

CLINICAL STUDY PROTOCOL

PRODUCT: M923

STUDY TITLE: A Phase 3 Randomized, Double-blind, Multicenter Study to Evaluate Efficacy, Safety, and Immunogenicity of M923 (a Proposed Adalimumab Biosimilar) and Humira® in Subjects with Moderate to Severe Chronic Plaque-type Psoriasis

STUDY SHORT TITLE: Phase 3 Study of M923 and Humira® in Subjects with Chronic Plaque-type Psoriasis

PROTOCOL IDENTIFIER: 911401

CLINICAL TRIAL PHASE 3

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Replaces: Amendment 2: 2015 OCT 08

ALL VERSIONS:

Amendment 3: 2016 AUG 04

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Study Sponsor(s):

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1. STUDY PERSONNEL

1.1 Authorized Representative (Signatory) / Responsible Party

PPD [REDACTED], MD
Vice President, Clinical Development
Baxalta US Inc.

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.

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2. SERIOUS ADVERSE EVENT REPORTING

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

Questions pertaining to an SAE should be directed to:

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ALL SAEs ARE TO BE REPORTED ON THE ELECTRONIC CASE REPORT FORM (eCRF) AND TRANSMITTED TO THE SPONSOR WITHIN 24 HOURS AFTER BECOMING AWARE OF THE EVENT

<p>See eCRF for contact information.</p> <p>Further details are also available in the study team roster.</p>
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For definitions and information on the assessment of these events, refer to the following:

- Adverse events (AE), [Section 12.1](#)
 - SAE, [Section 12.1.1.1](#)
 - Assessment of AEs, [Section 12.1.2](#)
-

3. SYNOPSIS

INVESTIGATIONAL PRODUCT	
Name of Investigational Product (IP)	M923, a proposed adalimumab biosimilar
Name(s) of Active Ingredient(s)	Adalimumab
CLINICAL CONDITION(S)/INDICATION(S) Moderate to Severe Plaque Psoriasis	
PROTOCOL ID	911401
PROTOCOL TITLE	A Phase 3 Randomized, Double-blind, Multicenter Study to Evaluate Efficacy, Safety, and Immunogenicity of M923 (a Proposed Adalimumab Biosimilar) and Humira® in Subjects with Moderate to Severe Chronic Plaque-type Psoriasis
Short Title	Phase 3 Study of M923 and Humira® in Subjects with Chronic Plaque-type Psoriasis
STUDY PHASE	Phase 3
PLANNED STUDY PERIOD	
Initiation	2015 AUG
Primary Completion	2017 FEB
Study Completion	2017 MAY
Duration	Approximately 86 weeks
STUDY OBJECTIVES AND PURPOSE	
Study Purpose The purpose of the study is to evaluate efficacy, safety, and immunogenicity of M923 (a proposed adalimumab biosimilar) and a non-US-approved comparator (EU-approved Humira®) referred to as the Reference Protein Product (EU RPP) in subjects with moderate to severe chronic plaque-type psoriasis.	
Primary Objective Demonstrate equivalence in measures of efficacy between M923 (test) and EU RPP in subjects with moderate to severe chronic plaque-type psoriasis	
Secondary Objective(s) <ol style="list-style-type: none">1. Evaluate the continued efficacy, safety, immunogenicity, and tolerability of M923 compared with EU RPP2. Evaluate the transition from EU RPP to M923 based on safety and immunogenicity compared with continuous use of EU RPP3. Evaluate drug concentrations over time	

STUDY DESIGN	
Study Type/ Classification/ Discipline	Bioequivalence, Efficacy, Pharmacokinetic, Safety, Immunogenicity
Control Type	Concurrent (Active)
Study Indication Type	Treatment
Intervention model	Parallel
Blinding/Masking	Double-Blind
Study Design	<p>This study is a Phase 3, controlled, randomized, double-blind, multicenter study to evaluate efficacy, safety, and immunogenicity of M923 (a proposed adalimumab biosimilar) versus EU RPP in 516 randomized subjects with moderate to severe chronic plaque-type psoriasis to yield 490 subjects (in 2 arms) completing through Week 16.</p> <p><u>Arm A:</u> M923 from Weeks 0 to 48 (last dose at Week 47; n = 258 subjects)</p> <p><u>Arm B:</u> Reference Protein Product from Weeks 0 to 15 (last dose at Week 15); then randomized again at Week 16 into Arms B1 and B2:</p> <p style="padding-left: 40px;">Arm B1: Continues EU RPP from Weeks 17 through 48 (last dose at Week 47; n = up to 129 subjects)</p> <p style="padding-left: 40px;">Arm B2: Transition to M923 at Week 17, then to EU RPP at Week 25; and then to M923 at Week 37 (last dose at Week 47; n = up to 129 subjects)</p> <p>Subjects who complete the treatment period will have a safety follow-up visit at Week 52.</p>
Planned Duration of Subject Participation	Approximately 56 weeks: 4-week screening period, 48-week treatment period, and 4-week safety follow-up period
Primary Outcome Measure Proportion of subjects with Psoriasis Area and Severity Index 75% improvement (PASI75) response at Week 16 with M923 vs EU RPP	
Secondary Outcome Measures Efficacy <ol style="list-style-type: none"> 1. Proportion of subjects with response by static Physician Global Assessment (sPGA) of clear or almost clear (6-point scale) at Week 16 in subjects treated with M923 vs EU RPP 2. PASI50, PASI75, PASI90, and sPGA response rates over time in subjects treated with M923 or EU RPP 3. Absolute PASI score over time in subjects treated with M923 and EU RPP 4. Health-related quality of life during treatment with M923 and EU RPP based on the Dermatology Life Quality Index (DLQI) and the EuroQoL 5-Dimension Health Status Questionnaire (EQ-5D-5L) 	

Safety <ol style="list-style-type: none"> 1. Clinical safety and tolerability of M923 compared with EU RPP as assessed by vital signs, clinical laboratory results, electrocardiograms (ECGs), and adverse events (AEs) (including serious AEs [SAEs], withdrawal from the study because of an AE, discontinuation of study-specific therapy because of an AE, and injection site reactions) 2. Clinical safety and tolerability of the transitions between EU RPP and M923 (occurring twice in arm B2) compared with continuous use of EU RPP (arm B1) – See Figure 1 	
Pharmacokinetics and Immunogenicity <ol style="list-style-type: none"> 1. Exposure to M923 and EU RPP assessed as serum levels collected periodically throughout the treatment period 2. Immunogenicity of M923 and EU RPP assessed as proportion experiencing seroconversion, titer of anti-drug antibody (ADA) levels over time, and neutralizing ADA 3. Immunogenicity, as evidenced by the presence of ADAs, following the transition from EU RPP to M923 compared with continuous use of EU RPP assessed as proportion of subjects experiencing seroconversion; titer of ADA levels over time; and neutralizing ADA over time. 	
INVESTIGATIONAL PRODUCT(S), DOSE, AND MODE OF ADMINISTRATION	
Active Product	M923, a proposed adalimumab biosimilar Dosage form: 40 mg (0.8 mL) prefilled syringe for injection Dosage frequency: 80 mg at Week 0 and then 40 mg every 2 weeks (Q2W) starting at Week 1 Mode of Administration: subcutaneous (SC)
Comparator	Non-US-approved comparator (EU-approved Humira [®]) referred to as the EU Reference Protein Product Dosage form: 40 mg (0.8 mL) prefilled syringe for injection Dosage frequency: 80 mg at Week 0 and then 40 mg Q2W starting at Week 1 Mode of Administration: SC
SUBJECT SELECTION	
Targeted Accrual	516 subjects planned for randomization 572 subjects actually randomized
Number of Groups/Arms/Cohorts	258 subjects planned to be randomly assigned to Arm A and 258 subjects randomly assigned to Arm B. At Week 16, subjects in Arm B planned to be randomly assigned again to Arms B1 and B2 (up to 129 subjects each)
Inclusion Criteria <ol style="list-style-type: none"> 1. Subjects must be ≥ 18 years old at the time of screening 2. Must be able to understand and communicate with the investigator and comply with the requirements of the study (including administration of SC injections at home) and must give a written, signed, and dated informed consent before any study-related activity. Where relevant, a legal representative will also sign the informed study consent according to local laws and regulations 	

3. Chronic plaque-type psoriasis diagnosed for at least 6 months before screening
4. Stable plaque-type psoriasis, defined as no significant change in lesional area or severity, for a period of 2 months or more before screening
5. **All countries except Canada:** History of receipt of or candidate for systemic therapy or phototherapy with active plaque-like psoriasis despite topical therapy.
Canada only: History of receipt of or candidate for systemic therapy with active plaque-like psoriasis despite topical therapy.
Canada only: History of phototherapy treatment that was ineffective or phototherapy judged by the treating physician to be inappropriate for the subject
6. Moderate to severe psoriasis at screening and baseline (Visit 2), defined as:
 - a. PASI score ≥ 12
 - b. sPGA score ≥ 3 (based on a scale of 0 to 5)
 - c. Body Surface Area (BSA) affected by plaque-type psoriasis $\geq 10\%$
7. Must be willing and able to self-administer SC injections or have a caregiver available to administer injections
8. Male subjects must either abstain from sexual intercourse or 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 investigational product (IP) until completion of study procedures. Alternatively, male subjects may have been vasectomized, with confirmation of sterility.
9. Female subjects must have a negative pregnancy test at screening and baseline and must not be lactating. Female subjects must also meet one of the conditions below for the entire duration of the study:
 - a. Abstain from sexual intercourse
 - b. Use a method of contraception, as described for female partners in Inclusion Criterion 8, and have their male partner use a condom until 5 months after the last administration of the IP
 - c. Be of non-childbearing potential, confirmed at screening by fulfilling 1 of the following criteria:
 - i. Postmenopausal, defined as amenorrhea for at least 12 months following cessation of all exogenous hormonal treatments and with follicle-stimulating hormone levels drawn during screening within the laboratory-defined postmenopausal range or postmenopausal with amenorrhea for at least 24 months and on hormonal replacement therapy
 - ii. 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. Presence of forms of psoriasis other than chronic plaque-type (eg, pustular, erythrodermic, or guttate psoriasis)
2. History of or current drug-induced psoriasis (eg, from beta-blockers or lithium)
3. Presence of other skin conditions, including skin infections, which would interfere with assessment of psoriasis
4. Presence of chronic or ongoing medical conditions other than psoriasis for which systemic corticosteroids were used in the last year prior to screening, eg, asthma
5. Presence of other inflammatory conditions other than psoriasis or psoriatic arthritis, eg, rheumatoid arthritis, gout, or inflammatory bowel disease
6. Subject must have no major deviations regarding concomitant medication, such as prior use of systemic tumor necrosis factor (TNF) inhibitor therapy, investigational or licensed (ie, other investigational biosimilar TNF inhibitor therapy exposure is not permitted), or 2 or more non-TNF biologic therapies required concomitantly
7. Ongoing use of prohibited psoriasis treatments (eg, prohibited topical corticosteroids, systemic corticosteroids, ultraviolet (UV)-therapy including excessive sun exposure, immunosuppressant therapy, including methotrexate); washout periods detailed in the Medications and Non-Drug Therapies section of the protocol must be followed
8. Ongoing use of other non-psoriasis prohibited treatments; washout periods detailed in the Medications and Non-Drug Therapies section of the protocol must be followed
9. All other prior non-psoriasis concomitant treatments must be on a stable dose for at least 4 weeks before baseline
10. Laboratory abnormalities at screening deemed clinically significant by the investigator and/or:
 - a. Hemoglobin < 8 g/dL for women or 8.5 g/dL for men
 - b. White blood cell count < $3.5 \times 10^9/L$
 - c. Platelet count < $120 \times 10^9/L$
 - d. Aspartate transaminase or alanine transaminase > 1.5 times the upper limit of normal
 - e. Creatinine > 1.5 mg/dL if < 65 years old, or > upper limit of normal if ≥ 65 years old
11. 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 or sponsor pose an unacceptable safety risk
12. History of latex allergy
13. History of or current signs or symptoms or diagnosis of a demyelinating disorder
14. History of or current Class III or IV New York Heart Association congestive heart failure
15. History or current signs, symptoms, or diagnosis of lymphoproliferative disorders, lymphoma, leukemia, myeloproliferative disorders, or multiple myeloma
16. Current 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; no more than 3 lifetime basal cell and squamous cell carcinomas permitted

17. Chronic infections, recurrent infections (3 or more of the same infection requiring anti-infective treatment in any rolling 12 month period); any recent infection requiring hospitalization or any infection requiring parenteral anti-infective therapy within 30 days or oral infective therapies within 14 days of baseline (Visit 2); 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, coccidiomycosis, histoplasmosis, toxoplasmosis)
18. History of or presence of human immunodeficiency virus (HIV), or Hepatitis B (HBV) or C virus (HCV)
19. History of active tuberculosis (TB) or untreated or inadequately treated latent TB. Subjects must have a negative QuantiFERON, T-SPOT, or purified protein derivative (PPD) test, and a radiograph or comparable imaging with negative finding for TB or other similar infections at the Screening visit or within 3 months prior to Screening visit
20. Subject has been exposed to an IP within 30 days prior to enrollment or is scheduled to participate in another clinical study involving an IP or investigational device during the course of this study
21. Subject is a family member or employee of the investigator or site staff or study team

STATISTICAL ANALYSIS

Sample Size Calculation

1. Primary analysis: Test equivalence of M923 compared with EU RPP using the PASI75 response rate at 16 weeks, CCI [REDACTED]
2. CCI [REDACTED]
3. 516 subjects randomized (258 in Arm A and 258 in Arm B), CCI [REDACTED]

Equivalence Margin Justification:

The treatment effect versus placebo, based on PASI75 at 16 weeks from a Phase 3 study (REVEAL¹), was estimated to be 0.647 (lower bound of 2-sided 95% confidence interval 0.460).

The treatment effect versus placebo, based on PASI75 at 16 weeks from the other pivotal Phase 3 study (CHAMPION²), was estimated to be 0.64 (lower bound of 2-sided 95% confidence interval 0.597).

Margin for US:

An 18% equivalence margin was selected based on observed variation in response rates in adalimumab's Phase 2³ vs Phase 3 studies at 12 weeks, and on the statistical (M1) margins in the Phase 3 studies at 16 weeks. Based on the meta-analysis of the REVEAL¹ and CHAMPION² studies, the 95% confidence bound for the difference in proportions of PASI75 is 0.5975 to 0.6744. The acceptable margins (M1) statistically from the Phase 3 studies were 0.298 at 16 weeks. The proposed margin of 18% preserves 70% of the treatment effect, and is well within both the inter-trial variation in response rates and the M1 from Phase 3 and comprises a conservative margin for assessment of equivalence.

Margin for EU:

A 15% equivalence margin was selected based on observed variation in response rates in adalimumab's Phase 2³ vs Phase 3 studies at 12 weeks, and on the statistical (M1) margins in the Phase 3 studies at 16 weeks. Based on the meta-analysis of the REVEAL¹ and CHAMPION² studies, the 95% confidence bound for the difference in proportions of PASI75 is 0.5975 to 0.6744. The acceptable margins (M1) statistically from the Phase 3 studies were 0.298 at 16 weeks. The proposed margin of 15% preserves 75% of the treatment effect, and is well within both the inter-trial variation in response rates and the M1 from Phase 3 and comprises a conservative margin for assessment of equivalence.

Planned Statistical Analysis

Primary Objective: The PASI75 response rate will be described at Week 16 for subjects on M923 (Arm A) vs EU RPP (Arm B).

Secondary Objective: The sPGA response rate will be described at Week 16 for subjects on M923 (Arm A) vs EU RPP (Arm B). The treatment arms (Arm A and Arm B, as well as Arm A to Arm B1) will be compared using descriptive statistics for PASI50, PASI75, PASI90, and sPGA response rates over time.

Safety Objective: Assess safety.

- All treatment-emergent adverse events will be summarized by System Organ Class and Preferred Term and by treatment arm
- The clinical safety and tolerability of the transition from EU RPP to M923 as compared with continuous use of EU RPP with regard to AEs will be evaluated
- Physical examination, vital signs, laboratory parameters, and ECGs will be presented by treatment group for each visit
- The clinical safety and tolerability of the transition from EU RPP to M923 as compared with continuous use of EU RPP will be evaluated using the descriptive statistics provided over time

Pharmacokinetics and immunogenicity: Assess pharmacokinetics and immunogenicity by time point.

- The serum levels will be summarized by treatment arm at each scheduled collection. Summaries will be further stratified by ADA formation. The within-subject variability in trough concentrations over time (from Week 17 to Week 41) will be determined for each subject and then compared between treatment arms
- Transition from EU RPP to M923 as compared with continuous use of EU RPP with regard to PK will be evaluated using the descriptive statistics at each schedule time point and statistical comparison of within-subject variability. A summary of the number and percent of subjects testing positive for ADA or neutralizing antibodies before the dose of M923 or EU RPP and at scheduled postdose assessments will be presented by treatment arm. The time to seroconversion will be summarized
- The number and percentage of subjects who had at least one ADA-positive result will be provided by treatment arm
- Immunogenicity following the transition from EU RPP to M923 as compared with continuous use of EU RPP will be evaluated with the number and percentage of subjects who had at least once ADA-positive by treatment arm and by treatment period

Response Rate Justification:

Adalimumab response rates were 71.0% (n = 578/814) and 79.6% (n = 86/108) in 2 previous pivotal psoriasis studies. Based on a meta-analysis, the estimated treatment effect was 63.6% (95% confidence interval of 59.8% - 67.4%), which was used as the basis for sample size calculation.

Primary Analysis

The methods of analysis for the primary outcome measure will be done on the per protocol (PP) population.

The PASI75 response rate will be described at Week 16 for subjects on M923 (Arm A) vs EU RPP (Arm B). The Non-Responder Imputation (NRI) method will be used to handle missing data.

For the FDA, all equivalence comparisons will be made using 90% confidence intervals and an equivalence margin of 18%. For the EMA, all equivalence comparisons will be made using 95% confidence intervals and an equivalence margin of 15%.

A confidence interval for differences between M923 and EU RPP will be calculated using the stratified Newcombe confidence interval.

The null hypothesis of differences in PASI75 proportions of at least 15% for EMA and 18% for FDA will be rejected if the 95% confidence interval for EMA and 90% confidence interval for FDA for the difference in PASI75 is wholly contained within the equivalence region; in this case, equivalence will be declared.

The primary analysis will be repeated on the intent-to-treat (ITT) population as a sensitivity analysis.

CCI

An administrative interim database lock will occur at Week 25 to perform the primary analysis, as well as safety, PK and immunogenicity analysis over this time period. The purpose of the interim database lock is to provide an analysis of the primary endpoint data to regulatory agencies before the completion of the study. No trial-related decisions will be made based on the interim analysis. The interim analysis will be executed by an unblinded team, as appropriate, distinct from the study team. The study team will remain blinded until final database lock.

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	12
5. LIST OF ABBREVIATIONS	16
6. BACKGROUND INFORMATION	18
6.1 Description of Investigational Product	18
6.2 Clinical Condition/Indication	19
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.....	20
6.6 Compliance Statement.....	20
7. STUDY PURPOSE AND OBJECTIVES	20
7.1 Study Purpose	20
7.2 Primary Objective.....	20
7.3 Secondary Objectives	20
8. STUDY DESIGN.....	21
8.1 Brief Summary	21
8.2 Study Design	21
8.3 Duration of Study Period(s) and Subject Participation	21
8.4 Outcome Measures	22
8.4.1 Primary Outcome Measure	22
8.4.2 Secondary Outcome Measures	22
8.4.2.1 Efficacy	22
8.4.2.2 Safety.....	22
8.4.2.3 Pharmacokinetics and Immunogenicity	22
8.5 Randomization and Blinding	23
8.6 Study Stopping Rules.....	23
8.7 Investigational Product(s)	24

8.7.1 Packaging, Labeling, and Storage	24
8.7.2 Administration	25
8.7.2.1 Injection training	25
8.7.3 Description of Treatment	25
8.7.4 Investigational Product Accountability	26
8.8 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	32
10.1 Informed Consent and Enrollment	32
10.2 Subject Identification Code.....	32
10.3 Screening and Study Visits.....	32
10.3.1 Screening and Baseline Assessments.....	32
10.3.2 Treatment Visits.....	34
10.3.3 Study Completion/Termination.....	36
10.3.4 Safety Follow-up	36
10.4 Medications and Non-Drug Therapies.....	37
10.5 Subject Diary	39
10.6 Subject Completion/Discontinuation	39
10.7 Procedures for Monitoring Subject Compliance	40
 11. ASSESSMENT OF EFFICACY, IMMUNOGENICITY, AND PHARMACOKINETICS	41
11.1 Primary Efficacy Assessment	41
11.2 Secondary Efficacy Assessments	41
11.2.1 Static Physician Global Assessment	41
11.2.2 Psoriasis Area and Severity Index.....	41
11.2.3 Body Surface Area	42
11.2.4 Patient-reported Outcomes – Dermatology Life Quality Index (DLQI) and EuroQoL 5-Dimension Health Status Questionnaire	42
11.3 Pharmacokinetics Assessments.....	42
11.4 Immunogenicity Assessments	43
 12. ASSESSMENT OF SAFETY.....	44
12.1 Adverse Events	44
12.1.1 Definitions.....	44
12.1.1.1 Serious Adverse Events	44
12.1.1.2 Non-Serious Adverse Events.....	45

12.1.1.3 Unexpected Adverse Events	45
12.1.1.4 Preexisting Diseases	45
12.1.2 Assessment of Adverse Events	45
12.1.2.1 Severity	46
12.1.2.2 Causality	47
12.2 Urgent Safety Measures	48
12.3 Untoward Medical Occurrences.....	49
12.4 Non-Medical Complaints	49
12.5 Medical, Medication, and Non-Drug Therapy History	49
12.6 Physical Examinations.....	50
12.7 Clinical Laboratory Parameters.....	51
12.7.1 Hematology and Clinical Chemistry	51
12.7.2 Urinalysis	51
12.7.3 Assessment of Laboratory Values	51
12.7.3.1 Assessment of Abnormal Laboratory Values.....	51
12.8 Vital Signs.....	52
12.9 Electrocardiograms	52
12.10 Injection Site Evaluations	52
 13. STATISTICS	 54
13.1 Sample Size and Power Calculations	54
13.1.1 Sample Size Calculation	54
13.2 Populations and Analysis Cohorts.....	55
13.3 Handling of Missing, Unused, and Spurious Data	56
13.4 Methods of Analysis.....	56
13.4.1 Disposition and Withdrawals.....	57
13.4.2 Demographic and other Baseline Characteristics	57
13.4.3 Primary Outcome Measure.....	57
13.4.4 Secondary Outcome Measures	58
13.4.4.1 Efficacy	58
13.4.4.2 Safety.....	58
13.4.4.3 Pharmacokinetics and Immunogenicity	59
13.5 Planned Interim Analysis of the Study	60
 14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS	 61
 15. QUALITY CONTROL AND QUALITY ASSURANCE	 62
15.1 Investigator's Responsibility.....	62
15.1.1 Final Clinical Study Report	62
15.2 Training	62
15.3 Monitoring.....	62
15.4 Auditing	62
15.5 Non-Compliance with the Protocol	63

15.6 Laboratory and Reader Standardization	63
16. ETHICS	64
16.1 Subject Privacy	64
16.2 Ethics Committee and Regulatory Authorities	64
16.3 Informed Consent	64
16.4 Data Monitoring Committee.....	65
17. DATA HANDLING AND RECORD KEEPING.....	66
17.1 Confidentiality Policy	66
17.2 Study Documentation and Case Report Forms	66
17.3 Document and Data Retention.....	66
18. FINANCING AND INSURANCE	67
19. PUBLICATION POLICY.....	67
20. SUPPLEMENTS	68
20.1 Study 911401 Schematic.....	68
20.2 Schedule of Study Procedures and Assessments	69
21. REFERENCES.....	74
22. SUMMARY OF CHANGES.....	76
INVESTIGATOR ACKNOWLEDGEMENT.....	82

Tables

Table 1 Schedule of Study Procedures and Assessments	69
Table 2 Laboratory Parameters.....	72
Table 3 Injection Site Reaction Grading Scheme	73

Figures

Figure 1 Study Design for Baxalta Clinical Study 911401.....	68
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5. LIST OF ABBREVIATIONS

Abbreviation	Definition
ADA	anti-drug antibody
ADCC	antibody-dependent cell-mediated cytotoxicity
AE	adverse event
BSA	body surface area
BTL	bilateral tubal ligation
CDC	complement dependent cytotoxicity
CV	coefficient of variation
DLQI	Dermatology Life Quality Index
EC	ethics committee
ECG	electrocardiogram
eCRF	electronic case report form
EQ-5D-5L	EuroQoL 5-Dimension Health Status Questionnaire
ETV	end of treatment visit
EU	European Union
EU RPP	Reference Protein Product, the non-US-approved comparator (EU-approved Humira)
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IgG1	immunoglobulin G subclass 1
IP	investigational product
IRT	Interactive Response Technology
ITT	intent-to-treat population
mBOCF	modified baseline observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed models for repeated measures
MTX	methotrexate
NMC	Non-medical complaint

Abbreviation	Definition
NRI	non-responder imputation
PA	posterior-anterior
PASI	Psoriasis Area and Severity Index
PASI50	Psoriasis Area and Severity Index 50% improvement
PASI75	Psoriasis Area and Severity Index 75% improvement
PASI90	Psoriasis Area and Severity Index 90% improvement
PK	pharmacokinetics
PP	per protocol population
PPD	purified protein derivative
PUVA	psoralens and long-wave ultraviolet radiation
Q2W	every 2 weeks
QTcF	QT interval corrected for heart rate using Fridericia's equation
QT	a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SIC	subject identification code
sPGA	static Physician Global Assessment
TB	Tuberculosis
TEAE	treatment-emergent adverse event
TNF	tumor necrosis factor
US	United States
US RP	Humira approved for use in the US; ie, the US-licensed Reference Product
UV	ultraviolet

6. BACKGROUND INFORMATION

6.1 Description of Investigational Product

M923 is a proposed adalimumab biosimilar. HUMIRA[®] (hereafter referred to as Humira) is the United States (US)-licensed reference product and contains adalimumab as the active substance. Adalimumab is a recombinant human immunoglobulin G subclass 1 (IgG1) monoclonal antibody specific for human tumor necrosis factor–alpha (TNF)-alpha. Unlike etanercept, adalimumab does not bind to TNF–beta.

Humira is licensed for use in the US and European Union (EU); Humira approved in the EU, which is the Reference Protein Product (EU RPP) in this study, is not approved for use in the US and hence is considered an investigational new drug. Hereafter, Humira licensed in the US is referred to as the US Reference Product (US RP), and the non-US-approved comparator (EU-approved Humira) is referred to as the EU RPP.

M923 injection is a preservative-free, sterile solution for subcutaneous (SC) administration and is provided as single-use, 1.0 mL prefilled glass syringes that deliver 40 mg (0.8 mL) of M923. M923 is produced by recombinant deoxyribonucleic acid technology in a Chinese hamster ovary mammalian cell expression system and is purified by a process that includes specific viral inactivation and removal steps. The amino acid sequences of M923 and adalimumab are identical. The M923 formulation has a different buffer composition than the EU RPP and the US RP; however, the solution characteristics (pH, osmolality) of M923 are found to be within pre-specified acceptance criteria to those of the EU RPP and are expected to exhibit corresponding physiologic effects. There are no new components in the M923 buffer.

The M923 dose selected for this study is based on the recommended dose of US RP and EU RPP for adult patients with active chronic plaque psoriasis, ie, an initial dose of 80 mg administered SC, followed by 40 mg SC given every other week starting 1 week after the initial dose.⁴ The safety profile of M923 is anticipated to correspond to the EU RPP. Investigators should carefully monitor for all adverse events (AEs), including AEs not described as associated with the EU RPP. The pharmacokinetic (PK) profile of M923 is currently being evaluated in an ongoing PK Phase 1 clinical study; results are not yet available.

6.2 Clinical Condition/Indication

The EU RPP is indicated for the treatment of moderate to severe chronic plaque psoriasis in adult patients who failed to respond to or who have a contraindication to, or are intolerant to other systemic therapy including cyclosporine, methotrexate (MTX), or phototherapy (psoralens and long-wave ultraviolet radiation [PUVA]).⁴

The medical need for a biosimilar to the EU RPP (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 rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, ulcerative colitis, and plaque psoriasis.

Provided that comparability of M923 to the EU RPP is demonstrated in all aspects of safety and efficacy, then the medical need for this product is also established.

6.3 Population to Be Studied

The study population will include 516 subjects with moderate to severe chronic plaque-type psoriasis. Adult (≥ 18 years) male and female subjects will be considered to be eligible provided that they satisfy all of the inclusion criteria listed in [Section 9.1](#) and none of the exclusion criteria listed in [Section 9.2](#).

6.4 Findings from Nonclinical and Clinical Studies

Multiple lots of the US RP and EU RPP have been extensively characterized in nonclinical pharmacology, PK, and immunogenicity studies and compared with the investigational M923 proposed adalimumab biosimilar product. The results of these comparisons showed that the biological activities of M923 corresponded to the comparators (both US RP and EU RPP). Specifically, the results were within the acceptance range for M923, EU RPP, and US RP for binding to soluble human TNF- α , the human Fc γ receptor, C1q complex, and the human neonatal Fc receptor; activity in the antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) assays; potency in the L929 mouse fibroblast cell line assay; PK and in vitro immunogenicity. A Phase 1 PK study with M923 in healthy volunteers is currently ongoing.

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 (both the EU RPP and the US RP) apply to M923 (see Appendix A of the Investigator's Brochure [IB] for M923). However, investigators should carefully monitor for all AEs, including AEs not described as associated with the EU RPP and the US RP.

6.6 Compliance Statement

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

7. STUDY PURPOSE AND OBJECTIVES

7.1 Study Purpose

The purpose of the study is to evaluate efficacy, safety, and immunogenicity of M923 (a proposed adalimumab biosimilar) and a non-US-approved comparator (EU-approved Humira[®]) referred to as the Reference Protein Product (EU RPP) in subjects with moderate to severe chronic plaque-type psoriasis.

7.2 Primary Objective

The primary objective of the study is to demonstrate equivalence in measures of efficacy between M923 (test) and EU RPP (reference) in subjects with moderate to severe chronic plaque-type psoriasis.

7.3 Secondary Objectives

The secondary objectives of the study are to:

1. Evaluate the continued efficacy, safety, immunogenicity, and tolerability of M923 compared with EU RPP
 2. Evaluate the transition from EU RPP to M923 based on safety and immunogenicity compared with continuous use of EU RPP
 3. Evaluate concentrations over time
-

8. STUDY DESIGN

8.1 Brief Summary

This study is a Phase 3, active-controlled, randomized, double-blind, multicenter study to determine the clinical equivalence of M923 and EU RPP in a total of 516 randomized subjects (258 subjects in the M923 group and up to 129 subjects in each of 2 EU RPP crossover groups) with moderate to severe chronic plaque-type psoriasis.

8.2 Study Design

The 2 treatment arms will include:

- Arm A: M923 from Weeks 0 to 48 (last dose at Week 47)
- Arm B: EU RPP from Weeks 0 to 16 (last dose at Week 15); then randomized again at Week 16 into Arms B1 and B2:
 - Arm B1: Continues EU RPP from Weeks 17 through 48 (last dose at Week 47; n = up to 129 subjects)
 - Arm B2: Transition to M923 at Week 17; then to EU RPP at Week 25; and to M923 at Week 37 (last dose at Week 47; n = up to 129 subjects)

Subjects who complete the treatment period will have a safety follow-up visit at Week 52.

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 86 weeks from study initiation (ie, first subject enrolled) to study completion (ie, last subject last visit). The recruitment period was expected to be 8 months (actual duration was 7 months).

The subject participation period is approximately 56 weeks (4-week screening period, 48-week treatment period, and 4-week follow-up period) from enrollment to subject completion (ie, last study visit), unless prematurely discontinued.

8.4 Outcome Measures

8.4.1 Primary Outcome Measure

The primary outcome measure is the Psoriasis Area and Severity Index 75% improvement (PASI75) response rate at Week 16 in subjects treated with M923 vs EU RPP.

8.4.2 Secondary Outcome Measures

8.4.2.1 Efficacy

1. Proportion of subjects with response by static Physician Global Assessment (sPGA) of clear or almost clear (6-point scale) at Week 16 in subjects treated with M923 vs EU RPP
2. PASI50, PASI75, PASI90, and sPGA response rates over time in subjects treated with M923 or EU RPP
3. Absolute PASI score over time in subjects treated with M923 and EU RPP
4. Health-related quality of life during treatment with M923 and EU RPP based on the Dermatology Life Quality Index (DLQI) and the EuroQoL 5-Dimension Health Status Questionnaire (EQ-5D-5L)

8.4.2.2 Safety

1. Clinical safety and tolerability of M923 compared with EU RPP as assessed by vital signs, clinical laboratory results, electrocardiograms (ECGs), and AEs (including serious AEs [SAEs], withdrawal from the study because of an AE, discontinuation of study-specific therapy because of an AE, and injection site reactions)
2. Clinical safety and tolerability of the transitions between EU RPP and M923 (occurring twice in arm B2) compared with continuous use of EU RPP (arm B1) – See [Figure 1](#).

8.4.2.3 Pharmacokinetics and Immunogenicity

1. Exposure to M923 and EU RPP assessed as serum levels collected periodically throughout the treatment period
 2. Immunogenicity of M923 and EU RPP assessed as proportion experiencing seroconversion, titer of anti-drug antibody (ADA) levels over time, and neutralizing ADA
-

3. Immunogenicity, as evidenced by the presence of ADAs, following the transition from EU RPP to M923 compared with continuous use of EU RPP assessed as proportion of subjects experiencing seroconversion; titer of ADA levels over time; and neutralizing ADA over time

8.5 Randomization and Blinding

This is a randomized, double-blind, active treatment clinical study. In order to minimize/avoid bias, subjects will be randomly assigned at the beginning of the study to 1 of 2 treatment regimens (M923 or EU RPP) at a ratio of 1:1, stratified by region (North America, Western Europe, and Eastern Europe/Asia).

At Week 16, subjects who were randomly assigned to EU RPP at the screening visit will be randomly assigned again into 1 of 2 treatment regimens (continue EU RPP from Weeks 17 through 48; or transition between M923 and EU RPP approximately every 12 weeks from Weeks 17 to 48) at a ratio of 1:1. Stratification will ensure balance of treatment assignment within region. The blocking scheme will be specified in the randomization specifications. Randomization will occur via an Interactive Response Technology (IRT) System until the targeted number of subjects in each treatment arm is achieved.

The investigational product (IP) blind shall not be broken by the investigator unless information concerning the IP is necessary for the medical treatment of the subject. In the event of a medical emergency, if possible, the medical monitor should be contacted before the IP blind is broken to discuss the need for unblinding.

For unblinding a subject's data, the investigator can obtain the treatment assignment by utilizing the IRT System.

An administrative interim database lock will occur at Week 25 to perform the primary analysis, as well as safety, PK and immunogenicity analysis over this time interval. The interim analysis will be executed by an unblinded team distinct from the study team. The study team will remain blinded, as appropriate, until final database lock.

8.6 Study Stopping Rules

This study will be stopped if 1 or more of the following criteria are met:

1. The sponsor or investigator, based on emerging data, considers there to be an unfavorable risk-benefit
 2. The sponsor or investigator considers continuation of the trial unjustifiable for medical or ethical reasons
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3. Recruitment of sufficient number of subjects is considered to be impractical in the required time frame (NB: recruitment requirements are met)
4. The sponsor decides to discontinue development of M923
5. An ethics committee and/or competent authority determines the trial should be terminated

8.7 Investigational Product(s)

8.7.1 Packaging, Labeling, and Storage

The IPs for this study are EU RPP and M923, which are both clear, colorless solutions essentially free from visible particles supplied in 40-mg (0.8 mL) prefilled syringes.

CCI

M923 for injection will be supplied by Baxalta or representative, and stored in compliance with Good Manufacturing Practice (GMP) conditions and labeled in accordance with local regulations. The excipients for EU RPP are sodium chloride, monobasic sodium phosphate dihydrate, dibasic sodium phosphate dihydrate, sodium citrate, citric acid, mannitol, polysorbate 80, and water for injection. Each EU RPP syringe will contain 0.86 mL to allow the entire labeled volume of 0.8 mL to be expelled from the syringe.

A sufficient quantity of 1.0 mL syringes (each syringe will contain 0.86 mL as described in [Section 8.7.1](#)) containing M923 (40 mg) or EU RPP (40 mg) will be supplied to each study site by Fisher Clinical Services. Fisher will package and label M923 and EU RPP, which will be released by a Qualified Person at Fisher to each study site.

Individual subject treatments will be dispensed at each study site in 1.0 mL syringes labeled in accordance with GMP Annex 13 requirements.

All study medication will be stored in the original container in a refrigerator at 2°C to 8°C, protected from light, in a secure, temperature-controlled, locked environment with restricted access. The study medication will not be frozen.

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.

8.7.2 Administration

M923 or EU RPP in prefilled syringes (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 (± 3 days) at the same time of day every 2 weeks. Directions for used materials will be provided.

8.7.2.1 Injection training

The study staff will train subjects (or a caregiver) on the SC injection procedure. This training should occur at the Baseline Visit. At the Baseline Visit, 2 prefilled syringes are required to be administered. Site staff will show the subject or caregiver how to administer with the first syringe, and the subject (or caregiver) will demonstrate the injection technique by self-administering with the second syringe. The training and performance of self-injection will be documented in the subject's source documents. The Visit at Week 1 may be used for additional training. It is expected that subjects (or caregiver) will self-administer from Week 1 forward. At visits where the subject is to self-inject at the clinic, site staff should observe the injection to ensure it is being performed correctly and to provide retraining as required.

Subjects are to be instructed that used syringes must be placed in a safety container provided by the sponsor. This safety container should be returned to the investigational site for disposal. This training will be documented in the subject's source documents.

8.7.3 Description of Treatment

Subjects will be administered 80 mg of M923 or EU RPP at Week 0 and then 40 mg every 2 weeks (Q2W) starting at Week 1 of the study. Self-injections should occur on the same day (± 3 days) each treatment week according to a predetermined randomization schedule with 2 arms indicated as follows:

- Arm A: M923 from Weeks 0 to 48 (n = 258 subjects)
 - Arm B: EU RPP from Weeks 0 to 16 (last dose at Week 15); then randomized again at Week 16 into Arms B1 and B2:
 - Arm B1: Continues EU RPP from Weeks 17 through 48 (last dose at Week 47; n = up to 129 subjects)
 - Arm B2: Transition to M923 at Week 17; then to EU RPP at Week 25; and to M923 at Week 37 (last dose at Week 47; n = up to 129 subjects)
-

At Weeks 0, 1, 17, 19, 21, 25, 27, 37, and 39, injections will be administered in the clinic after all required assessments and blood sample collections have been completed. All other injections will be administered by the subjects or caregiver at home (but after assessments completed if a planned injection date coincides with a planned visit date [Weeks 29, 33, 41, and 45]). When injection occurs in the clinic, subjects should be observed for 2 hours in the clinic post-injection at Weeks 0, 1, 17, 25, and 37; at Weeks 19, 21, 27, and 39, subjects should be observed for 30 minutes after injection.

At any time during the study, any of the IPs 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.

When injection occurs in the clinic, the investigator or a qualified designee will evaluate the current injection sites 30 minutes (\pm 10 minutes) after study drug administration in the clinic at Weeks 0, 1, 17, 19, 21, 25, 27, 37, and 39. They should also evaluate immediately prior injection site at each subsequent visit as applicable ([Section 12.10](#)). For injections given at home, injection site reactions will be recorded in the subject diary ([Section 10.5](#)). There will be no injection at Week 48 (Visit 19), but injection site evaluation for previous injections will occur.

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

8.7.4 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 kit number, date of manufacture or expiration date, amount received, and disposition. IP must be dispensed only at the study site or other suitable location, as applicable per study design. 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.

8.8 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 trial that are necessary for the reconstruction and evaluation of the trial. 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, and subject files including records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical study.

No data will be entered directly onto the eCRF.

For additional information on study documentation and eCRFs, 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 must be ≥ 18 years old at the time of screening
 2. Must be able to understand and communicate with the investigator and comply with the requirements of the study (including administration of SC injections at home) and must give a written, signed, and dated informed consent before any study-related activity. Where relevant, a legal representative will also sign the informed study consent according to local laws and regulations
 3. Chronic plaque-type psoriasis diagnosed for at least 6 months before screening
 4. Stable plaque-type psoriasis, defined as no significant change in lesional area or severity, for a period of 2 months or more before screening
 5. **All countries except Canada:** History of receipt of or candidate for systemic therapy or phototherapy with active plaque-like psoriasis despite topical therapy.
Canada only: History of receipt of or candidate for systemic therapy with active plaque-like psoriasis despite topical therapy
Canada only: History of phototherapy treatment that was ineffective or phototherapy judged by the treating physician to be inappropriate for the subject.
 6. Moderate to severe psoriasis at screening and baseline (Visit 2), defined as:
 - a. PASI score ≥ 12
 - b. sPGA score ≥ 3 (based on a scale of 0 to 5)
 - c. Body Surface Area (BSA) affected by plaque-type psoriasis $\geq 10\%$
 7. Must be willing and able to self-administer SC injections or have a caregiver available to administer injections
 8. Male subjects must either abstain from sexual intercourse or 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 completion of study procedures. Alternatively, male subjects may have been vasectomized, with confirmation of sterility.
 9. Female subjects must have a negative pregnancy test at screening and baseline and must not be lactating. Female subjects must also meet one of the conditions below for the entire duration of the study:
-

- a. Abstain from sexual intercourse
- b. Use a method of contraception, as described for female partners in Inclusion Criterion 8, and have their male partner use a condom until 5 months after the last administration of the IP
- c. Be of non-childbearing potential, confirmed at screening by fulfilling 1 of the following criteria:
 - i. Postmenopausal, defined as amenorrhea for at least 12 months following cessation of all exogenous hormonal treatments and with follicle-stimulating hormone levels drawn during screening within the laboratory-defined postmenopausal range or postmenopausal with amenorrhea for at least 24 months and on hormonal replacement therapy
 - ii. 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. Presence of forms of psoriasis other than chronic plaque-type (eg, pustular, erythrodermic, or guttate psoriasis)
 - 2. History of or current drug-induced psoriasis (eg, from beta-blockers or lithium).
 - 3. Presence of other skin conditions, including skin infections, which would interfere with assessment of psoriasis
 - 4. Presence of chronic or ongoing medical conditions other than psoriasis for which systemic corticosteroids were used in the last year prior to screening, eg, asthma
 - 5. Presence of other inflammatory conditions other than psoriasis or psoriatic arthritis, eg, rheumatoid arthritis, gout, or inflammatory bowel disease
 - 6. Subject must have no major deviations regarding concomitant medication, such as prior use of systemic TNF inhibitor therapy, investigational or licensed (ie, other investigational biosimilar TNF inhibitor therapy exposure is not permitted), or 2 or more non-TNF biologic therapies required concomitantly
 - 7. Ongoing use of prohibited psoriasis treatments (eg, prohibited topical corticosteroids, systemic corticosteroids, ultraviolet (UV)-therapy including excessive sun exposure, immunosuppressant therapy, including MTX); washout periods detailed in [Section 10.4](#) must be followed
 - 8. Ongoing use of other non-psoriasis prohibited treatments; washout periods detailed in [Section 10.4](#) must be followed
-

9. All other prior non-psoriasis concomitant treatments must be on a stable dose for at least 4 weeks before baseline
 10. Laboratory abnormalities at screening deemed clinically significant by the investigator and/or:
 - a. Hemoglobin < 8 g/dL for women or 8.5 g/dL for men
 - b. White blood cell count < $3.5 \times 10^9/L$
 - c. Platelet count < $120 \times 10^9/L$
 - d. Aspartate transaminase or alanine transaminase > 1.5 times the upper limit of normal
 - e. Creatinine > 1.5 mg/dL if < 65 years old, or > upper limit of normal if ≥ 65 years old
 11. 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 or sponsor pose an unacceptable safety risk
 12. History of latex allergy
 13. History of or current signs or symptoms or diagnosis of a demyelinating disorder
 14. History of or current Class III or IV New York Heart Association congestive heart failure
 15. History or current signs, symptoms, or diagnosis of lymphoproliferative disorders, lymphoma, leukemia, myeloproliferative disorders, or multiple myeloma
 16. Current 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; no more than 3 lifetime basal cell and squamous cell carcinomas permitted
 17. Chronic infections, recurrent infections (3 or more of the same infection requiring anti-infective treatment in any rolling 12 month period); any recent infection requiring hospitalization or any infection requiring parenteral anti-infective therapy within 30 days or oral infective therapies within 14 days of baseline (Visit 2); 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, coccidiomycosis, histoplasmosis, toxoplasmosis)
 18. History of or presence of human immunodeficiency virus (HIV), or Hepatitis B (HBV) or C virus (HCV)
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19. History of active tuberculosis (TB) or untreated or inadequately treated latent TB. Subjects must have a negative QuantiFERON, T-SPOT or purified protein derivative (PPD), and a radiograph or comparable imaging with negative finding for TB or other similar infections at the Screening visit or within 3 months prior to Screening visit
20. Subject has been exposed to an IP within 30 days prior to enrollment or is scheduled to participate in another clinical study involving an IP or investigational device during the course of this study
21. Subject is a family member or employee of the investigator or site staff or study team

9.3 Withdrawal and Discontinuation

Any subject may voluntarily withdraw (ie, reduce the degree of participation in the study) consent for continued participation and data collection. The reason for withdrawal will be recorded on the End of Study eCRF. Assessments to be done at the termination visit (including in cases of withdrawal or discontinuation) are described in [Section 10.6](#) and [Section 20.2](#).

Discontinuation (ie, complete withdrawal from study participation) may be due to dropout (ie, active discontinuation by subject) or loss to follow-up (ie, discontinuation by subject without notice or action). 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 withdrawn from treatment or discontinued from further study participation for the following reasons:

- Failure to achieve at least a PASI 50 response at Week 25
 - 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
 - AEs/SAEs that in the investigator or sponsor opinion, poses 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, despite evidence of retraining of the subject. The subject will be discontinued 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 subject who provides informed consent (ie, signs and dates the informed consent form [ICF]) is considered enrolled in the study.

10.2 Subject Identification Code

PPD

All study documents (eg, eCRFs, 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 the eCRFs, regardless of screening outcome. If a subject is re-screened with the approval of the medical advisor, the End of Study eCRF should be completed, and a new ICF, new SIC, and new eCRF are required for that subject.

The overall study design is illustrated in the [Figure 1](#). Details on the procedures to be done at each study visit, including screening, can be found in [Section 20.2](#).

10.3.1 Screening and Baseline Assessments

After informed consent has been obtained, subjects will be screened for eligibility based on the inclusion and exclusion criteria defined in [Section 9.1](#) and [Section 9.2](#), respectively. Screening procedures must be done within 28 days of the baseline visit (Visit 2; Week 0).

Screening assessments (Visit 1; Week -4 to baseline) include the following:

- Eligibility evaluation (review of inclusion/exclusion criteria)

- Relevant medical and surgical history and all medications according to the instructions below:
 - Medications/therapies for psoriasis: 8 weeks prior to screening
 - Non-psoriatic medications/therapies: 4 weeks prior to screening
 - All prior biologic medications/therapies (including investigational biologics)
- Review of concomitant medications/non-drug therapies
- TB screening
- sPGA, PASI, BSA evaluation
- Serology tests for HBV, HCV, and HIV-1/HIV-2
- Complete physical examination (see [Section 12.6](#))
- 12-lead ECG (see [Section 12.9](#))
- Vital signs (body temperature, pulse rate, blood pressure, respiratory rate, and measure body weight and height; see [Section 12.8](#))
- Clinical laboratory assessments (hematology and serum chemistry; see [Section 12.7.1](#))
- Urinalysis (see [Section 12.7.2](#))
- Serum pregnancy test (female subjects of childbearing potential only)

At the baseline visit (Visit 2; Week 0), subject eligibility will be confirmed and the following baseline assessments done:

- Patient-reported questionnaires: DLQI and EQ-5D-5L (to be completed prior to any other assessments being done; see [Section 11.2.4](#))
 - Eligibility evaluation reviewed (inclusion/exclusion criteria)
 - Review of concomitant medications/non-drug therapies
 - sPGA, PASI, BSA evaluation (see [Section 11.2.1](#) and [Section 11.2.2](#))
 - AE monitoring
 - Vital signs (body temperature, pulse rate, blood pressure, respiratory rate, and measure body weight)
 - Brief physical examination
-

- 12-lead ECG
- PK and immunogenicity
- Clinical laboratory assessments (hematology and serum chemistry)
- Urinalysis
- Urine pregnancy test (female subjects of childbearing potential only)

After all baseline assessments have been completed, subjects will be randomized and begin treatment with administration of their first dose of IP as below:

- Randomization of eligible subjects to the following treatment arms:
 - Arm A: M923 from Weeks 0 to 48
 - Arm B: EU RPP from Weeks 0 to 16
- Injection site training
- Study drug injection (as directed by study site staff) and evaluation of self-administration
- Post-injection monitoring at 30 minutes (\pm 10 minutes) after injection and there will be an observation period for a minimum of 2 hours post injection (see [Section 12.10](#))

10.3.2 Treatment Visits

During the double-blind treatment period (Weeks 1 to 48), subjects will return to study site according to the schedule presented in [Table 1](#).

Subjects will self-administer 40 mg of M923 or EU RPP every 2 weeks (Q2W) starting at Week 1 of the study.

Prior to administration of IP, the following assessments will be done at all visits unless otherwise indicated:

- Patient-reported questionnaires: DLQI and EQ-5D-5L (to be completed prior to any other assessments being done [Weeks 16, 25, and 37])
 - Review of concomitant medications/non-drug therapies
 - AE monitoring
 - sPGA, PASI, BSA evaluation
-

- Brief physical examination (Weeks 4, 8, 17, 19, 25, 27, 37, and 39; complete physical examination at Week 16)
- Vital signs (body temperature, pulse rate, blood pressure, respiratory rate, and measure body weight)
- 12-lead ECG (Weeks 16, 25, and 37)
- PK and immunogenicity (Weeks 8, 16, 17, 21, 25, 29, 37, and 41)
- Clinical laboratory assessments (hematology and serum chemistry; all visits, except Weeks 12, 27, 33, 39, and 45)
- Urinalysis (Weeks 4, 8, 16, 17, 19, 21, 25, and 37)
- Urine pregnancy test (female subjects of childbearing potential only; all visits, except Weeks 1, 19, 27, 39 and 45)
- Study drug dispensing
- Study drug injection in clinic by subject or caregiver (as directed by study site staff)(Weeks 1, 17, 19, 21, 25, 27, 37, and 39)
 - Post-injection monitoring for 2 hours post-injection (clinic only; Weeks 1, 17, 25, and 37)
 - Post-injection observation for 30 minutes post-injection (clinic only; Weeks 19, 21, 27, and 39)
- Study drug injection at home, but after assessments completed at clinic visit (Weeks 29, 33, 41, and 45)
- Study drug injection at home in-between clinic visits (Weeks 3, 5, 7, 9, 11, 13, 15, 23, 31, 35, 43, and 47)
- Injection site evaluation either by clinical staff (at clinic visits) or by the subject or caregiver (administration at home) per [Section 12.10](#)

At Week 16, subjects in Arm B will be randomly assigned again to a new treatment group:

- Arm B1: Continues EU RPP from Weeks 17 through 48 (last dose at Week 47; n = up to 129 subjects)
 - Arm B2: Transition to M923 at Week 17; then to EU RPP at Week 25; and to M923 at Week 37 (last dose at Week 47; n = up to 129 subjects)
-

10.3.3 Study Completion/Termination

At study completion (Week 48/end of treatment visit [ETV]), the following assessments will be done:

- Patient-reported questionnaires: DLQI and EQ-5D-5L (should be completed prior to any other assessments are done)
- Review of concomitant medications/non-drug therapies
- AE monitoring
- sPGA, PASI, BSA evaluation
- Complete physical examination
- Vital signs (body temperature, pulse rate, blood pressure, respiratory rate, and measure body weight)
- 12-lead ECG
- PK and immunogenicity
- Clinical laboratory assessments (hematology and serum chemistry)
- Urinalysis
- Urine pregnancy test (female subjects of childbearing potential only)
- Injection site evaluation
- Study drug return

10.3.4 Safety Follow-up

At the safety follow-up visit (Visit 20; Safety Follow-up, Week 52 \pm 2 weeks), the following assessments will be performed:

- Review of concomitant medications/non-drug therapies
 - AE monitoring
 - sPGA, PASI, BSA evaluation
 - Brief physical examination
 - Vital signs (body temperature, pulse rate, blood pressure, and respiratory rate and measure body weight)
 - PK and immunogenicity
-

- Clinical laboratory assessments (hematology and serum chemistry)
- Urinalysis
- Urine pregnancy test (female subjects of childbearing potential only)

The safety follow-up visit is done by subjects who completed the study treatment as per protocol requirements and those who have withdrawn from the study early.

If the subject does not show up to the clinical visit, the site should try contacting the subject by phone for at least 8 weeks after the scheduled follow-up visit and obtain information regarding the occurrence of adverse events, treatments for psoriasis as well as other concomitant medications and pregnancy status. In case the subject is a female of childbearing potential, at Week 48 a urine dipstick pregnancy test should be provided.

Information collected after Week 52 visit will be collected only as source data and not included in the eCRF.

At the safety follow-up visit the investigator should consider the next therapy to prescribe to the subject off-study, in order to maintain clinical benefit.

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 psoriasis therapies. Subjects may take allowed additional concomitant medication(s) as needed for medical management during this study. All medications taken 4 weeks prior to screening and concomitant medication use should be recorded in the appropriate eCRF. Exposure to all biologic medications at any time should be collected.

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

- Medications:
 - Systemic TNF inhibitor therapy, or B-cell depleting therapy, including other investigational biosimilar TNF inhibitors or B-cell depleting therapies, or 2 or more non-TNF biologic therapies
 - Other biologic immunomodulating therapies such as ustekinumab or other licensed or investigational biologics within 24 weeks prior to baseline (Visit 2) and during the duration of the study. Prior exposure to more than one such biologic immunomodulating therapy not permitted
-

- Systemic treatment with licensed or investigational immunosuppressive or targeted agents such as, but not limited to, cyclosporine, tacrolimus, MTX, azathioprine, 6-mercaptopurine, or hydroxyurea within 8 weeks prior to baseline (Visit 2) and during the duration of the study; excepting apremilast, tofacitinib within 4 weeks prior to baseline and during the duration of the study
- Systemic and topical retinoid or Vitamin D analog therapy within 4 weeks prior to baseline and during the duration of the study. Up to 1000 IU/day average dose of Vitamin D therapy is permitted if stable dose for 4 weeks prior to screening and during the duration of the study
- Topical calcineurin inhibitors, such as pimecrolimus, within 4 weeks prior to baseline and during the duration of the study
- Topical or systemic corticosteroids for treatment of psoriasis within 4 weeks prior to baseline and during the duration of the study. Topical steroids of weak potency (World Health Organization group VII) will be permitted for use during the study, but must not be used within 24 hours of study visits. Systemic corticosteroids used within the last year prior to screening for conditions other than psoriasis are not permitted
- Topical treatments containing acetylsalicylic acid, if used for psoriasis
- Topical tar derivatives within 2 weeks prior to baseline and during the course of the study
- Phototherapy and photochemotherapy within 4 weeks prior to baseline and during the course of the study. Subjects should be advised to avoid tanning booths and excessive sun exposure, eg, sun bathing
- Shampoos, moisturizers, and emollients that do not contain salicylic acid, tar, corticosteroids, and vitamin D analogs are allowed but must not be used in the 12 hours prior to study visits
- All other prior non-psoriasis concomitant treatments must be on a stable dose for at least 4 weeks prior to baseline
- Injectable anti-infective therapy within 30 days, or oral infective therapies within 14 days of baseline
- Live/attenuated vaccination within 6 weeks prior to baseline and during the duration of the study is not allowed

A subject who has taken any of these medications or received any of these non-drug therapies will be discontinued.

10.5 Subject Diary

A paper subject diary will be provided to each subject at each visit to record the following information, as applicable according to [Table 1](#):

1. Time, date, and location of IP administration; including whether the full dose was administered and, if not, why the full dose was not administered (eg, device malfunction)
2. IP administrator (self or caregiver)
3. AEs, including injection site reactions

Subjects and/or their legally authorized representatives will be trained on use of the diary. The diary will be provided in paper format and the subject should bring the completed diary to the site at each visit. The investigator will review the diary for completeness, request missing information periodically and in a timely manner, photocopy the applicable pages, store them in the source documents until such time when the original subject diary is collected. Untoward events recorded in the diary will be reported as AEs according to the investigator's discretion and clinical judgment.

During the treatment period, at Week 25, the subject diary may be collected and a new diary provided to the subject and retrieved at Week 48.

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

10.6 Subject Completion/Discontinuation

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 according with the protocol (with or without protocol deviations).

Reasons for completion/discontinuation will be reported on the Completion/Discontinuation eCRF, 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 deviation(s), recovery, study terminated by sponsor
- 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 eCRF.

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 done at the termination visit (including in cases of withdraw or discontinuation) can be found in [Table 1](#) and [Table 2](#).

After the discontinuation visit, if the subject agrees, a follow-up visit performing the same assessments as the Week 52 visit should be conducted 5 weeks after last IP dose.

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 done 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 or EU RPP.

Subjects receiving less than 18 doses (75% compliance) will be considered non-compliant

11. ASSESSMENT OF EFFICACY, IMMUNOGENICITY, AND PHARMACOKINETICS

11.1 Primary Efficacy Assessment

The primary efficacy outcome measure is the proportion of subjects treated with M923 vs EU RPP who achieve a 75% reduction in PASI from Week 0 (baseline) to Week 16 of the treatment period. Psoriasis will be assessed using the PASI, which is a measure of the average redness, thickness, and scaliness of the lesions (each graded on a 0 to 4 scale, weighed by the area of involvement. PASI score will be recorded by the investigator/site staff at clinic visits as shown in the schedule in [Table 1](#).

11.2 Secondary Efficacy Assessments

Secondary efficacy outcome measures consisting of response as measured by the sPGA, PASI scores over time, and health-related quality of life by the DLQI and the EQ-5D-5L will be evaluated in subjects treated with M923 vs EU RPP as detailed in [Section 11.2.1](#), [Section 11.2.2](#), and [Section 11.2.4](#).

11.2.1 Static Physician Global Assessment

The proportion of subjects with response by sPGA of clear or almost clear (6-point scale) at Week 16 in subjects treated with M923 vs EU RPP treatment will be assessed. In addition, the sPGA response rate of subjects treated with M923 vs EU RPP over time will be compared.

The sPGA will be evaluated by a qualified investigator at the site. The sPGA is the physician's determination of the subject's psoriasis lesions overall at a given time point. The sPGA is recommended as an endpoint to use to assess efficacy in the treatment of psoriasis.⁵ Overall lesions are categorized by descriptions for induration, erythema, and scaling. For the analysis of responses, the subject's psoriasis is assessed at a given time point on a 6 point scale in which 0 = cleared, 1 = minimal, 2 = mild, 3 = moderate, 4 = severe, 5 = very severe. The sPGA evaluations will be recorded on the eCRF by the investigator/site staff at clinic visits as shown in the schedule in [Table 1](#).

11.2.2 Psoriasis Area and Severity Index

A comparison of the proportion of subjects treated with M923 vs EU RPP who achieve 50%, 75%, and 90% reductions in psoriasis severity over time, as well as the response of subjects treated with M923 and EU RPP over time based on the absolute PASI score, will be assessed.

The PASI will be evaluated by a qualified investigator at the site. The PASI combines assessments of the extent of body-surface involvement in 4 anatomical regions (head [10% of BSA], arms [20% of BSA], trunk [30% of BSA], and legs [40% of BSA]) and the severity of desquamation (scaling), erythema (redness), and induration (thickness) in each region, yielding an overall score of 0 for no disease to 72 for the most severe disease.⁶ Each of the body areas is scored by itself, and then the four scores are combined into the final PASI. For each body area, the percent of area of skin involved is estimated and then transformed into a score from 0 to 6: 0 = 0% of involved area, 1 = < 10% of involved area, 2 = 10% to 29% of involved area, 3 = 30% to 49% of involved area, 4 = 50% to 69% of involved area, 5 = 70% to 89% of involved area, 6 = 90% to 100% of involved area. Severity parameters are measured on a five point scale in which 0 = None, 1 = Slight, 2 = Moderate, 3 = Severe, 4 = Very Severe. The sum of all 3 severity parameters is then calculated for each body area, multiplied by the area score for that area and multiplied by weight of respective section (0.1 for head, 0.2 for arms, 0.3 for trunk and 0.4 for legs). Subjects achieving PASI 50, 75, 90, or 100 are defined as having an improvement of at least 50%, 75%, 90%, or 100%, respectively, in the PASI compared with baseline. Information required to calculate the PASI will be recorded on the eCRF by the investigator/site staff at clinic visits as shown in the schedule in [Table 1](#).

11.2.3 Body Surface Area

The investigator will evaluate the percentage involvement of psoriasis on each subject's BSA on a continuous scale from 0% = no involvement to 100% = full involvement, where 1% corresponds to the size of the subject's handprint including the palm, fingers, and thumb.⁷

11.2.4 Patient-reported Outcomes – Dermatology Life Quality Index (DLQI) and EuroQoL 5-Dimension Health Status Questionnaire

Health-related quality of life during treatment with M923 and EU RPP will be evaluated by the DLQI and the EQ-5D-5L questionnaires. The assessments will be recorded on the eCRF by the investigator/site staff at clinic visits as shown in the schedule in [Table 1](#).

11.3 Pharmacokinetics Assessments

Blood samples for analysis of serum M923 or EU RPP in terms of serum levels will be collected at the times shown in the schedule in [Table 1](#). Samples should be obtained prior to administering study drug if an administration occurs at that visit and before any hematology/chemistry samples to be drawn at that visit. Samples will be collected and aliquotted into primary and back-up specimens. Back-up specimens should be stored at -20 °C or -70 °C until shipment. Blood sample processing and handling details will be presented in a separate laboratory manual.

Bioanalysis

Samples for determination of M923 or EU RPP concentrations in serum will be analyzed by Quintiles BioSciences, on behalf of Baxalta US Inc., using appropriate bioanalytical methods, which will be described in a separate bioanalytical report. All samples still within the known stability of the analytes of interest (ie, M923 or EU RPP) at time of receipt by the bioanalytical laboratory will be analyzed.

11.4 Immunogenicity Assessments

Blood samples for analysis of and ADA levels to M923 and EU RPP will be collected at the times shown in the schedule in [Table 1](#). ADA analysis will be conducted using a screening assay based on M923 to identify potentially positive ADA samples.

Subsequently, confirmatory assays based on EU RPP and M923 will be used to confirm the positive status of 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 and an iso-typing assay will be done. 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.

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.), disease (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.

12.1.1.1 Serious Adverse Events

A SAE is defined as an untoward medical occurrence that at any dose meets 1 or more of the following criteria:

- Outcome is fatal/results in death
 - 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
 - Requires inpatient hospitalization or results in prolongation of an existing hospitalization – inpatient hospitalization refers to any inpatient admission, regardless of length of stay
 - Hospitalizations occurring during the study and planned before subject randomization will not be considered SAEs and should be clearly stated in the subject's medical history
 - Results in persistent or significant disability/incapacity (ie, a substantial disruption of a person's ability to conduct normal life functions)
 - Is a congenital anomaly/birth defect
 - 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 1 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, hepatitis A virus, HBV, HCV, hepatitis E virus, or parvovirus B19
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12.1.1.2 Non-Serious Adverse Events

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

12.1.1.3 Unexpected Adverse Events

An unexpected AE is an AE whose nature, severity, specificity, or outcome is not consistent with the term, representation, or description used in the Reference Safety Information (eg, IB, package insert). “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 drug, but are not specifically mentioned as occurring with the particular drug under investigation.

For the purposes of this study, each unexpected AE reported by a subject undergoing study treatment or a study-related procedure will be recorded on the AE eCRF.

12.1.1.4 Preexisting Diseases

Preexisting 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 preexisting disease, the event must be described on the AE eCRF.

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 or EU RPP treatment will be recorded on the AE eCRF; however, these events will not be considered as AEs and will not be included in the analysis of AEs.

Each treatment-emergent AE (non-serious AE or SAE) from the first M923 or EU RPP treatment until study completion/discontinuation (Week 48) or 4 weeks following the last M923 or EU RPP treatment (for early termination subjects) will be described on the AE eCRF 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:

- Seriousness as defined in [Section 12.1.1.1](#)
 - Severity as defined in [Section 12.1.2.1](#)
-

- Causal relationship to IP exposure or study procedure 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 withdrawn, not applicable, or unknown) will also be recorded on the AE eCRF. Recovering/resolving AEs will be followed until resolution, medically stabilized, or 30 days 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.

Deviations from the protocol-specified dosage (including overdosing [any dose that is at least 20% higher than the highest explored dose level], underdosing [any dose that is lower than the intended explored dose level by 10%], abuse, and withdrawal [see [Section 9.3](#)]), 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 or EU RPP will be reported on a Pregnancy Form and followed-up at 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 SAE Form **within 24 hours after awareness**; no additional reporting on eCRFs is necessary.

A post-trial SAE report (SAER) form in paper will be used to report SAEs after a subject's completion.

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:

- 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
- Moderate
 - The AE produces limited impairment of function and may require therapeutic intervention
 - The AE produces no sequela/sequelae
- 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, dechallenge/rechallenge 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:

- Not related (both circumstances must be met)
 - Is due to underlying or concurrent illness, complications, concurrent treatments, or effects of concurrent drugs
 - Is not associated with the IP (ie, does not follow a reasonable temporal relationship to the administration of IP or has a much more likely alternative etiology)
 - Unlikely related (either 1 or both circumstances are met)
 - Has little or no temporal relationship to the IP
 - A more likely alternative etiology exists
 - Possibly related (both circumstances must be met)
 - Follows a reasonable temporal relationship to the administration of IP
-

- An alternative etiology is equally or less likely compared with the potential relationship to the IP
- Probably 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 (positive rechallenge)
 - 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 after IP administration, 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.

12.2 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 trial from immediate harm. Urgent safety measures may be taken by the sponsor or clinical investigator, and may include any of the following:

- Immediate change in study design or study procedures
- Temporary or permanent halt of a given clinical trial or trials
- Any other immediate action taken in order to protect clinical trial 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 is notified of the urgent measures taken in such cases according to local regulations.

12.3 Untoward Medical Occurrences

Untoward medical occurrences occurring before the first exposure to M923 or EU RPP are not considered AEs (according to the definition of AE, see [Section 12.1](#)). However, each **serious** untoward medical occurrence reported before the first M923 or EU RPP treatment (ie, from the time of signed informed consent up to but not including the first M923 or EU RPP treatment) will be described on the SAE Report.

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**. NMCs include but are not limited to the following:

- A failure of a product to exhibit its expected pharmacological activity and/or design function, eg reconstitution difficulty
- Missing components
- Damage to the product or unit carton
- A mislabeled product (eg, potential counterfeiting/tampering)
- 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 for 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, 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, throat, chest/respiratory, heart/cardiovascular, gastrointestinal/liver, gynecological/urogenital, musculoskeletal/extremities, skin, neurological/psychiatric, endocrine/metabolic, hematologic/lymphatic, allergies/drug sensitivities, past surgeries, substance abuse or any other diseases or disorders.

Subjects' history of TB will be reviewed at screening; subjects with a negative history will proceed to QuantiFERON-TB Gold testing, T-SPOT, or PPD, and a radiograph or comparable imaging with negative finding for TB or other similar infections (PA, or PA and lateral view).

Subjects will be assessed for a history of or current diagnosis of active TB, or untreated latent TB infection (LTBI). Subjects may present documentation of results (PPD, T-SPOT, or QuantiFERON and radiograph or comparable imaging test) completed within 3 months of the screening visit. If these results are unavailable, one of the following will be done at the screening visit: PPD (onsite), QuantiFERON (central lab), or T-SPOT (ELISPOT) test (onsite). History of or current diagnosis of active TB, or untreated latent TB infection (LTBI), is defined as a TB skin test with PPD as evidenced by induration ≥ 5 mm; a positive QuantiFERON; or positive or borderline T-SPOT (ELISPOT).

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, and will be eligible for the study (minimum treatment period with a recognized and regionally appropriate regimen of 4-6 weeks prior to start of IP).

Clinically significant radiograph report per investigator opinion or evidence of active TB on radiograph will be documented. Radiograph must have been done within 3 months prior to the screening visit or during the screening period.

All medications taken and non-drug therapies received from enrollment until completion/termination will be recorded on the concomitant medications and non-drug therapies eCRFs.

12.6 Physical Examinations

At screening and subsequent study visits (as described in [Table 1](#)), a physical examination will be done on 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. Details regarding the procedures and tests to be conducted at the complete and brief physical exams are provided in the Schedule of Study Procedures and Assessments ([Table 1](#)). At screening, if an abnormal condition is detected, the condition will be described on the medical history eCRF. At study visits, if a new abnormal or worsened abnormal pre-existing condition is detected, the condition will be described on the AE eCRF. If the abnormal value was not deemed an AE because it was due to an error, due to a preexisting disease (described in [Section 12.1.1.4](#)), 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

12.7.1 Hematology and Clinical Chemistry

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

The clinical chemistry panel will consist of sodium, potassium, chloride, bicarbonate, protein, albumin, ALT, AST, GGT, CPK, bilirubin, lactate dehydrogenase, C-reactive protein, cholesterol, triglycerides, calcium, phosphate, uric acid, alkaline phosphatase, blood urea nitrogen, creatinine, and glucose.

Blood will be obtained for assessment of hematology and clinical chemistry parameters according to the schedule detailed in [Table 1](#). A list of parameters to be assessed is included in [Table 2](#).

Hematology and clinical chemistry assessments will be done on EDTA-anticoagulated whole blood and serum, respectively, at the central laboratory.

In addition, serum samples for pregnancy tests for females of childbearing potential will be done.

12.7.2 Urinalysis

Urine will be collected according to the schedule detailed in [Table 1](#). A list of parameters to be assessed is included in [Table 2](#).

12.7.3 Assessment of Laboratory Values

12.7.3.1 Assessment of Abnormal Laboratory Values

The investigator will assess each laboratory value. 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 eCRF), is a symptom or related to a previously recorded AE, is due to a pre-existing disease (described in [Section 12.1.1.4](#)), 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 preexisting disease, due to a laboratory error, due to variation within the healthy population, 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.

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; screening visit only) and weight (lb or kg) will also be collected.

Vital signs will be measured at screening and prior to administration of M923 or EU RPP, at each study visit, and at study completion/termination. Blood pressure will be measured when subjects are in the supine position and after resting for at least 5 minutes.

Vital sign values are to be recorded on the eCRF. 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 eCRF).

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 is done at study visits according to the schedule described in [Table 1](#). The following parameters will be recorded in the eCRF: ventricular rate, PR interval, QRS duration, QT, and QT interval corrected for heart rate using Fridericia's equation (QTcF). QTcF will be calculated as follows: $QTcF = QT / (3\sqrt{RR})$.

ECGs done at regular study visits will be interpreted locally.

12.10 Injection Site Evaluations

The current and prior site of SC injection of the study drug to the lower abdomen or thigh will be assessed for immediate local reactions 30 minutes (\pm 10 minutes) after injection. In addition, there will be an observation period for a minimum of 2 hours post injection after administration of M923 or EU RPP onsite at Weeks 0, 1, 17, 25, and 37. For injections given at home, injection site reactions will be recorded in the subject diary as described in [Section 10.5](#).

Injection site evaluations will be made by clinical staff or by the subject or caregiver, 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 1](#), 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 3](#); 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 judgment, based on the AE grading schemes presented in [Section 12.1.2.1](#)).

13. STATISTICS

13.1 Sample Size and Power Calculations

13.1.1 Sample Size Calculation

Primary analysis: Test equivalence of M923 compared with EU RPP using the PASI75 response rate at 16 weeks. CCI [REDACTED]

[REDACTED] A total of 516 subjects will be randomized (258 in Arm A and 258 in Arm B)

CCI [REDACTED]

Response Rate Justification:

Adalimumab response rates were 71.0% (n = 578/814) and 79.6% (n = 86/108) in 2 previous pivotal psoriasis studies. Based on a meta-analysis, the estimated treatment effect was 63.6% (95% confidence interval of 59.8% - 67.4%), which was used as the basis for sample size calculation.

Equivalence Margin Justification:

The treatment effect versus placebo, based on PASI75 at 16 weeks from a Phase 1 study (REVEAL¹), was estimated to be 0.647 (lower bound of 2-sided 95% confidence interval 0.460).

The treatment effect versus placebo, based on PASI75 at 16 weeks from the other pivotal Phase 3 study (CHAMPION²), was estimated to be 0.64 (lower bound of 2-sided 95% confidence interval 0.597).

Margin for USA:

An 18% equivalence margin was selected based on observed variation in response rates in adalimumab's Phase 2³ vs Phase 3 studies at 12 weeks, and on the statistical (M1) margins in the Phase 3 studies at 16 weeks. Based on the meta-analysis of the REVEAL and CHAMPION studies, the 95% confidence bound for the difference in proportions of PASI75 is 0.5975 to 0.6744. The acceptable margins (M1) statistically from the Phase 3 studies were 0.298 at 16 weeks. The proposed margin of 18% preserves 70% of the treatment effect, and is well within both the inter-trial variation in response rates and the M1 from Phase 3 and comprises a conservative margin for assessment of equivalence.

Margin for EU:

An 15% equivalence margin was selected based on observed variation in response rates in adalimumab's Phase 2³ vs Phase 3 studies at 12 weeks, and on the statistical (M1) margins in the Phase 3 studies at 16 weeks. Based on the meta-analysis of the REVEAL¹ and CHAMPION² studies, the 95% confidence bound for the difference in proportions of PASI75 is 0.5975 to 0.6744. The acceptable margins (M1) statistically from the Phase 3 studies were 0.298 at 16 weeks. The proposed margin of 15% preserves 75% of the treatment effect, and is well within both the inter-trial variation in response rates and the M1 from Phase 3 and comprises a conservative margin for assessment of equivalence.

13.2 Populations and Analysis Cohorts**Intent-to-treat (ITT):**

The ITT population will include all consenting subjects randomized to study treatment (Arm A or Arm B). Subjects will be assigned to treatment groups based on randomization.

Per-Protocol (PP):

The PP population is a subgroup of the ITT population which will include all subjects who do not have any major protocol deviations and received at least 1 dose of study medication.

Major protocol deviations will include, but are not limited to: deviation of inclusion/exclusion criteria, administration of prohibited medications and erroneous administration of study treatment. The criteria for grading protocol deviations will be established by the Quintiles Therapeutic Medical Advisor. Major protocol deviations will be determined on a case-by-case basis by the medical reviewer prior to database lock and unblinding. Subjects will be assigned to treatment groups based on randomization.

Safety:

The safety population will include all subjects who received at least 1 dose of study medication (M923 or EU RPP). Subjects will be assigned to treatment groups based on what they actually received.

Pharmacokinetics (PK):

The PK population will include all subjects who received at least 1 dose of study medication (M923 or EU RPP) and have at least 1 measured concentration at a scheduled PK time point after start of dosing. If any subjects are found to be noncompliant with respect to dosing or have incomplete data, a decision will be made on a case-by-case basis as to their inclusion in the analysis.

13.3 Handling of Missing, Unused, and Spurious Data

Non-Responder Imputation (NRI) for Clinical Response: Subjects will be considered as non-responders for the NRI analysis if they do not meet the clinical response criteria for categorical responses (PASI50, PASI75, PASI90, sPGA) at a time point of interest (Week 16). All non-responders at Week 16, as well as all subjects who discontinue study treatment prior to Week 16 for any reason, will be defined as non-responders for the NRI analysis for all categorical PASI and sPGA analyses at the time point of interest.

Modified Baseline Observation Carried Forward (mBOCF): The continuous efficacy and health outcome variables will be based on a modified baseline observation carried forward (mBOCF) approach. For subjects who discontinue the study treatment due to AE, the baseline observation will be carried forward to the corresponding time point for evaluation. For subjects who discontinued the study treatment due to any other reason, the last non-missing observation before discontinuation will be carried forward to the corresponding time point for evaluation. Randomized subjects without at least 1 post-baseline observation will not be included for evaluation with the exception of subjects who discontinued the study treatment due to AE.

Mixed Models for Repeated Measures (MMRM): As a supportive analysis, continuous endpoints will be imputed based on mixed-effects model repeated measures (MMRM) for the ITT population⁸. Categorical endpoints derived from continuous measures will be derived from the imputed continuous measure.

13.4 Methods of Analysis

In general, all efficacy, safety, PK, and immunogenicity variables will be summarized using descriptive statistics. Continuous variables will be summarized by sample size, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized in frequency tables (n, frequencies, and percentages). Individual subject data will be presented in listings.

The study consists of a treatment period of 48 weeks and subsequent safety follow up. The analysis of primary outcome will use data from the first 16 weeks.

The default significant level will be (5%); confidence intervals will be 95% and all tests will be 2-sided, unless otherwise specified in the description of the analyses. Details of the statistical analysis will be specified in the Statistical Analysis Plan (SAP), which will be finalized prior to treatment assignment unblinding. The SAP will contain the details of the missing data modeling, including model specification, the analysis of the secondary and pharmacokinetic endpoints, and the presentation of safety data.

13.4.1 Disposition and Withdrawals

All subjects who provided informed consent will be accounted for in this study. Subject disposition and withdrawals, and protocol deviations (including inclusion and exclusion criteria) will be presented for the ITT population.

13.4.2 Demographic and other Baseline Characteristics

Demographic data and other baseline characteristics will be described for the ITT and PP populations overall and by treatment arm. No statistical testing will be carried out for demographic or other baseline characteristics.

13.4.3 Primary Outcome Measure

The methods of analysis for the primary outcome measure (see [Section 8.4](#)) will be done on the PP population.

The PASI75 response rate will be described at Week 16 for subjects on M923 (Arm A) vs EU RPP (Arm B). The NRI method (see [Section 13.3](#)) will be used to handle missing data.

For the FDA, all equivalence comparisons will be made using 90% confidence intervals and an equivalence margin of 18%. For the EMA, all equivalence comparisons will be made using 95% confidence intervals and an equivalence margin of 15%.

A confidence interval for differences between M923 and EU RPP will be calculated using the Newcombe confidence interval.^{9,10} The null hypothesis of differences in PASI75 proportions of at least 15% for EMA and 18% for FDA will be rejected if the 95% confidence interval for EMA and 90% confidence interval for FDA for the difference in PASI75 is wholly contained within the equivalence region; in this case, equivalence will be declared.

The primary analysis will be repeated on the ITT population as a sensitivity analysis using the NRI, mBOCF, and MMRM methods of imputation. The MMRM model will include baseline, treatment group (A, B1, or B2), region (North America, Western Europe, or Eastern Europe), and the treatment-by-visit interaction. An unstructured variance-covariance matrix will be estimated. If the procedure fails to converge then the treatment-by-visit term will be removed from the model. If the model still fails to converge, a heterogeneous Toeplitz structure will be used for the variance-covariance matrix. The Kenward-Roger method will be used for estimating degrees of freedom.¹¹

13.4.4 Secondary Outcome Measures

13.4.4.1 Efficacy

The methods of analysis for the secondary efficacy outcome measures (see [Section 8.4.2.1](#)) will be done on the PP population and repeated on the ITT population.

The sPGA response rate will be described at Week 16 for subjects on M923 (Arm A) vs EU RPP (Arm B).

The NRI method (see [Section 13.3](#)) will be used to handle missing data. A 95% confidence interval for differences between M923 and EU RPP will be calculated using the stratified Newcombe confidence interval.

The treatment arms (Arm A and Arms B1 and B2) will be compared using descriptive statistics for PASI50, PASI75, PASI90, and sPGA response rates over time. The NRI method (see [Section 13.3](#)) will be used to handle missing data.

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13.4.4.2 Safety

The methods of analysis for the secondary safety outcome measures (see [Section 8.4.2.2](#)) will be done on the safety population.

AEs will be coded using Medical Dictionary for Regulatory Activities dictionary.

Treatment-emergent adverse events (TEAEs) are defined as AEs that started or worsened in severity on or after the first dose of study medication.

All TEAEs (including SAEs, AEs related to study drug, AEs leading to discontinuation, and injection site reactions) will be summarized by System Organ Class and Preferred Term and by treatment arm (Arm A and Arms B1 and B2). All AEs will be included in the listings (non-TEAEs and TEAEs).

The clinical safety and tolerability of the transition from EU RPP to M923 as compared with continuous use of EU RPP with regard to AEs will be evaluated with a summary of all TEAEs by treatment arm and by treatment period:

- Period 1 from Week 0 to Week 16 (included)
- Period 2 from Week 16 to Week 25 (included)
- Period 3 from Week 25 to Week 37 (included)
- Period 4 from Week 37 to Week 48 (included)
- Follow-up

Physical examination, vital signs, laboratory parameters, and ECGs will be presented by treatment group for each visit. Descriptive statistics of value and change from baseline will be provided for vital signs and laboratory parameters.

The clinical safety and tolerability of the transition from EU RPP to M923 as compared with continuous use of EU RPP with regard to all safety endpoints will be evaluated using the descriptive statistics provided over time.

13.4.4.3 Pharmacokinetics and Immunogenicity

The methods of analysis for the secondary PK outcome measures (see [Section 8.4.2.3](#)) will be done on the PK population.

The serum levels will be summarized by treatment arm at each scheduled collection. In addition to descriptive statistics described in [Section 13.4](#), the geometric mean, corresponding 95% confidence interval, and the geometric coefficient of variation (CV) will also be presented. To evaluate whether of anti-adalimumab antibody formation will affect exposure, the summaries will be further stratified by ADA formation (subjects who did not form antibodies, subjects who formed ADAs, versus subjects who formed neutralizing ADAs). The within-subject variability (CV) in trough concentrations over time (from Week 17 to Week 41) will be determined for each subject, which will then be compared between treatment arms using an analysis of variance model with treatment as a fixed effect.

The transition from EU RPP to M923 as compared with continuous use of EU RPP with regard to PK will be evaluated using the descriptive statistics at each schedule time point and statistical comparison of within-subject variability.

Pharmacokinetic data from the study may also be used for population PK/pharmacodynamic analyses. If done, a separate analysis plan will be prepared and results will be reported separately from the Clinical Study Report. Population PK/PD analyses are not planned following the administrative interim database lock at Week 25.

The immunogenicity analysis will be done on the safety population.

Immunogenicity data (overall ADA results and titers, and neutralizing ADA results and isotype of ADA where applicable, and time to seroconversion) will be listed. A summary of the number and percent of subjects testing positive for ADA or neutralizing antibodies before the dose of M923 or EU RPP and at scheduled postdose assessments will be presented by treatment arm. The time to seroconversion will be summarized by treatment arm using mean, median, standard deviation and range where appropriate.

The number and percentage of subjects who had at least one ADA-positive result will be provided by treatment arm. Similar analysis may be done for subjects with predose ADA-negative results and with at least one postdose ADA-positive results as appropriate.

The immunogenicity following the transition from EU RPP to M923 as compared with continuous use of EU RPP will be evaluated with the number and percentage of subjects who had at least once ADA-positive by treatment arm and by treatment period (as defined in the [Section 13.4.4.2](#)).

13.5 Planned Interim Analysis of the Study

An administrative interim database lock will occur at Week 25 to perform the primary analysis on the first 516 randomized subjects. The purpose of the interim database lock is to provide an analysis of the primary endpoint, safety, PK and immunogenicity up through Week 25 to regulatory agencies before the completion of the study. No trial-related decisions will be made based on the interim analysis. Since no trial-related decisions will be made based on this analysis, the Type I error rate is preserved and no multiplicity adjustment is needed. An interim clinical study report from the interim analysis week 25 (primary endpoint) will be to support regulatory submissions.

The interim analysis will be executed by an unblinded team distinct from the study team. The study team will remain blinded until final database lock. Data to be locked will include efficacy and safety up through Week 25 on the first 516 randomized subjects. The details of the interim analysis, including methodology to maintain the blind of the study team, will be discussed in a separate interim analysis plan.

The final analysis will include the total number of subjects (n=572) and a final clinical study report will be produced accordingly.

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 Study Agreement. 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 Clinical Study Agreement.

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 regulatory requirements as described in the Clinical Study Agreement. 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 regulatory guidelines/requirements. The investigator will permit the study monitor to visit the study site at appropriate intervals, as described in the Clinical Study Agreement. 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 regulatory guidelines/requirements.

The investigator will permit auditors to visit the study site, as described in the Clinical Study Agreement. 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 ethics committee 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 Clinical Study Agreement.

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 Clinical Study Agreement.

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 subjects and/or their legally authorized representative must sign an ICF before entering into the study according to applicable 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 regulatory requirements. Subjects or their legally authorized representative(s) will be allowed sufficient time to consider participation in the study. By signing the ICF, subjects or their legally authorized representative(s) 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 has 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.

16.4 Data Monitoring Committee

A Data Monitoring Committee is not used for this study for the following reason:

Subjects are on IP which is the same dose as a product that is already licensed.

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 Clinical Study Agreement.

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 8.8](#)), 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, eCRFs, SAE reports, 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 done 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 eCRFs. The eCRFs will be provided in electronic form.

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 Clinical Study Agreement.

18. FINANCING AND INSURANCE

The investigator will comply with investigator financing, investigator/sponsor insurance, and subject compensation policies, if applicable, as described in the Clinical Study Agreement.

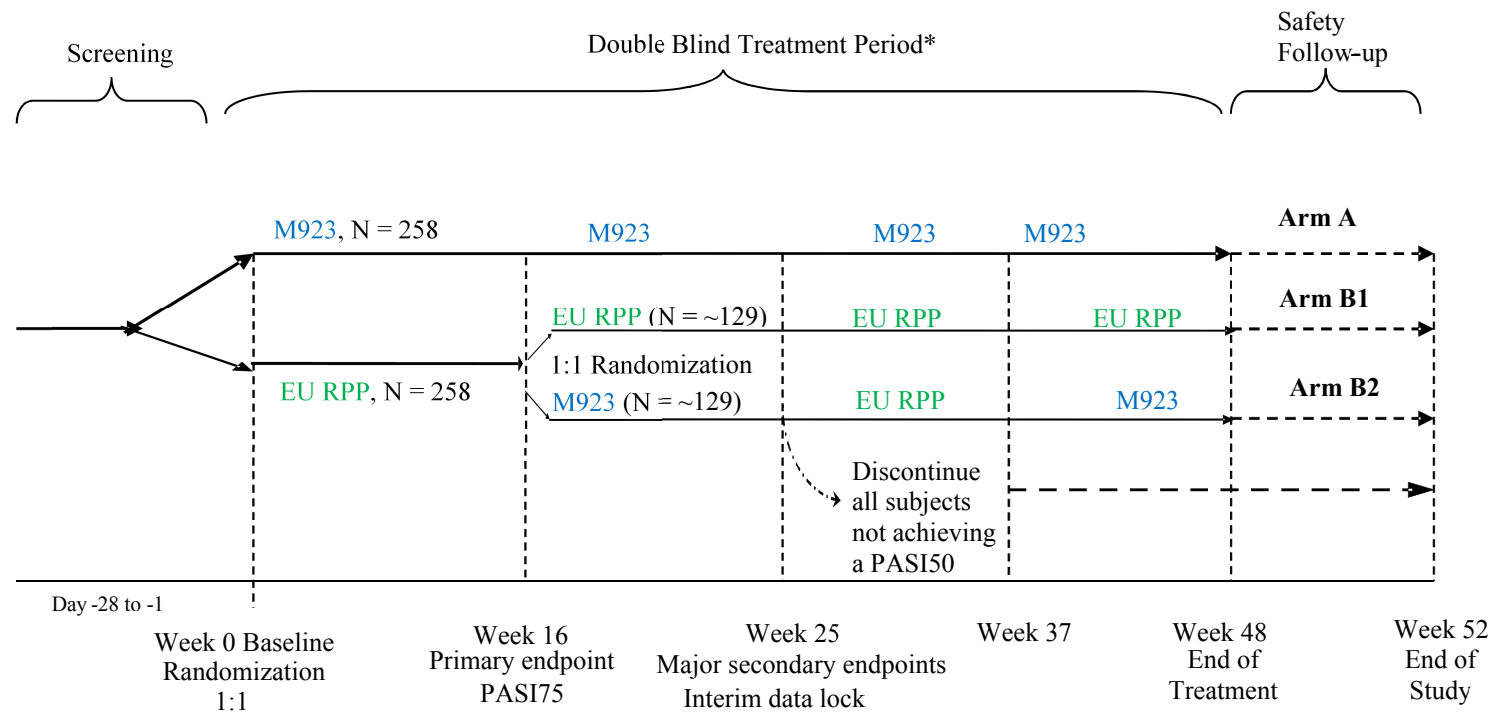
19. PUBLICATION POLICY

The investigator will comply with the publication policy as described in the Clinical Study Agreement.

20. SUPPLEMENTS

20.1 Study 911401 Schematic

Figure 1
Study Design for Baxalta Clinical Study 911401



*Injections administered subcutaneously at Weeks 0 and 1, and then every 2 weeks in each arm. Last dose at Week 47.

Subjects in Arm B are randomized again 1:1 at Week 16 into Arms B1 and B2.

D = Day; EU RPP = Reference Protein Product; N = number of subjects; PASI = Psoriasis Area and Severity Index.

Phase	Screen -ing	Double-Blind Period																		Safety Follow-up ^s
Week	-4 to 0	0	1	4	8	12	16	17	19	21	25	27	29	33	37	39	41	45	48/ ETV	52
Study Day	-28 to -1	1	8	29	57	85	113	120	134	148	176	190	204	232	260	274	288	316	337	365
Visit ^r	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Informed consent	X																			
Medical history and prior medications (including prior therapy, psoriasis, and surgeries)	X																			
Inclusion/exclusion criteria	X	X ^a																		
Concomitant therapy ^b	<div><-----></div>																			
Randomization		X					X ^c													
Tuberculosis screening	X ^d																			
sPGA, PASI, BSA ^e	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
DLQI and EQ-5D-5L ^f		X					X				X				X				X	
HIV, Hepatitis B and C viral testing	X																			
Adverse event monitoring	<div><-----></div>																			
Physical exam	X ^g	X		X	X		X ^g	X	X		X	X			X	X			X ^g	X
12-lead ECG ^h	X	X					X				X				X				X	
Vital signs ⁱ	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PK and immunogenicity ^j		X			X		X	X		X	X		X		X		X		X	X
Hematology, chemistry ^k	X	X	X	X	X		X	X	X	X	X		X		X		X		X	X
Urinalysis	X	X		X	X		X	X	X	X	X				X				X	X
Pregnancy test ^l	X	X		X	X	X	X	X		X	X		X	X	X		X		X	X

Table 1
Schedule of Study Procedures and Assessments

Phase	Screen-ing	Double-Blind Period																		Safety Follow-up ^s
Week	-4 to 0	0	1	4	8	12	16	17	19	21	25	27	29	33	37	39	41	45	48/ETV	52
Study Day	-28 to -1	1	8	29	57	85	113	120	134	148	176	190	204	232	260	274	288	316	337	365
Visit ^r	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Injection training ^m		X																		
Study drug injection onsite ⁿ		X	X					X	X	X	X	X			X	X				
Post-injection monitoring onsite ^o		X	X					X	X	X	X	X			X	X				
Injection site evaluation ^p		X	X					X	X	X	X	X	X	X	X	X	X	X	X	
Study drug dispensing			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Study drug return																			X	
Study diary dispensing/collection ^q		X									X								X	

AE = adverse event; BSA = body surface area; DLQI = Dermatology Life Quality Index; ECG = electrocardiogram; ETV = end of treatment visit; HIV = human immunodeficiency virus; EQ-5D-5L = EuroQoL-5 dimensions- 5 levels; PA: posterior-anterior, PASI = Psoriasis Area and Severity Index; PK = pharmacokinetics; PPD = purified protein derivative; sPGA = static Physician Global Assessment; TB = tuberculosis

^a Inclusion/exclusion criteria to be reviewed before randomization. The screening visit needs to occur with enough time prior to randomization to ensure eligibility requirements for the screening visit are met.

^b Concomitant therapy will include pharmacologic and nonpharmacologic therapies.

^c Subjects in Arm B are randomized again at this visit.

^d Subjects will receive testing if not received within previous 3 months and/or doesn't have documented history of prior positive TB test result or active TB infection. Testing includes QuantiFERON, T-SPOT, or PPD and a radiograph or comparable imaging with negative finding for TB or other similar infections (PA or PA and lateral view).

^e sPGA, PASI and BSA assessments should be conducted at screening and at baseline before randomization and study drug administration to ensure eligibility.

^f All subject-completed assessments (ie, patient-reported outcomes) should be completed before any other assessments are done.

^g Complete physical exam will be conducted at screening, Week 16, and 48. All other physical exams will be brief and should include heart, lungs, abdomen and extremities and skin, and any other assessments required to evaluate AEs.

^h ECG should be recorded before blood sampling.

ⁱ Vital signs should be taken before blood sampling. Height will be measured at Visit 1 only.

Table 1
Schedule of Study Procedures and Assessments

Phase	Screen-ing	Double-Blind Period																		Safety Follow-up ^s
Week	-4 to 0	0	1	4	8	12	16	17	19	21	25	27	29	33	37	39	41	45	48/ETV	52
Study Day	-28 to -1	1	8	29	57	85	113	120	134	148	176	190	204	232	260	274	288	316	337	365
Visit ^r	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20

^j PK and immunogenicity blood samples are to be collected in all subjects at these time points. Samples should be obtained prior to administering study drug if an administration occurs at that visit and before any hematology/chemistry samples to be drawn at that visit.

^k Blood samples will be taken before injection of study drug, 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. Serum test will be done at screening; all other assessments are done on urine.

^m Self-injection training should be provided with the first injection, with subject or caregiver performing the second injection at the first visit. Additional training can be provided with the Week 1 injection, if needed. At all other visits where the injection occurs in clinic, the subject or caregiver should administer the injection and be observed to ensure correct administration.

ⁿ Study drug will be administered in clinic after all required assessments and blood sample collections have been completed at Weeks 0, 1, 17, 19, 21, 25, 27, 37, and 39. Injections will occur at home in-between clinic visits on Weeks 3, 5, 7, 9, 11, 13, 15, 23, 31, 35, 43 and 47. At Weeks 29, 33, 41, and 45, the study drug injections will be completed at home after the assessments are completed at the clinic.

^o When injection occurs in the clinic, subjects should be observed for a minimum of 2 hours in the clinic after injection at Weeks 0, 1, 17, 25, and 37. Subjects should be observed for 30 minutes after injection at Weeks 19, 21, 27, and 39. At Week 48, only return of study drug will occur.

^p The investigator or a qualified designee will evaluate the current injection sites 30 minutes (\pm 10 minutes) after study drug administration in the clinic at Weeks 0, 1, 17, 19, 21, 25, 27, 37, and 39. They should also evaluate any immediately prior injection site at each subsequent visit as applicable. For injections given at home, injection site reactions will be recorded in the subject diary. There will be no injection at Week 48 (Visit 19), but injection site evaluation for previous injections will occur.

^q The subject should bring the diary at all visits between Weeks 1 and 48. The investigator will review the diary for completeness, request missing information periodically and in a timely manner, photocopy and store the applicable pages in the source documents until the original diary is collected. At Week 25, the subject diary will be collected by the investigator and a new one will be provided until Week 48.

^r Visit windows are \pm 1 day at Visit 3, \pm 3 days for Visits 4-19 and \pm 2 weeks for Visit 20. Reference for visit windows/study day is scheduling based on Visit 2/Baseline Visit.

^s If the subject does not show up to the clinical visit, the site should try to contact the subject by phone for at least 8 weeks after the scheduled follow-up visit and obtain information regarding the occurrence of adverse events, psoriatic and concomitant treatments and pregnancy status. Discontinuing subjects will be invited to perform this visit 5 weeks after last IP dose.

Table 2
Laboratory Parameters

Panel		Parameters
Hematology	Red blood cell count	Neutrophils (absolute and %)
	Hemoglobin	Lymphocytes (absolute and %)
	Hematocrit	Monocytes (absolute and %)
	Platelet count	Eosinophils (absolute and %)
	Mean cell volume	Basophils (absolute and %)
	White blood cell count (total leucocytes)	
Serum biochemistry	Aspartate transaminase	Sodium
	Alanine transaminase	Potassium
	Alkaline phosphatase	Chloride
	Gamma glutamyl transferase	Bicarbonate
	Total bilirubin	Urea
	Lactate dehydrogenase	Creatinine
	Creatine kinase	Albumin
	C-reactive protein	Calcium
	Cholesterol	Phosphate
	Triglycerides	Glucose
	Total protein	Uric acid
Urinalysis	Leucocytes	Ketones
	Protein	Blood
	Bilirubin	pH
	Urobilinogen	Nitrite
	Glucose	Specific gravity
Urine microscopy		To be done where clinically indicated
Viral serology	Hepatitis B surface antigen, anti-Hepatitis B surface antigen and anti-Hepatitis B core total (IgG and IgM)	Hepatitis C antibody
		Human immunodeficiency virus (HIV I and II)
Tuberculosis (TB)	QuantiFERON®-TB Gold test	T-SPOT
Serum/urine pregnancy test	Beta human chorionic gonadotropin	Follicle-stimulating hormone

IgG = immunoglobulin G; IgM = immunoglobulin M.

Table 3
Injection Site Reaction Grading Scheme

Reaction	Intensity Grading				
	Absent (0)	Mild ^a (1)	Moderate ^a (2)	Severe ^a (3)	Potentially Life-threatening (4)
Pain	Absent	Does not interfere with activity	Repeated use of non-narcotic pain reliever >24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Hospital visit (A and E) or hospitalization
Tenderness	Absent	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	A and E visit or hospitalization
Erythema/ redness	Absent	2.5 to 5.0 cm	5.1 to 10.0 cm	>10.0 cm	Necrosis or exfoliative dermatitis
Induration/ swelling	Absent	2.5 to 5.0 cm and does not interfere with activity	5.1 to 10.0 cm or interferes with activity	>10.0 cm or prevents daily activity	Necrosis
Other ^b	Absent	Present			

A and E = accident and emergency department; AE = adverse event.

^a Measurements refer to the reaction at the greatest single diameter. Measurements of less than 2.5 cm diameter for erythema or induration may be captured as mild per investigator discretion.

^b Any other reactions such as bruising, itching or ulceration will be recorded as absent or present and will be recorded as AEs; AEs will be categorized according to the investigator's judgment, using the guidance presented in [Section 12.1.2](#)

21. REFERENCES

1. Cook, D. Medical Review Humira (adalimumab) Injection, Solution for subcutaneous use. sBLA 125057/110, 80. 3-23-2007. U.S. Food and Drug Administration (FDA) and Center for Drug Evaluation and Research (CDER).
 2. Saurat JH, Stingl G, Dubertret L et al. Efficacy and safety results from the randomized controlled comparative study of adalimumab vs. methotrexate vs. placebo in patients with psoriasis (CHAMPION). Br.J.Dermatol. 2008;158:558-566.
 3. Gordon KB, Langley RG, Leonardi C et al. Clinical response to adalimumab treatment in patients with moderate to severe psoriasis: Double-blind, randomized controlled trial and open-label extension study. J.Am.Acad.Dermatol. 2006;55:598-606.
 4. Humira Summary of Product Characteristics. 2014. European Medicines Agency (EMA).
Link to Publisher's Site:
http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000481/human_med_000822.jsp&mid=WC0b01ac058001d124
 5. Committee for Medicinal Products for Human Use. Guideline on clinical investigation of medicinal products indicated for the treatment of psoriasis. CHMP/EWP/2454/02 corr, 18. 11-18-2014. London, European Medicines Agency (EMA). Link to Publisher's Site:
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003329.pdf
 6. Fredriksson T, Pettersson U. Severe psoriasis--oral therapy with a new retinoid. Dermatologica. 1978;157:238-244.
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7. van Voorhees A, Feldman SR, Koo JYM, Lebwohl MG, Menter A. The Psoriasis and Psoriatic Arthritis Pocket Guide: Treatment Algorithms and Management Options. Portland, OR: National Psoriasis Foundation; 2009.
 8. Mallinckrodt CH, Sanger TM, Dubé S et al. Assessing and interpreting treatment effects in longitudinal clinical trials with missing data. *Biol.Psychiatry* 2003;53:754-760.
 9. Yan X, Su XG. Stratified Wilson and Newcombe confidence intervals for multiple binomial proportions. *Stat.Biopharm.Res.* 2010;2:329-335.
 10. Kim Y, Won S. Adjusted proportion difference and confidence interval in stratified randomized trials. Cary, NC: SAS Institute, Inc.; 2013:
 11. Kenward MG, Roger JH. Small sample inference for fixed effects from restricted maximum likelihood. *Biometrics.* 1997;53:983-997.
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22. SUMMARY OF CHANGES

Protocol 911401 Amendment 3 (Global) 2016 AUG 04

Replaces: Amendment 2: 2015 OCT 08

In this section, changes made in this amendment from the previous version of the protocol, dated 2015 OCT 08, are described and their rationale is given.

1. Throughout the document

Description of Change: Minor grammatical and/or administrative changes have been made.

Purpose for Change: To improve the readability and/or clarity of the protocol.

2. Throughout the document

Description of Change: The following changes were applied to the PK sections of the protocol:

- Section 8.4.2.3: The outcome measure “Exposure to M923 and EU RPP assessed as trough serum levels” was updated to “Exposure to M923 and EU RPP assessed as serum levels”
- Section 11.3: “Blood samples for analysis of serum M923 or EU RPP in terms of trough serum levels will be collected at the times shown in the schedule in Table 1” was changed to “Blood samples for analysis of serum M923 or EU RPP in terms of serum levels will be collected at the times shown in the schedule in Table 1”
- Section 13.4.4.3:
 - “The trough serum levels will be summarized by treatment arm at each scheduled collection” was changed to “The serum levels will be summarized by treatment arm at each scheduled collection”
 - “To evaluate whether of anti-adalimumab antibody formation will affect trough exposure...” was changed to “To evaluate whether of anti-adalimumab antibody formation will affect exposure...”

Purpose for Change: Serum samples through Week 16 are collected at midpoint. For this reason, the term “trough” was removed in the aforementioned sections.

3. Section 1.2 Study Organization

Description of Change: Inclusion of information from the study medical monitors

Purpose for Change: To identify the study medical monitors

4. Section 2 Serious Adverse Event Reporting

Description of Change: Contact for SAE questions changed to “QLS_M923@quintiles.com”

Purpose for Change: This is the specific address for SAE processing, which was considered the ideal destination for SAE reports and queries

5. Section 7.2 Primary objective

Description of Change: Primary objective “to demonstrate equivalent efficacy between M923 (test) and EU RPP (reference) in subjects with moderate to severe chronic plaque-type psoriasis” was changed to “to demonstrate equivalence in measures of efficacy between M923 (test) and EU RPP (reference) in subjects with moderate to severe chronic plaque-type psoriasis”

Purpose for Change: To clarify the study objective

6. Section 7.3 Secondary Objectives

Description of Change: Secondary objective “Evaluate the safety, immunogenicity, and tolerability of M923 compared with EU RPP” was changed to “Evaluate the continued efficacy, safety, immunogenicity, and tolerability of M923 compared with EU RPP”

Purpose for Change: To clarify the study objective

7. Section 7.3 Secondary Objectives

Description of Change: Secondary objective “Evaluate exposure of EU RPP and M923” was changed to “Evaluate concentration summaries over time”

Purpose for Change: To clarify the study objective

8. Section 8.2 Study Design

Description of Change: The following sentence was added “Subjects who complete the treatment period will have a safety follow-up visit at Week 52”

Purpose for Change: To include a reference to the safety follow-up visit in this Section

9. Section 8.3 Duration of Study Period(s) and Subject Participation

Description of Change: The actual recruitment period that was observed in this study was added

Purpose for Change: To reflect the actual recruitment period

10. Section 8.4 Outcome measures

Description of Change: The following changes were applied

- On safety outcome measures 1 and 2, the starting words “Evaluate the” were removed
- On PK outcome measure 1, the word “trough” was removed and it was added that exposure would be assessed as serum levels “collected periodically throughout the treatment period”
- In PK outcome measure 3, it was reinforced that immunogenicity would be assessed as evidenced by the presence of ADAs

Purpose for Change: To clarify the outcome measures and they will be measured

11. Section 8.8 Source data

Description of Change: It was added in the text that “no data will be entered directly onto the eCRF”

Purpose for Change: To acknowledge that no source data will be entered directly onto the eCRF

12. Section 9.1 Inclusion Criteria

Description of Change: the following changes were added

- Minor typographical changes throughout the criteria
- In inclusion criterion 1, the term “any age” was removed, as it was incorrect
- In inclusion criterion 9, bullet b, it was added that male partners should use a condom “until 5 months after the last administration of IP”

Purpose for Change: To clarify a maximum period where male partners should use a condom

13. Section 9.2 Exclusion Criteria

Description of Change: the following changes were added

- Minor typographical changes throughout the criteria
 - In exclusion criterion 6, it was added that the subject must have no major deviations regarding concomitant medication
 - In exclusion criterion 8, the sentence “All other prior non-psoriasis concomitant treatments must be on a stable dose for at least 4 weeks before baseline (Visit 2)” was removed
 - In exclusion criterion 19, “x-ray” was replaced by “a radiograph or comparable imaging with negative finding for TB or other similar infections”
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Purpose for Change: For criterion 6, to clarify this criterion further. The sentence from exclusion criteria 8 was removed because it was reflected in exclusion criterion 9. For criterion 19, to clarify the type of imaging exam acceptable for this study.

14. Section 10.3.1 Screening and Baseline Assessments

Description of Change: the following instructions were added for screening evaluation of relevant medical and surgical history and all medications:

- Medications/therapies for psoriasis: 8 weeks prior to screening
- Non-psoriatic medications/therapies: 4 weeks prior to screening
- All prior biologic medications/therapies (including investigational biologics)

Purpose for Change: To clarify the time periods for concomitant medication history data collection

15. Section 10.3.4 Safety follow-up

Description of Change: Inclusion of additional instructions for safety follow-up visit, including eligibility to participate in this visit, time periods for clinical visits and phone contacts and collection of information in the eCRF

Purpose for Change: To clarify the safety follow-up procedures and requirements

16. Section 10.4 Medications and Non-Drug Therapies

Description of Change: Inclusion of topical treatments containing acetylsalicylic acid in the list of treatments not permitted during the course of the study

Purpose for Change: To clarify all non-permitted treatments

17. Section 10.5 Subject diary

Description of Change: The following was clarified in this Section

- At each visit, the investigator will photocopy the applicable diary pages, store them in the source documents until such time when the original subject diary is collected
- During the treatment period, at Week 25, the subject diary may be collected and a new diary provided to the subject and retrieved at Week 48

Purpose for Change: To clarify how the study diary will be handled during the study

18. Section 10.6 Subject Completion/Discontinuation

Description of Change: It was added that after the discontinuation visit, if the subject agrees, a follow-up visit should be conducted 5 weeks after last IP dose.

Purpose for Change: To clarify that a follow-up visit may be conducted in agreeing subjects who discontinue the study, for safety purposes

19. Section 10.7 Procedures for Monitoring Subject Compliance

Description of Change: Inclusion of criteria for minimum IP compliance in order for subjects to be considered eligible for per protocol analysis

Purpose for Change: To clarify the IP compliance criteria

20. Section 11.3 Pharmacokinetics Assessments

Description of Change: Storage temperature of back-up specimens was updated (to be stored at -20 °C or -70 °C)

Purpose for Change: To provide accurate acceptable storage temperatures

21. Section 12.1.1.1 Serious Adverse Events

Description of Change: In the SAE definition, it was clarified that hospitalizations occurring during the study period but planned before subject inclusion will not be considered SAEs

Purpose for Change: To clarify SAE definition

22. Section 12.5 Medical, Medication, and Non-Drug Therapy History

Description of Change: The following changes were carried out, along with other typographical updates:

- “x-ray” was replaced by “a radiograph or comparable imaging with negative finding for TB or other similar infections”
- A minimum treatment period for LTBI was clarified to be “with a recognized and regionally appropriate regimen of 4-6 weeks prior to start of IP”

Purpose for Change: To clarify the minimum LTBI treatment period and the acceptable imaging tests

23. Section 13.4.4.1 Efficacy

Description of Change: Formula updated

Purpose for Change: Typographical error in mathematical formula corrected

24. Section 13.4.4.2 Safety

Description of Change: Periods defined for the analysis of AEs were re-defined. Additionally the sentence “Frequency and percentages of changes between normal and abnormal for physical examination and ECGs will be calculated” was removed

Purpose for Change: To clarify and simplify the analysis

25. Section 13.4.4.3 Pharmacokinetics and Immunogenicity

Description of Change: the following changes were made, together with minor typographical updates:

- “Maximum likelihood estimator of the coefficient of variation” was replaced by “the geometric coefficient variation”
- The following sentence was added “population PK/PD analyses are not planned following the administrative interim database lock at Week 25”
- Purpose for Change: To clarify PK and immunogenicity analysis

26. Section 13.5 Planned Interim Analysis of the Study

Description of Change: It was clarified that the interim analysis would be done for the first randomized subjects and would analyze primary endpoint data and PK up through Week 25. It was also clarified that the final analysis would be carried out in all subjects recruited (n=572)

Purpose for Change: To clarify interim and final analysis procedures

27. Section 20.2 Schedule of Study Procedures and Assessments

Description of Change: Table 1 was updated to include study diary dispensing and returning procedures, as well as specifying drug returning procedures and reflect the changes mentioned in the amendment

Purpose for Change: To improve clarity and coherence throughout the protocol

28. Section 20.2 Schedule of Study Procedures and Assessments

Description of Change: Table 2 was updated to include the following parameters:

- Viral serology: Hepatitis B surface antigen, anti-Hepatitis B surface antigen and anti-Hepatitis B core total (IgG and IgM)
- Tuberculosis: T-SPOT

Purpose for Change: To clarify test parameters

INVESTIGATOR ACKNOWLEDGEMENT

PRODUCT: M923

STUDY TITLE: A Phase 3 Randomized, Double-blind, Multicenter Study to Evaluate Efficacy, Safety, and Immunogenicity of M923 (a Proposed Adalimumab Biosimilar) and Humira[®] in Subjects with Moderate to Severe Chronic Plaque-type Psoriasis

PROTOCOL IDENTIFIER: 911401

CLINICAL TRIAL PHASE 3

AMENDMENT 3 (Global): 2016 AUG 04

Replaces: Amendment 2: 2015 OCT 08

ALL VERSIONS:

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Amendment 1: 2015 JUL 27

Original: 2015 MAY 13

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NCT Number: NCT02581345

IND NUMBER: 115119

By signing below, the investigator acknowledges that he/she has read and understands this protocol, and provides assurance that this study will be conducted according to all requirements as defined in this protocol, clinical study agreement, ICH GCP guidelines, and all applicable regulatory requirements.

Signature of Investigator

Date

Print Name and Title of Investigator

Signature of Sponsor Representative

Date

PPD, MD, Vice President, Clinical Development
