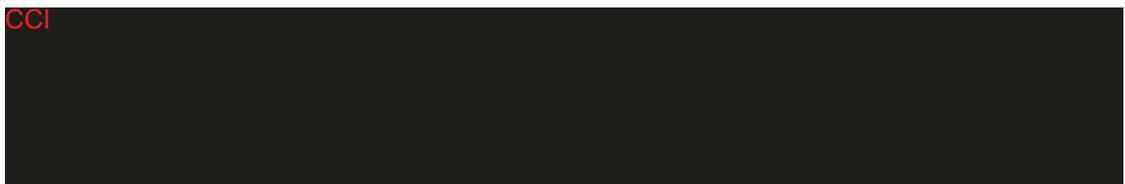
Adverse events will be summarized using number of observations and incidence of AEs by preferred term, and by preferred term within system organ class. Serious AEs and AEs leading to premature withdrawal will be listed separately.

Injection site reactions will be summarized by scheduled visit using number of observations and proportions.

Laboratory and ECG measurements and change from Baseline will be summarized by scheduled visit using number of observations, mean, SD, minimum, median, and maximum.

Immunogenicity will be summarized using by scheduled visit using number of observations, mean, SD, coefficient of variation, minimum, median, maximum, and the proportion of subjects with positive antibody titers, and the proportion of subjects with positive neutralizing antibody titers.

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13.5 Planned Interim Analysis of the Study

An interim analysis is planned to be conducted at the end of the 4-week treatment period once enrollment is completed. The database will be locked after the last subject completes the Week 4 and this interim analysis will include the primary analysis of usability at Week 4. An interim Clinical Study Report will be written from these results and the Clinical Study Report will be supplemented with the data collected after Week 4 once the last subject completes the last visit.

14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The investigator/study site will cooperate and provide direct access to study documents and data, including source documentation for monitoring by the study monitor, audits by the Sponsor or Sponsor's representatives, review by the EC, and inspections by applicable regulatory authorities, as described in the Clinical Trial Agreement (CTA). If contacted by an applicable regulatory authority, the investigator will notify the Sponsor of contact, cooperate with the authority, provide the Sponsor with copies of all documents received from the authority, and allow the Sponsor to comment on any responses, as described in the CTA.

15. QUALITY CONTROL AND QUALITY ASSURANCE

15.1 Investigator's Responsibility

The investigator will comply with the protocol (which has been approved/given favorable opinion by the EC), ICH GCP, and applicable national and local regulatory requirements as described in the CTA. The investigator is ultimately responsible for the conduct of all aspects of the study at the study site and verifies by signature the integrity of all data transmitted to the Sponsor. The term "investigator" as used in this protocol as well as in other study documents, refers to the investigator or authorized study personnel that the investigator has designated to perform certain duties. Sub-investigators or other authorized study personnel are eligible to sign for the investigator, except where the investigator's signature is specifically required.

15.1.1 Final Clinical Study Report

The investigator, or coordinating investigator(s) for multicenter studies, will sign the clinical study report. The coordinating investigator will be selected before study start.

15.2 Training

The study monitor will ensure that the investigator and study site personnel understand all requirements of the protocol, the investigational status of the IP, and his/her regulatory responsibilities as an investigator. Training may be provided at an investigator's meeting, at the study site, and/or by instruction manuals. In addition, the study monitor will be available for consultation with the investigator and will serve as the liaison between the study site and the Sponsor.

15.3 Monitoring

The study monitor is responsible for ensuring and verifying that each study site conducts the study according to the protocol, standard operating procedures, other written instructions/agreements, ICH GCP, and applicable national and local regulatory guidelines/requirements. The investigator will permit the study monitor to visit the study site at appropriate intervals, as described in the CTA. Monitoring processes specific to the study will be described in the clinical monitoring plan.

15.4 Auditing

The Sponsor and/or Sponsor's representatives may conduct audits to evaluate study conduct and compliance with the protocol, standard operating procedures, other written instructions/agreements, ICH GCP, and applicable national and local regulatory guidelines/requirements. The investigator will permit auditors to visit the study site, as described in the CTA. Auditing processes specific to the study will be described in the auditing plan.

15.5 Non-Compliance with the Protocol

The investigator may deviate from the protocol only to eliminate an apparent immediate hazard to the subject. In the event(s) of an apparent immediate hazard to the subject, the investigator will notify the Sponsor immediately by phone and confirm notification to the Sponsor in writing as soon as possible, but within 1 calendar day after the change is implemented. The Sponsor (Baxalta) will also ensure the responsible EC and relevant competent authority is notified of the urgent measures taken in such cases according to local regulations.

If monitoring and/or auditing identify serious and/or persistent non-compliance with the protocol, the Sponsor may terminate the investigator's participation. The Sponsor will notify the EC and applicable regulatory authorities of any investigator termination.

15.6 Laboratory and Reader Standardization

Not applicable; a central laboratory/reader will be used for all clinical assessments.

16. ETHICS

16.1 Subject Privacy

The investigator will comply with applicable subject privacy regulations/guidance as described in the CTA.

16.2 Ethics Committee and Regulatory Authorities

Before enrollment of subjects into this study, the protocol, ICF, any promotional material/advertisements, and any other written information to be provided will be reviewed and approved/given favorable opinion by the EC and applicable regulatory authorities. The IB will be provided for review. The EC's composition or a statement that the EC's composition meets applicable regulatory criteria will be documented. The study will commence only upon the Sponsor's receipt of approval/favorable opinion from the EC and, if required, upon the Sponsor's notification of applicable regulatory authority(ies) approval, as described in the CTA.

If the protocol or any other information given to the subject is amended, the revised documents will be reviewed and approved/given favorable opinion by the EC and applicable regulatory authorities, where applicable. The protocol amendment will only be implemented upon the Sponsor's receipt of approval and, if required, upon the Sponsor's notification of applicable regulatory authority(ies) approval.

16.3 Informed Consent

Investigators will choose subjects for enrollment considering the study eligibility criteria. The investigator will exercise no selectivity so that no bias is introduced from this source.

All patients must sign an ICF before entering into the study according to applicable national and local regulatory requirements and ICH GCP. Before use, the ICF will be reviewed by the Sponsor and approved by the EC and regulatory authority(ies), where applicable (see [Section 16.2](#)). The ICF will include a comprehensive explanation of the proposed treatment without any exculpatory statements, in accordance with the elements required by ICH GCP and applicable national and local regulatory requirements. Patients will be allowed sufficient time to consider participation in the study. By signing the ICF, subjects agree that they will complete all evaluations required by the study, unless they withdraw voluntarily or are terminated from the study for any reason.

The Sponsor will provide to the investigator in written form any new information that significantly bears on the subjects' risks associated with IP exposure. The informed consent will be updated, if necessary. This new information and/or revised ICF, that have

been approved by the applicable EC and regulatory authorities, where applicable, will be provided by the investigator to the subjects who consented to participate in the study (see [Section 16.3](#)).

16.4 Data Monitoring Committee

No Data Monitoring Committee (DMC) will be established for this study for the following reason:

Subjects are on IP which is the same dosage and form as the product that is already licensed; however, the device that delivers the IP is different from the licensed product.

The Sponsor or designee will be responsible for reviewing accumulating data from the ongoing clinical study on a regular basis.

17. DATA HANDLING AND RECORD KEEPING

17.1 Confidentiality Policy

The investigator will comply with the confidentiality policy as described in the CTA.

17.2 Study Documentation and Case Report Forms

The investigator will maintain complete and accurate paper format study documentation in a separate file. Study documentation may include information defined as “source data” (see [Section 8.7](#)), records detailing the progress of the study for each subject, signed ICFs, correspondence with the EC and the study monitor/Sponsor, enrollment and Screening information, CRFs, SAERs, laboratory reports (if applicable), and data clarifications requested by the Sponsor.

The investigator will comply with the procedures for data recording and reporting. Any corrections to paper study documentation must be performed as follows: 1) the first entry will be crossed out entirely, remaining legible; and 2) each correction must be dated and initialed by the person correcting the entry; the use of correction fluid and erasing are prohibited.

The investigator is responsible for the procurement of data and for the quality of data recorded on the CRFs. Case Report Forms will be provided in electronic form. If electronic format CRFs are provided by the sponsor, only authorized study site personnel will record or change data on the CRFs. If data are not entered on the CRFs during the study visit, the data will be recorded on paper, and this documentation will be considered source documentation. Changes to a CRF will require documentation of the reason for each change. An identical (electronic/paper) version of the complete set of CRFs for each subject will remain in the investigator file at the study site in accordance with the data retention policy (see [Section 17.3](#)).

The handling of data by the Sponsor, including data quality assurance, will comply with regulatory guidelines (eg, ICH GCP) and the standard operating procedures of the Sponsor. Data management and control processes specific to the study will be described in the data management plan.

17.3 Document and Data Retention

The investigator will retain study documentation and data (paper and electronic forms) in accordance with applicable regulatory requirements and the document and data retention policy, as described in the CTA.

18. FINANCING AND INSURANCE

The investigator will comply with investigator financing, investigator/Sponsor insurance, and subject compensation policies, if applicable, as described in the CTA.

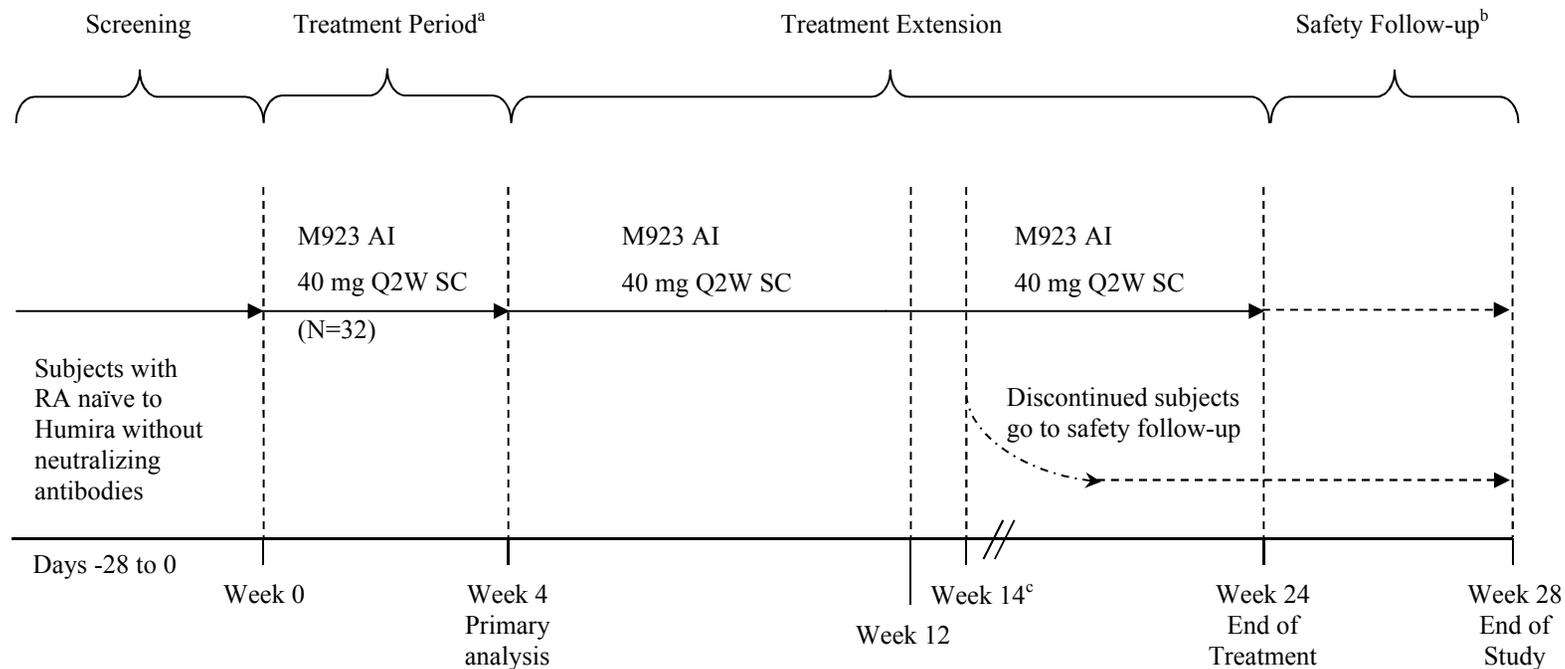
19. PUBLICATION POLICY

The investigator will comply with the publication policy as described in the CTA.

20. SUPPLEMENTS

20.1 Study Flow Chart

Figure 1
Study Design for Baxalta Clinical Study 911502



AI=autoinjector; N=number of subjects; Q2W=every 2 weeks; RA=rheumatoid arthritis; SC=subcutaneous; SIAQ=Self-injection Assessment Questionnaire.

^a SC injections administered at Weeks 0, 2 and 4 with SIAQ completed at each timepoint.

^b Subjects who are inadequate responders, or who withdraw early or choose not to continue to the treatment extension period, will directly enter the 4-week safety follow-up period; all other subjects will enter the safety follow-up period on completion of the treatment extension period.

^c Subjects with an inadequate response will be discontinued at Week 14, based upon <20% improvement in their swollen joint count and tender joint count from Baseline to Week 12.

Table 2
Schedule of Study Procedures and Assessments

Phase	Screening	Open-label Treatment Period/Treatment Extension												Safety Follow-up ^a	
		0	2	4	6	8	10	12	14	16	18	20	22		24/ EDV
Week	-4 to 0	0	2	4	6	8	10	12	14	16	18	20	22	24/ EDV	28
Study Day ^b	-28 to 0	Baseline/1	15	29	43	57	71	85	99	113	127	141	155	169	197
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
IP injection at office ^o		X	X	X				X						X	
IP injection at home ^o					X	X	X		X	X	X	X	X		
Injection site evaluation ^p		X	X	X											
Observer assessment of subject self-injection ^q		X	X	X											
Drug dispensing for at home dosing				X				X							

ACPA=anti-citrullinated protein antibody; AE=adverse event; AI=Autoinjector; ANA=antinuclear antibody; anti-dsDNA=anti-double-stranded deoxyribonucleic acid; ECG=electrocardiogram; EDV=early discontinuation visit; HIV=human immunodeficiency virus; IP=investigational product; IVRS=interactive voice response system; IWRS=interactive web response system; PA=posteroanterior; PGA=Patient Global Assessment; PK=pharmacokinetics; PPD=purified protein derivative; RA=rheumatoid arthritis; RF=rheumatoid factor; SIAQ=Self-Injection Assessment Questionnaire; TB=tuberculosis.

- ^a Subjects who are inadequate responders, or who withdraw early or choose not to continue to the treatment extension period, will directly enter the 4-week safety follow-up period; all other subjects will enter the safety follow-up period on completion of the treatment extension period.
- ^b Visit windows are ±3 days at Visits 3 and 4. Reference for visit windows/study day is scheduling based on Visit 2/Baseline Visit. Visit windows are ±3 days at each visit from Visits 5 to 15.
- ^c Subjects will be enrolled using the IVRS/IWRS at Screening or Baseline. The IVRS/IWRS should be contacted at Week 14 to determine which subjects should discontinue treatment due to non-response. At Week 28, the IVRS/IWRS should be contacted to record the end of treatment.
- ^d Inclusion/exclusion criteria are to be reviewed before enrollment. The Screening Visit needs to occur with enough time prior to enrollment to ensure eligibility requirements for enrollment are met.
- ^e Concomitant therapy will include pharmacologic and non-pharmacologic therapies.
- ^f Subject will be screened for TB if not tested within previous 3 months and/or does not have documented history of prior positive TB test result or active TB infection. Testing includes QuantiFERON[®], or PPD and chest imaging (ie, x-ray) with PA or PA and lateral view. QuantiFERON[®] is the preferred testing method, with PPD used in the absence of QuantiFERON[®].
- ^g A complete physical examination will be done at Screening. All other physical examinations should be limited to include heart, lungs, abdomen, extremities, and skin, and any other assessments required to evaluate AEs.

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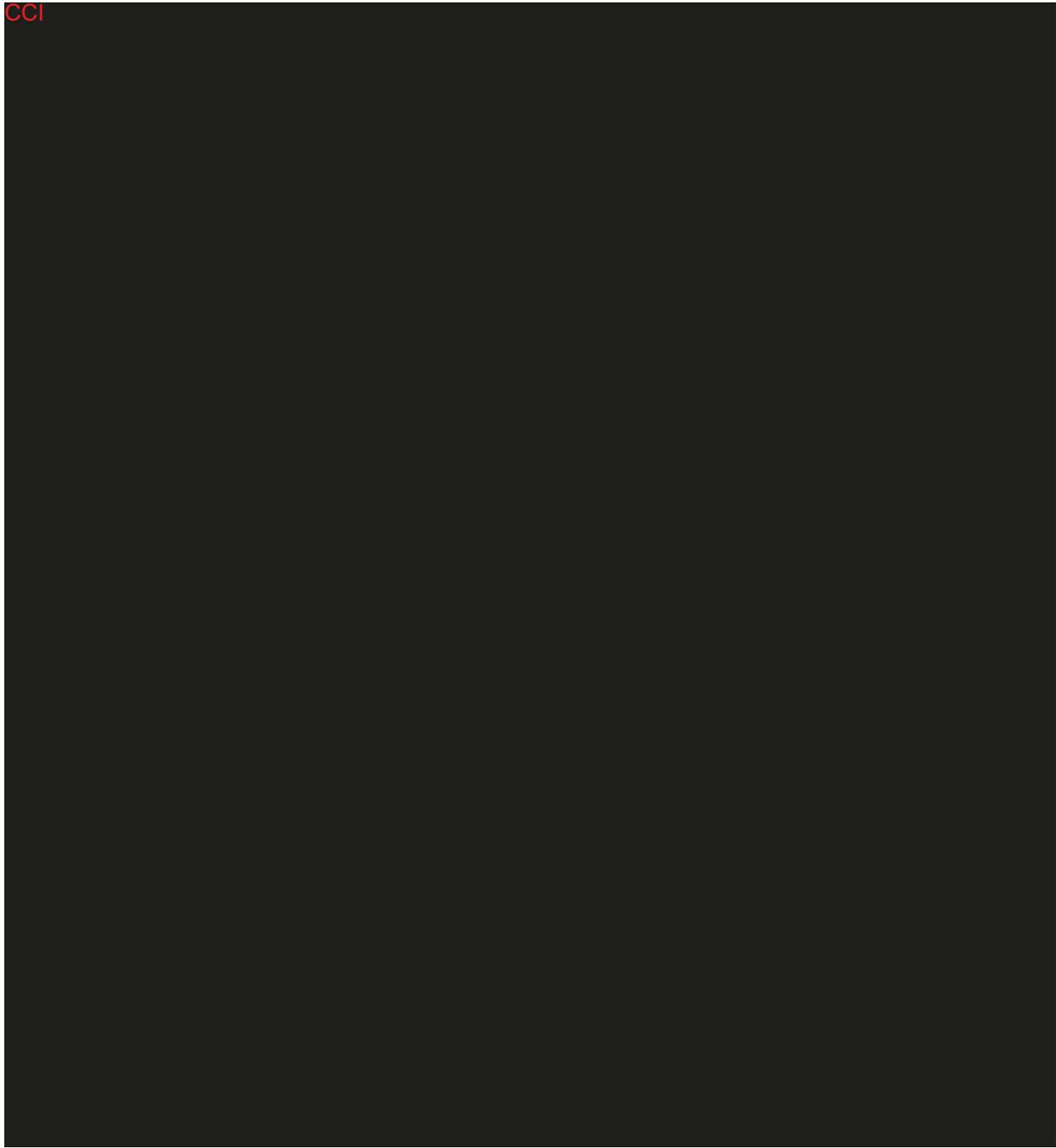
- ^h A 12-lead ECG should be performed before blood sampling.
 - ⁱ Vital signs assessments should be performed within 30 minutes before and after administration of IP at each study visit. Vital signs should be taken before blood sampling. Height will be measured at Screening only.
 - ^j PK and immunogenicity blood samples are to be collected at these timepoints in all subjects. Samples should be collected predose (ie, prior to administering IP) and before any hematology/chemistry samples to be drawn at that visit.
 - ^k Blood samples will be taken before injection of IP, after ECG and vital signs assessments, and after PK and immunogenicity sampling if applicable.
 - ^l Pregnancy testing is only required for female subjects of childbearing potential. A serum test will be performed at Screening; urine pregnancy tests will be performed at all other applicable visits.
 - ^m Subject should complete PRE-SIAQ prior to injecting, and POST-SIAQ after completing self-injection at each applicable visit.
 - ⁿ Self-injection training for the AI should be provided at Baseline prior to the first injection, with subjects performing the injection. If the subject requests it, additional training can be provided at prior to the second injection, but the subject should perform the injection.
 - ^o IP will be self-administered in the clinic after all required assessments and blood sample collections have been completed at Weeks 0, 2, and 4. Subjects should be observed for 2 hours post-injection at Weeks 0 and 2, and for 30 minutes post-injection at Week 4. All other injections will be at home.
 - ^p The investigator or a qualified designee will evaluate the injection site before IP administration (see [Section 12.10](#)) and 30 minutes after IP administration.
 - ^q Observer should observe the subject perform self-injection and complete observer questionnaire. Re-training of the subject should be provided after observation of full injection completed as necessary and prior to next injection.
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20.3 Clinical Laboratory Assessments

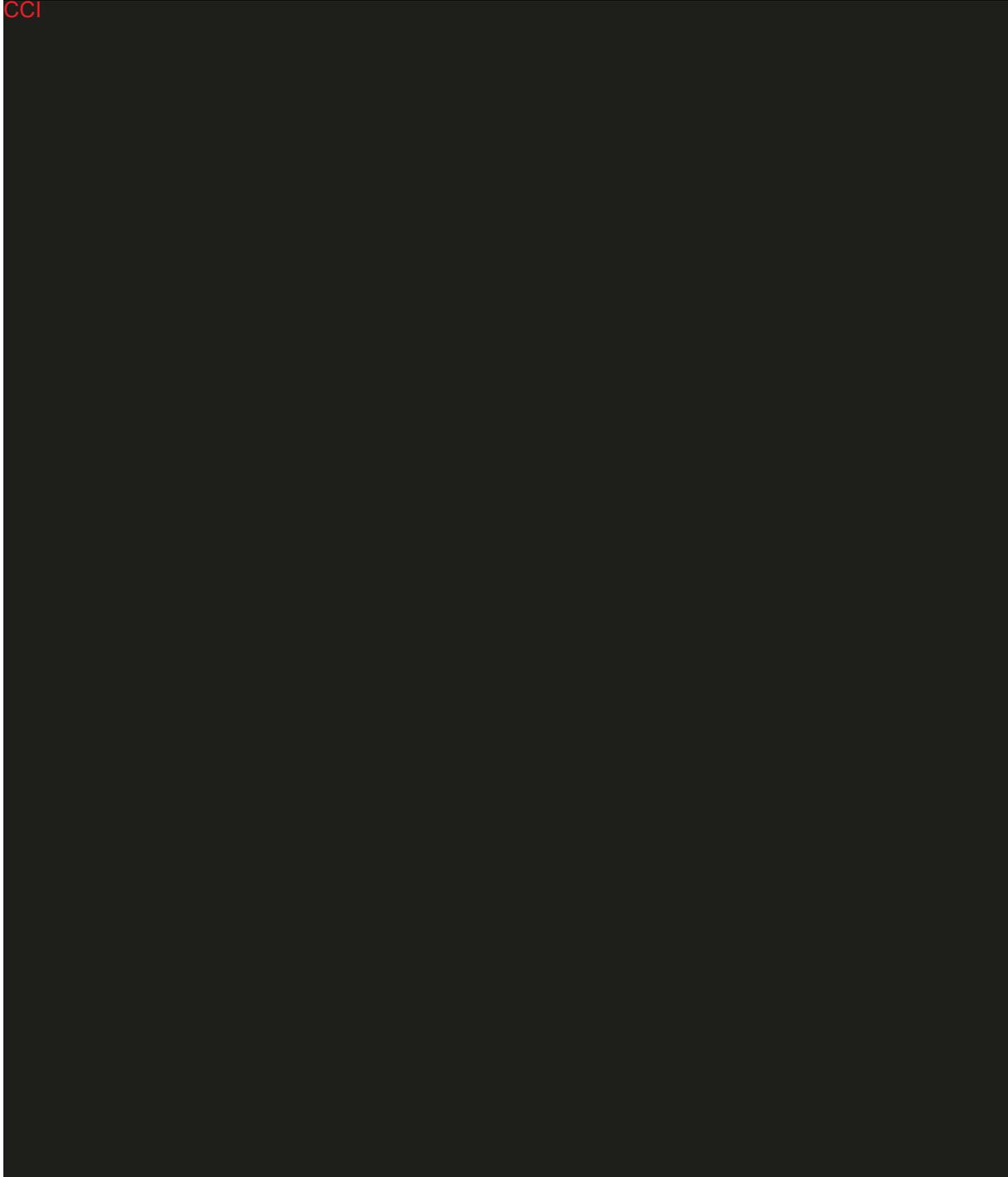
Table 3
Clinical Laboratory Parameters

Panel	Parameters		
Hematology	Red blood cell count Hemoglobin Hematocrit Platelet count Mean cell volume White blood cell count (total leucocytes)	Neutrophils (absolute and %) Lymphocytes (absolute and %) Monocytes (absolute and %) Eosinophils (absolute and %) Basophils (absolute and %)	
Serum biochemistry	Aspartate aminotransferase (AST) Alanine aminotransferase (ALT) Alkaline phosphatase Gamma-glutamyl transferase Total bilirubin Lactate dehydrogenase Creatine kinase C-reactive protein (CRP)	Cholesterol Triglycerides Total protein Sodium Potassium Chloride Blood urea nitrogen Creatinine	Albumin Calcium Phosphate Glucose Glycosylated hemoglobin (Hb _{A1c}) Uric acid Bicarbonate
Urinalysis	Leucocytes Protein Bilirubin	Urobilinogen Glucose Ketones	Blood pH Nitrite Specific gravity
Urine microscopy	Done only when clinically indicated		
Viral serology	Hepatitis B surface antigen and hepatitis B core antibodies, IgG and/or immunoglobulin M antibodies	Hepatitis C antibody Human immunodeficiency virus (HIV-I and -II)	
Tuberculosis (TB)	QuantiFERON [®] -TB Gold test or purified protein derivative (PPD) and chest imaging (ie, x-ray).		
Serum/urine pregnancy test Follicle-stimulating hormone (FSH)	Beta human chorionic gonadotropin		
Serology	Anti-nuclear antibody (ANA), anti-double-stranded DNA (anti-dsDNA), anti-citrullinated protein antibody (ACPA), rheumatoid factor (RF)		

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20.5 Self-Injection Assessment Checklist

No.	Instructions for Use (Indicated Steps)	Completion Required for Successful Administration? (Yes/No)
P1	Washed hands with soap and water	No
P2	Cleaned the injection site	No
P3	Removed the autoinjector from the outer box	No
P4	Checked expiration date on the autoinjector label	No
P5	Inspected the autoinjector for damage	No
P6	Inspected liquid for brown discoloration of particles	No
P7	Removed protective needle cap from autoinjector	Yes
P8	Discarded needle cap	No
P9	Pinched the skin at the injection site	No
P10	Press down on AI to insert the needle into the skin	Yes
P11	Held AI pressed fully down through second “click” sound	Yes
P12	Continued to hold down AI until 5 seconds after click	No
P13	Removed AI from injection site at 90° angle to skin.	No
P14	Disposed used autoinjector in a sharps container	No

20.6 Potential Hazards Checklist

No.	Potential Hazard ^a
H1	Was there a needle stick in a critical area (eg, eye, carotid artery)?
H2	Was there a needle stick in a non-critical area? ^b
H3	Was any part of the device swallowed? ^c
H4	Was an immediate-type allergic reaction to the device material noticed?
H5	Was increased pain noticed by the subject due to a bent needle?
H6	Was a breakage of the device observed? ^d
H7	Was swallowing of material debris observed? ^c
H8	Was any other problem observed? ^c
H9	Was less than the full dose administered? ^e

^a The following potential hazards were not included since these are not observable during self-injection observation: microbiological contamination, wrong drug, and transfer of transmissible diseases.

^b Excludes the actual injection into the appropriate injection site of the body.

^c If yes, then it is to be specified.

^d If yes, then it is to be specified under which circumstances breakage occurred and which parts were affected, and any additional problems (eg, injuries) due to the breakage are to be described.

^e If yes, then it is to be specified why (eg, leakage from the injection site, early removal).

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21. REFERENCES

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 8. Van Tuyl LH, Boers M. Patient's global assessment of disease activity: what are we missing? *Arthritis Rheum*. 2012;64(9):2811-2813.
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22. SUMMARY OF CHANGES

Protocol 911502 Amendment 1 2016 AUG 26

Replaces: Original: 2016 JAN 29

In this section, changes from the previous version of the Protocol, dated 2016 JAN 29, are described and their rationale is given.

1. Throughout the document
Description of Change: Changes made according to the updated Baxalta protocol template dated 2016 MAR 16.
Purpose for Change: Administrative, and to improve the readability and/or clarity of the protocol.
 2. Throughout the document
Description of Change: At home visits were added at Weeks 6, 10, 16, 20, and 22, and visit numbers were updated as appropriate.
Purpose for Change: Administrative, updated for consistency.
 3. Section 3. SYNOPSIS; Section 9.1 Inclusion Criteria
Description of Change: The wording “Where relevant, a legal representative will also sign the informed study consent according to local laws and regulations.” was removed from Inclusion criterion 2. This change was requested by the Institutional Review Board.
Purpose for Change: Administrative, updated for clarity.
 4. Section 3. SYNOPSIS; Section 9.1, Inclusion Criteria
Description of Change: The units “mg/L” were deleted from Inclusion criterion 5 “Active disease defined as both DAS28-CRP >3.2 mg/L at Screening and 4 swollen and tender joints each on a 66/68 joint count at Screening and Baseline”.
Purpose for Change: Administrative, correction.
 5. Section 3. SYNOPSIS; Section 9.1, Inclusion Criteria
Description of Change: Inclusion criterion 9 was updated: “Female subjects must have a negative pregnancy test at Screening and on admission to the clinic and must not be lactating. Female subjects must also agree to or be one of the following for the duration of the study until **5 months** after the last dose...”.
Purpose for Change: Administrative, updated for consistency with the Summary of Product Characteristics for EU Humira.
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6. Section 3. SYNOPSIS; Section 9.2, Exclusion Criteria
Description of Change: The wording of Exclusion criterion 13 was updated to clarify the conditions under which patients with fibromyalgia can be included in the study: “Presence of fibromyalgia (**as a primary disease**), another autoimmune rheumatologic illness or inflammatory arthritis, eg, systemic lupus erythematosus, gout. The presence of secondary Sjogren’s syndrome is permitted. **At the discretion of the investigator, a patient with stable and low-grade fibromyalgia may be included in the study if the fibromyalgia is not a primary disease and will not interfere with the assessment of RA (specifically in the diagnosis, severity classification, monitoring, and outcomes).**”
Purpose for Change: Administrative, updated for clarity.
 7. Section 5. LIST OF ABBREVIATIONS
Description of Change: The abbreviations “**CTA, Clinical Trial Agreement**”, “**SUSAR, suspected unexpected serious adverse reactions**”, and “**RSI, Reference Safety Information**” were added. The abbreviations “B19V, parvovirus B19”, “HAV, hepatitis A virus”, and “HEV, hepatitis E virus” were deleted.
Purpose for Change: Administrative.
 8. Section 6.1, Description of Investigational Product
Description of Change: The M923 AI was used previously in a Phase I trial to assess the pharmacokinetics and safety of M923 administered via AI or prefilled syringe, in healthy subjects (clinical study protocol identifier: 911501; NCT02675023). Text was updated to indicate that the AI is not a new device: “**A** single-use, 1.0 mL autoinjector (AI; see Section 20.7) that delivers 40 mg (0.8 mL) of M923 via SC injection will be examined in this study.”
Purpose for Change: Administrative, correction.
 9. Section 6.2, Clinical Condition/indication
Description of Change: Text describing the medical need for the IP was condensed.
Purpose for Change: Administrative, updated for clarity.
 10. Section 6.3, Population to be Studied; Section 20.1, Study Flow Chart
Description of Change: The number of subjects to be enrolled was erroneously stated as 34 in the original protocol; this was corrected to 32 subjects.
Purpose for Change: Administrative, correction.
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11. Section 8.1, Brief Summary

Description of Change: The M923 AI was used previously in a Phase I trial to assess the pharmacokinetics and safety of M923 administered via AI or prefilled syringe, in healthy subjects (clinical study protocol identifier: 911501; NCT02675023). Text was updated to indicate that the AI is not a new device: “The proposed biosimilar M923 will be provided in a form for administration via an AI for SC self-injection in subjects with active, moderate to severe RA.”

Purpose for Change: Administrative, correction.

12. Section 10.3.5, Treatment Extension Period Assessments

Description of Change: Wording clarified to indicate that home-dosing would not be performed at Weeks 12 and 24/EDV “Following Visit 4, subjects will self-administer IP at home, **except at Visits 8 and 14**”. Additional home-dosing visits were added at Weeks 6, 10, 16, 20, and 22; study visit numbering was revised accordingly: “Visits will be conducted at the following timepoints (± 3 days targeted) during the treatment extension period: **Visit 5 (Week 6)**, Visit 6 (Week 8), **Visit 7 (Week 10)**, Visit 8 (Week 12), Visit 9 (Week 14), **Visit 10 (Week 16)**, Visit 11 (Week 18), **Visit 12 (Week 20)**, **Visit 13 (Week 22)**, and Visit 14 (Week 24).” Additional detail was added to clarify the timings of the following assessments: “28 joint count **at Visits 8 and 14/EDV** (see Section 11.4.1)”, “Vital signs **at Visits 8 and 14/EDV**, performed prior to blood sampling (when taken at Visits 8 and 14/EDV), within 30 minutes before and after administration of IP (see [Section 12.8](#))” and “Drug dispensing at Visit 8 (**6 weeks’ supplies of M923 AIs**)”.

Purpose for Change: Administrative, updated for clarity.

13. Section 10.5, Subject Diary and Patient-reported Outcomes; Section 16.3, Informed consent

Description of Change: The wording “and/or legally authorized representatives” was removed from subject informed consent statements. This change was requested by the Institutional Review Board.

Purpose for Change: Administrative, updated for clarity.

14. Section 11.1, Primary Usability Assessment

Description of Change: The version number of the SIAQ tool was updated from v2.0 to v2.1.

Purpose for Change: Administrative, correction.

15. **CCI** [REDACTED]
[REDACTED]
[REDACTED]
Purpose for Change: Administrative, updated for clarity.
16. Section 12.1.2, Assessment of Adverse Events
Description of Change: Text was updated to account for SAEs that could occur during the pre-exposure period: “For the purposes of this study, each non-serious untoward medical occurrence reported by a subject undergoing study-related procedure(s) before the first M923 treatment will be recorded on the AE CRF; **for SAEs the SAE Report (SAER) form is to be used, in addition;** however, these events will not be included in the analysis of AEs.”
Purpose for Change: Administrative, updated for clarity.
17. Section 12.1.2, Assessment of Adverse Events
Description of Change: Text was updated to reflect the 4-week Safety Follow-Up: “Recovering/resolving AEs will be followed until resolution, medically stabilized, or **4 weeks** after the study completion/termination visit, whichever comes first.”
Purpose for Change: Administrative, correction.
18. Section 12.3, Untoward Medical Occurrences
Description of Change: Text describing untoward medical occurrences was updated: “Untoward medical occurrences **that occur before** the first exposure to M923 **and are not related to study procedures** are not considered AEs (according to the definition of AE, see [Section 12.1](#)). However, each serious untoward medical occurrence **that is** experienced before the first M923 exposure (ie, from the time of signed informed consent up to but not including the first M923 exposure) **and is not related to study procedures** will be described on the AE CRF and **on the SAER Form**. These events will **not** be considered as SAEs and will **not** be included in the analysis of SAEs. For the purposes of this study, each non-serious untoward medical occurrence experienced by a subject undergoing Screening study-related procedure(s) before the first M923 exposure will be recorded on the AE CRF (see [Section 12.1](#)); these events will not be included in the analysis of AEs. Serious untoward medical occurrences reported before the first administration of M923 (ie, from the time of signed informed consent up to but not including the first administration of M923) will be reported as an SAE.”
Purpose for Change: Administrative, updated for clarity and consistency.
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19. Section 12.1.1, Definitions; Section 12.5, Medical, Medication, and Non-drug Therapy History; Section 12.7.3.1, Assessment of Abnormal Laboratory Values
Description of Change: HAV, HEV and B19 virology assessments are not planned for this study and were therefore removed.
Purpose for Change: Administrative, correction.
 20. Section 13.4.2, Datasets and Analysis Cohorts
Description of Change: The text describing the number of instructions in the self-injection assessment checklist was corrected: “Similarly, the number and proportion of subjects who successfully completed all **14** instructions will be summarized, along with 95% CI for the proportion using Wilson’s score method.”
Purpose for Change: Administrative, correction.
 21. Section 16.4, Data Monitoring Committee
Description of Change: The text describing the reason for not establishing a DMC was updated “Subjects are on IP which is the same dosage **and** form **as** the product that is already licensed; **however, the device that delivers the IP is different from the licensed product.**”
Purpose for Change: Administrative, updated for clarity.
 22. Section 20.2, Schedule of Study Procedures and Assessments; throughout the document
Description of Change: The following changes were made to Table 2, Schedule of Study Procedures and Amendments: home-dosing visits were added at Weeks 6, 10, 16, 20, and 22; concomitant therapy assessments were added at Screening and Weeks 0, 2, 4, 8, and 14; 28 joint counts were removed at Weeks 8, 14, and 18; vital sign assessments were added at screening and Weeks 0, 2, 4, 12, 24, and 28; AE monitoring assessments were added at Screening and Weeks 0, 2, 4, 8, and 14; pregnancy testing was removed at Weeks 8, and 18; IP injection at home was added at Weeks 6, 8, 10, 12, 14, 16, 18, 20, 22, and 24; the heading “IP injection” was split into two separate rows: “**IP injection at home**” (Weeks 6, 8, 10, 14, 16, 18, 20, and 22) and “**IP injection at office**” (Weeks 0, 2, 4, 12, and 24/EDV); the heading “Drug dispensing” was changed to “**Drug dispensing for at home dosing**”; visit numbers were updated in the table footnote.
Purpose for Change: Administrative, updated for clarity.
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23. CCI [REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

Purpose for Change: Administrative, correction.

24. Investigator Acknowledgement Form

Description of Change: The investigator acknowledgement form for the Coordinating Investigator was deleted.

Purpose for Change: Administrative, a form is required for the Principal Investigator only.

INVESTIGATOR ACKNOWLEDGEMENT

PRODUCT: M923

STUDY TITLE: An open-label single-arm multicenter study to evaluate usability of a subcutaneous autoinjector for a proposed adalimumab biosimilar (M923) in subjects with moderate to severe rheumatoid arthritis

PROTOCOL IDENTIFIER: 911502

CLINICAL TRIAL PHASE 3

AMENDMENT 1: 2016 AUG 26

Replaces: Original: 2016 JAN 29

ALL VERSIONS:

Amendment 1: 2016 AUG 26

Original: 2016 JAN 29

OTHER ID(s)

NCT Number: NCT02722044

IND NUMBER: 115119

By signing below, the Investigator acknowledges that he/she has read and understands this protocol, and will comply with the requirements for obtaining informed consent from all study subjects prior to initiating any protocol-specific procedures, obtaining written initial and ongoing EC(s) protocol review and approval, understands and abides by the requirements for maintenance of source documentation, and provides assurance that this study will be conducted according to all requirements as defined in this protocol, Clinical Trial Agreement, ICH GCP guidelines, and all applicable national and local regulatory requirements.

Signature of Principal Investigator

Date

Print Name of Principal Investigator
