

STATISTICAL ANALYSIS PLAN

PRODUCT: M923

CLINICAL TRIAL PHASE 3

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

Study Sponsor(s):	Baxalta US Inc. One Baxter Way Westlake Village, CA 91362	Baxalta Innovations GmbH Industriestrasse 67 A-1221 Vienna, AUSTRIA
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1. INTRODUCTION AND OBJECTIVES

1.1 Study Objectives

1.1.1 Primary Objective

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

1.1.2 Secondary Objective(s)

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 drug concentration summaries over time.

2. STUDY DESIGN

This study is a Phase 3, active-controlled, randomized, double-blind, multicenter study to determine the clinical equivalence between M923 (a proposed adalimumab biosimilar) and EU RPP.

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period, and 4-week follow-up period) from enrollment to subject completion (i.e., last study visit), unless prematurely withdrawn.

2.1 Study Population

The study population will include 516 randomized subjects (258 subjects randomized to the M923 group and 258 subjects randomized to the EU RPP group) with moderate to severe chronic plaque-type psoriasis. Subjects will be eligible for the study provided that they satisfy all of the eligibility criteria listed in the study protocol.

The 2 treatment arms are:

- 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)

At Week 25, subjects not achieving at least a PASI50 response will be discontinued from the study. The last dose of study drug will be administered at Week 47. Subjects will be followed for safety until Week 52.

The overall study design can be seen in the study protocol ([Figure 1](#))

2.2 Sample Size and Power Calculations

Primary analysis: Test equivalence of M923 compared with EU RPP using the PASI75 response rate (i.e., the proportion of subjects who achieve at least 75% improvement in Psoriasis Area and Severity Index score from baseline) at Week 16, CCI

A total of 516 subjects will be randomized (258 in Arm A and 258 in Arm B) CCI

Rationale for the sample size calculations can be found in section 13 of the Protocol 911401.

Should over recruitment occur, the interim analysis will include the first 516 randomized subjects and the final analysis will include all subjects enrolled in the study.

2.3 Randomization

This is a randomized, double-blind, active treatment controlled 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.

2.4 Blinding/Unblinding

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 period (see section 5.1). 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.

2.5 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
3. Recruitment of sufficient number of subjects is considered to be impractical in the required time frame
4. The sponsor determines to discontinue development of M923
5. An ethics committee and/or competent authority determines the trial should be terminated.

2.6 Study Assessments

A Schedule of Study Procedures and Assessments can be found in [section 15.1](#).

3. STUDY OUTCOME MEASURES

3.1 Efficacy Outcome Measures

3.1.1 Primary Efficacy 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.

3.1.2 Secondary Efficacy Outcome Measures

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 and percent change from baseline in 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).

3.1.2.1 Exploratory Outcome Measures

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3.2 Safety Outcome Measures

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 transition from EU RPP to M923 compared with continuous use of EU RPP.

3.3 Pharmacokinetic and Immunogenicity Outcome Measures

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 over time.
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 through Week 25.

4. ANALYSIS SETS

4.1 Intent-to-treat (ITT) Analysis Set

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.

4.2 Per-Protocol (PP) Analysis Set

The PP population is a subgroup of the ITT population which will include all subjects who do not have any deviations from the protocol deemed significant enough for exclusion from efficacy analysis and received at least 1 dose of study medication. See [section 6.7](#) for a definition of exclusion. Subjects will be assigned to treatment groups based on randomization.

4.3 Modified Intent-to-treat (mITT) Analysis Set

The ITT population will include all consenting subjects randomized to study treatment (Arm A or Arm B) and contributed post-baseline data for at least one efficacy endpoint. Subjects will be assigned to treatment groups based on randomization.

4.4 Safety Analysis Set

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 treatment actually received.

4.5 Pharmacokinetic (PK) Analysis Set

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, a decision will be made on a case-by-case basis and documented as to their inclusion in the analysis. Subjects will be assigned to treatment groups based on treatment actually received.

5. STATISTICAL CONSIDERATIONS

In general, all efficacy, safety, PK, and immunogenicity variables will be summarized using descriptive statistics. Continuous variables will be summarized by sample size [n], mean, standard deviation [SD], median, minimum and maximum. Categorical variables will be summarized in frequency tables (n, frequencies, and percentages). Additional statistics will be provided for PK and immunogenicity data as described in [Section 9](#).

Individual subject data will be presented in listings.

In summary tables, minimum and maximum should have the same number of decimals as the original data; means, medians to have one more, SDs should have two more decimal. Percentages, including percentage changes, will be shown to 1 decimal place.

The equivalence testing of the primary outcome measure will use 90% confidence intervals for FDA submission and 95% confidence intervals for EMA submission. Formal hypothesis testing will be performed only for the equivalence testing of the primary outcome measure. For the other outcome measures, the treatment difference and both 90% and 95% confidence intervals for treatment differences will be displayed.

5.1 Interim Analyses

An interim analysis will occur when the first 516 subjects have completed Week 25, The purpose of the interim analysis 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 on this analysis, the Type I error rate is preserved and no multiplicity adjustment is needed. An interim clinical study report for the interim analysis will be to support regulatory submissions.

The analysis will include summaries of subject disposition, demographic and baseline characteristics, AEs including injection site reactions, laboratory assessments, vital signs, and PK and immunogenicity data, as appropriate.

This document contains all the statistical methods and data presentations needed for the content of the both interim CSR and final CSR.

The interim analysis will be executed by an unblinded team distinct and separated from the study team. The operational study team will remain blinded until final database lock. The details of the interim analysis are included in this SAP, the methodology to maintain the blind of the study team, will be discussed in a separate unblinding plan.

5.2 Handling of Missing, Unused, and Spurious Data

Efficacy Measures

Imputation for missing PASI scores will be limited to assessments performed from the Week 0 to Week 16 visits. NRI imputation will be applied to data beyond the Week 16 visit for subjects who continued to receive M923 after Week 16 and those originally administered EU RPP and re-randomized at Week 16.

The primary analysis will be based on the non-responder imputation (NRI) method. Sensitivity analyses for PASI75, PASI50, and PASI90 will include modified baseline observation carried forward (mBOCF) and mixed model for repeated measures (MMRM) methods. This section describes the details of each of the imputation procedures.

Non-Responder Imputation (NRI) for Clinical Response: For binary endpoints PASI75, PASI50, PASI90, and sPGA, the primary analysis will be based on NRI.

Subjects will be considered as non-responders at a time point of interest for the NRI analysis in any of the following situations:

- No valid PASI score at baseline.
- No valid post-baseline PASI score for any reason at the time point of interest.
- No improvement in PASI score from baseline or an improvement of less than 50%, 75%, and 90% for response measures PASI50, PASI75 and PASI90, respectively, at the time point of interest. No improvement in sPGA of clear or almost clear at the time point of interest.

Modified Baseline Observation Carried Forward (mBOCF): As a supportive analysis, continuous PASI scores will be imputed based on a modified baseline observation carried forward (mBOCF) approach. Categorical endpoints will be derived from the imputed continuous measure.

Missing values at a time point of interest will be imputed as follows:

- For subjects who discontinue the study treatment due to AE(s) or death before the Week 16 visit, the baseline observation will be carried forward to the corresponding time point for evaluation (BOCF).
- For subjects who discontinue the study treatment due to any other reason other than AE or death before the Week 16 visit, the last non-missing observation before discontinuation will be carried forward to the corresponding time point for evaluation (LOCF).
- For subjects who complete the study treatment through the Week 16 visit, the last non-missing observation will be carried forward to the corresponding time point for evaluation (LOCF).
- For subjects who do not have any post-baseline data and did not discontinue the study treatment due to AE(s) or death prior to the Week 16 visit, missing values will not be imputed and subjects will be excluded from the analysis.

Mixed Models for Repeated Measures (MMRM): As a supportive analysis, continuous PASI scores will be imputed based on mixed-effects model for repeated measures (MMRM). Categorical endpoints will be derived from the imputed continuous measure. The MMRM model will use PASI data from the Week 0 to Week 16 visits and will

include covariates for baseline PASI score (continuous), treatment group (A, B), visit (Week 1, 4, 8, 12 and 16), region (North America, Western Europe, or Eastern Europe/Asia), and the treatment-by-visit interaction. An unstructured variance-covariance matrix will be estimated. If the procedure fails to converge a heterogenous Toeplitz structure will be used for the variance-covariance matrix. The Kenward-Roger method will be used for estimating degrees of freedom.

Observed Case: As a supportive analysis for PASI scores, the observed data, with no imputation for missing data, will be summarized with descriptive statistics.

Adverse Events

At database lock and before the unblinding occurs, all AEs will be checked for missing causality assessment and/or severity grades. Any missing cases, will be reviewed by pharmacovigilance monitor or designee and appropriate data handling decisions will be provided on case by case.

Other Outcome Measures

Unless otherwise specified, for all other outcome measures, descriptive statistics will be presented in tables, with no action to handle missing data (observed case). Subjects who withdraw prior to the last planned observation in the study period will be included in the analyses up to the time of withdrawal.

Extra measurements (such as unscheduled or repeat assessments) will not be included in the descriptive statistics, but will be included in subject listings.

5.3 Definition of Baseline

Baseline is defined as the last scheduled observation prior to dosing. In most cases Visit 2 will act as baseline with assessments done on Day 1, before dose. However, if the required data for a subject is missing for baseline, the previous non-missing evaluation will become the baseline value. If no baseline or previous to baseline evaluations exist then the baseline value will be treated as missing. This definition will be used for all the outcome measures unless otherwise specified.

5.4 Analysis Periods

Analysis periods will be defined using the two randomization dates. The first analysis period (Week 0 to Week16) is defined from the Week 0 visit to the end of Week 16 visit. The second analysis period (>Week 16) is defined as starting after Week 16 to the end of the study.

For the first analysis period (Week 0 to Week 16), summary tables will be displayed by treatment arm A and B. For the second analysis period (>Week 16), summary tables will be displayed by treatment arm A, B1, and B2.

5.5 Changes from the Planned Statistical Analysis in Protocol

There are no significant changes from the planned statistical analysis in the protocol.

The PP Analysis Set definition has been amended to clarify that only those protocol deviations that are deemed significant enough to affect the primary analysis will result in exclusion from this population.

The modified Intention-To-Treat (mITT) Analysis Set has been added as an additional supplementary analysis for Primary Analysis.

Health Outcome Variables

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Clinical Safety and Tolerability

The protocol specified that 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. However, the number of periods for analysis was redefined to display results

6. STUDY SUBJECTS

6.1 Disposition of Subjects

Subject disposition will be tabulated for each study treatment and all subjects including the number of subjects who are enrolled (i.e., those who have provided informed consent), the number of screen failures as well as the number of subjects who are randomized, treated, complete the study, withdraw with the reason for early withdrawal, and the total count of subjects in each analysis set (as defined in [Section 4](#)). A listing will be presented to describe dates of completion or early withdrawal and the reason for early withdrawal, if applicable, for each subject.

6.2 Demographic and Baseline Characteristics

Demographic characteristics such as age, gender, race, ethnicity, height, weight, and body mass index (BMI) will be summarized by treatment and for all subjects overall. Descriptive statistics will be presented for age, height, weight, and BMI. Frequency counts and percentages will be presented for sex, race, and ethnicity.

Individual subject demographics and baseline characteristics (results from serology screening, pregnancy and follicle-stimulating hormone (FSH) tests, urine alcohol and drug screen, and anti-citrullinated protein antibodies) will be presented in listings. Listings of treatment randomization and study drug administration will also be provided.

6.3 Medical History

Listings of both medical history and tuberculosis history and test will be presented by patient and treatment.

6.4 Prior and Concomitant Medications

Prior medications are defined as any medication discontinued prior to randomization and administration of study drug. Concomitant medications are defined as any medication initiated or continued during the course of the study. Subject listings of all prior and concomitant medications and non-drug therapies will be presented.

All medications will be coded using the latest version of the World Health Organization Drug Dictionary (WHO DD).

6.5 Extent of Exposure

Exposure to study medication will be provided. Exposure will be calculated overall as well as for exposure up to Week 16 and for week 16 onwards. The number of days on study medication (duration of exposure = date of last dose of IP in given time period minus date of first dose of IP +1; if either date is missing, the duration is unknown) will be summarized for each treatment group, presenting mean, median, standard deviation, and range.

Exposure will also be calculated and summarized in terms of patient treatment years.

6.6 Treatment Compliance

Treatment compliance will be calculated as the ratio of the number of injections taken over the total exposure period (determined by a count of Study Drug Administrations) divided by the number of doses that should have been taken over the same period.

The number of doses that should be taken will be calculated based on the week the subject completed or discontinued the study.

If the subject completed/discontinued on an even week (day 1 (Week 0),2,4,...,48) the number of doses that should be taken over the period is calculated as the week of completion or discontinuation, divided by 2, adding one for the day 1 (Week 0) dose:

$$\frac{\text{Week number}}{2} + 1 \text{ (day 1, Week 0)}$$

If the subject completed/discontinued on an odd week (1,3,5,...,47) the number of doses that should be taken over the period is calculated as the week of completion or discontinuation, plus one, divided by 2, adding one for the day 1, week 0 dose:

$$\frac{\text{Week number} + 1}{2} + 1 \text{ (day 1, Week 0)}$$

The exposure period for a subject is calculated from the first day the subject took study medication to 13 days after the last day the subject took study medication, inclusive. Study drug compliance will not be calculated for subjects who were distributed but never took study medication.

Treatment compliance will be summarized by study treatment arm (A and B) and subgroup of treatment arm B (B1 and B2) for the safety and PP populations.

6.7 Protocol Deviations

Protocol deviations will be classified as Minor, Important/Major or Critical/Priority. For analysis and reporting purposes, deviations leading to exclusion from the PP Analysis set will include, but are not limited to: deviation from eligibility criteria, administration of prohibited medications and erroneous administration of study treatment. The criteria for grading protocol deviations will be proposed by the Quintiles Therapeutic Medical Advisor and aligned with the Baxalta Physician. All protocol deviations leading to exclusion from PP analyses are determined together with the Baxalta Physician 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 actual treatment.

7. EFFICACY EVALUATION

All efficacy measures will be summarized and evaluated utilizing the PP Analysis set and repeated using the mITT Analysis set as sensitivity analysis. Listings will be presented using the ITT Analysis set,

For the Primary and Secondary analysis, visit windowing conventions are will at occur at Week 16 for the purpose of equivalence testing. Based on a target day of 113, a lower bound of window (day) 103 and an upper bound of window (day) 123 will be used.

If more than one visit falls within the same visit Week 16 window, the data from the visit closest to the target day will be used for the visit summary. If two visits within the same visit window are equidistant from the target day, the data from the later visit will be used for the protocol specified visit.

Data will be listed and summarized with descriptive statistics, by randomized treatment group. Further details are provided in the following sub-sections.

7.1 Analysis of Primary Efficacy Outcome Measure

The primary efficacy objective will be met by demonstrating that subjects randomized to M923 (Arm A) and those randomized to EU RPP (Arm B) have a statistically equivalent PASI75 response rate at Week 16 (Visit 7).

The primary efficacy variable is the PASI75 response rate at Week 16 (Visit 7). A PASI75 responder at Week 16 is defined as a subject who achieves at least 75% improvement in PASI score from baseline at Week 16. The primary efficacy analysis is a test for equivalence between M9223 and EU RPP groups (as randomized) and will be performed on the PP analysis set. Where missing data occurs, the NRI method (see [Section 5.2](#)) will be used to impute values.

The primary efficacy objective will be met by demonstrating that subjects randomized to M923 (Arm A) and those randomized to EU RPP (Arm B), have a statistically equivalent PASI75 response rate at Week 16 (Visit 7).

7.1.1 Hypothesis Regarding Primary Efficacy Outcome Measure

All equivalence testing will be made using 90% confidence intervals (per FDA) and an equivalence margin of 18%. For the EMA, all equivalence testing will be made using 95% confidence intervals and an equivalence margin of 15%, for rationale see Protocol section 13.1

For PASI75 response rate in each individual treatment arm, 95% confidence intervals will be calculated using Clopper-Pearson method. Confidence intervals for differences in PASI75 response rate between M923 and EU RPP will be calculated using the Newcombe score method and stratified by geographic region (North America, Western Europe, and Eastern Europe/Asia). 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 entirely contained within the equivalence margin; in this case, statistical equivalence will be declared.

7.1.2 Derivation of Primary and Secondary Efficacy Outcome Measure Using PASI

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. 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, or 90 response are defined as having an improvement, i.e. a reduction of at least 50%, 75% or 90%, respectively, in the PASI score compared with baseline. Information required to calculate the PASI will be recorded on the eCRF by the investigator/site staff at clinic visits.

7.2 Analysis of Secondary Efficacy Outcome Measure

The analysis of the secondary efficacy outcome measures (see [Section 3.1.2](#)) will be performed on the PP population and repeated on the mITT population.

Secondary efficacy outcome measures include PASI50, PASI90, and sPGA response rate at Week 16 (Visit 7). A PASI50 (or PASI90) responder at Week 16 is defined a subject who achieves at least 50% (or 90%) improvement in PASI score from baseline at Week 16. The sPGA response rate will be described as the proportion of subjects who have achieved a clear or almost clear response (sPGA score of 0 or 1) at Week 16

At Week 16, the treatment arms (Arm A and B) will be compared using PASI50, PASI90, and sPGA response rates. For response rates in each individual treatment arm, 95% confidence intervals will be calculated using the Clopper-Pearson method. Treatment differences and corresponding 90% and 95% confidence intervals in response rates between M923 and EU RPP will be calculated using the Newcombe score method and stratified by geographic region (North America, Western Europe, and Eastern Europe/Asia). The NRI method (see [Section 5.2](#)) will be used to handle missing data.

Descriptive statistics and 95% confidence intervals for the mean of PASI total score and percentage change from baseline will be provided by treatment arm and analysis period (Arm A and B up to Week 16; Arm A, B1, and B2 after Week 16) for each scheduled time point. No imputation for missing data will be applied (observed case).

PASI50, PASI75, PASI90, and sPGA response rate and 95% confidence intervals calculated using the Clopper-Pearson method will be summarized by treatment arm and analysis period (Arm A and B up to Week 16; Arm A, B1, and B2 after Week 16) for each scheduled time point.

Figures will be created to display the response rates and mean percentage change in PASI score over time and by treatment arm and analysis period (Arm A and B up to Week 16; Arm A, B1 and B2 after Week 16).

Health-related quality of life measures, DLQI and the EQ-5D-5L, will be summarized by treatment arm and analysis period (Arm A and B up to Week 16; Arm A, B1 and B2 after Week 16) and scheduled time point.

7.2.1 Hypothesis Regarding Secondary Efficacy Outcome Measure

No formal hypothesis testing of equivalence will be performed for the comparison between M923 and EU RPP using the secondary efficacy outcome measures.

7.2.2 Derivation of Secondary Efficacy Outcome Measure

Derivation of PASI response rates are described in [section 7.1.2](#).

The static Physician Global Assessment (sPGA) is a 6-point scale ranging from 0 (clear), 1(minimal), 2(mild), 3(moderate), 4(severe) and 5(very severe). For the purpose of analysis, clear or almost clear (6-point scale) is determined by a score of 0 or 1 at a given visit.

Dermatology Life Quality Index (DLQI) and the EuroQoL 5-Dimension Health Status Questionnaire (EQ-5D-5L) derivations are described in [section 10.1](#) and [10.2](#) respectively.

7.3 Sensitivity Analyses

For the primary efficacy measure, PASI75 response rate at the Week 16 visit, sensitivity analyses will include repeating the primary analysis using:

- mITT population with NRI method for missing data,

- PP and mITT populations with mBOCF for missing data, and
- PP and mITT populations with MMRM for missing data.

8. SAFETY EVALUATION

All safety assessments will be summarized and evaluated utilizing the safety analysis set, including AEs, physical examinations, clinical laboratory evaluations, vital signs, 12-lead ECG results and injection site reactions and will be listed and summarized with number and proportion of subjects or descriptive statistics, as appropriate, by treatment arm and analysis period (Arm A and B up to Week 16; Arm A, B1 and B2 after Week 16). Subjects who withdraw from the study prematurely will have their Early withdrawal visit summarized as an individual visit. No formal hypothesis testing of safety data is planned.

Further details are provided in the following sub-sections.

8.1 Adverse Events

Adverse events will be coded using the latest version of MedDRA.

Treatment-emergent adverse events (TEAEs) are defined as AEs that started or worsened in severity on or after the first dose of study medication, until study completion/withdrawal (Week 48) or 30 days following the last M923 or EU RPP treatment for early withdrawn subjects.

All TEAEs (including SAEs, AEs related to study drug, AEs leading to withdrawal, and injection site reactions) will be presented in summary tables. Summary tables shall indicate the number of subjects who experienced adverse events. In addition, tables will be prepared to list each AE, the number of subjects in each treatment arm who experienced an adverse event at least once, and the rate of subjects with AE(s). AEs will be grouped by system organ class and preferred term. Each event will then be divided into defined severity grades (mild, moderate, severe). The tables will also divide the AEs into those considered related (a “possibly related” or a “probably related” AE will be considered as a “related AE”) to the treatment and those considered unrelated (an “unlikely related” or a “not related” AE will be considered as an “unrelated” AE). In addition a summary of subject incidence of the top 5% of AEs will be produced.

All AEs for each subject, including the same event on several occasions, will be listed, giving both MedDRA preferred term and the original term used by the investigator, system organ class, severity grade, seriousness, relation to the treatment, onset date, and stop date.

AEs that occurred before first dose of study drug will be listed separately.

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

The number and percentage of subjects with any AE, any related AE, any severe AE, any related severe AE, any SAE, and any related SAE, as well as the total number of events for each category, will be summarized by treatment group. The number of deaths due to an AE, hospitalization due to an AE and study discontinuation due to an AE will be summarized by treatment arm and analysis period (Arm A and B up to Week 16; Arm A, B1 and B2 after Week 16).

The number and percentage of subjects with an AE, as well as the total number of AEs, will be summarized for each treatment arm and analysis period (Arm A and B up to Week 16; Arm A and B2 after Week 16). This tabulation will be repeated by relationship and severity.

AEs that occurred before first dose of study drug will be listed separately. Any adverse events reported more than 30 days after a subject has completed or withdrawn early from the study, will not be summarized but will be listed.

8.2 Clinical Laboratory Evaluations

For hematology and clinical chemistry parameters, summary statistics of the value and change from baseline values will be summarized by scheduled study visit for each treatment arm and analysis period (Arm A and B up to Week 16; Arm A, B1 and B2 after Week 16).

Each laboratory test result will be categorized according to the respective reference range as low (below the lower limit), normal (within the reference range), and high (above the upper limit). All laboratory results will be listed by subject and will include the result, reference range, and clinical significance.

Out of range laboratory values will be flagged in the data listings, with the corresponding investigator's judgment of clinical relevance, and a list of clinically significant abnormal values will be presented, as applicable.

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

8.3 ECG

Electrocardiogram data (Ventricular rate, PR interval, QRS duration, QT and QT intervals) will be listed with abnormalities indicated. QT interval corrected for heart rate using Fridericia's equation (QTcF) will be calculated as follows: $QTcF = QT / (3\sqrt{RR})$.

8.4 Vital Signs

Vital signs (body temperature, respiratory rate, pulse rate, systolic and diastolic blood pressure and weight) will be listed.

8.5 Physical Examination

Physical examinations (general appearance, head and neck, eyes and ears, nose and throat, chest, lungs, heart, abdomen, extremities and joints, lymph nodes, skin, and neurological), will be listed with abnormalities indicated.

9. EVALUATION OF PHARMACOKINETICS

Secondary PK outcome measures will be analyzed using the PK Analysis set.

For the interim analysis, this will include adalimumab concentration and immunogenicity data through Visit 11, Week 25 and will reflect 5 post-dose assessments on Weeks 8, 16, 17, 21 and 25.

Adalimumab serum levels will be summarized by treatment arm at each scheduled collection. In addition to the usual descriptive statistics, the geometric mean, corresponding 95% confidence interval (CI), and geometric coefficient of variation (CV) will also be presented. Concentrations that are below the limit of quantitation (BLQ) will be replaced with the lower limit of quantitation (LLOQ) for the computation of descriptive statistics. Missing concentrations will be treated as missing. Individual and geometric mean (95% CI) adalimumab concentrations will be graphically presented by treatment (A vs B through Week 16 and versus B1 and B2 following re-randomization).

To evaluate whether 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, subjects who did not form neutralizing ADAs, versus subjects who formed neutralizing ADAs), as appropriate.

Figures will also be generated to display arithmetic mean adalimumab concentrations versus study week grouped by treatment. Scatterplots and boxplots will also present

adalimumab concentrations stratified by ADA status and to explore the relationship between trough concentrations and ADA titres.

The within-subject variability (geometric CV) in trough concentrations (2 weeks postdose samples) over time (Week 17 to Week 41) will be determined for each subject, which will then be listed, summarized, and compared between treatment arms (EU RPP/EU RPP versus EU RPP/M923) using an analysis of variance model with treatment as a fixed effect. For the subgroup in the EU RPP treatment which is randomized to transition to M923 and back, the troughs

- collected in Weeks 21 and 25 fall into the first transition to M923,
- collected in Weeks 29 and 37 fall into the transition back to EU RPP,
- collected in Week 41 falls into the second transition to M923.

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 pharmacokinetic/pharmacodynamic analyses. If performed, a separate modelling analysis plan will be prepared and results will be reported separately from the Clinical Study Report.

10. EVALUATION OF IMMUNOGENICITY

The immunogenicity analysis will be performed 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 by analysis tier; specifically:

Tier 1: Screening assay ADA results (positive/negative)

Tiers 2 and 3 Humira and M923 will be used to confirm the positive status of samples scored potentially positive by the screening assay:

Tier 2: Confirmatory EU Humira assay (positive/negative); if negative this will be followed by

Tier 3: Confirmatory M923 assay (positive/negative)

Positive confirmatory assay results will be summarized by Tier (2 and 3) and overall positive (in either tier).

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 performed for subjects with predose

ADA-negative results and with at least one, two or three postdose ADA-positive result as appropriate. Similar analysis may also be performed for subjects with ADA titers within certain ranges (to be determined).

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 one ADA-positive by treatment arm and by treatment period (similar to those defined in the study protocol section 13.4.4.2). Analyses of immunogenicity will be performed both for ADA and nADA for AEs before and after ADA positive at any time. Overall AEs by ADA positive at any time or negative at all visits and Hypersensitivity reactions, including those identified via MedDRA SMQ vs ADA positive at any time. This will then be repeated for injection site reactions.

11. EVALUATION OF QUALITY OF LIFE

Descriptive statistics will be used to summarize the health-related quality of life by treatment group (Arm A and Arms B1 and B2) for observed values and change from baseline of DLQI and EQ-5D-5L scores and sub-scores by scheduled study visit for each treatment arm and analysis period (Arm A and B up to Week 16; Arm A, B1, B2, and B after Week 16).

11.1 Evaluation of DLQI

The DLQI score is calculated by summing the individual scores of each question at a given time point, resulting in a maximum of 30 and a minimum of 0. The higher the score, the more quality of life is impaired. For the analysis of responses, the subject's results are assessed on a scoring scale in which 3= Very much or Yes (applicable to question 7 only), 2= A lot, 1= A little, 0= Not at all or Not relevant. Interpretation of DLQI Scoring can be taken as 0 – 1= no effect at all on subject's life, 2 – 5 small effect on subject's life, 6 – 10 moderate effect on subject's life, 11 – 20 very large effect on subject's life and 21 – 30 extremely large effect on subject's life.

11.2 Evaluation of EQ-5D-5L

The euroqol-5 dimensions, five level (EQ-5D-5L) index comprises 5 dimensions of health (mobility, self-care, usual activities, pain/discomfort and anxiety/depression). For each dimension, respondents select which statement best describes their health on that day from a possible 5 options of increasing levels of severity (no problems, slight problems, moderate problems, severe problems and unable to/ extreme problems).

Responses for each dimension are coded as **Mobility**: 1= I have no problems in walking about; 2=I have slight problems in walking about; 3=I have moderate problems in walking about; 4= I have severe problems in walking about; 5= I am unable to walk about. **Self-Care**: 1= I have no problems washing or dressing myself; 2= I have slight

problems washing or dressing myself; 3= I have moderate problems washing or dressing myself; 4= I have severe problems washing or dressing myself; 5= I am unable to wash or dress myself. **Usual Activities:** 1= I have no problems doing my usual activities; 2= I have slight problems doing my usual activities; 3= I have moderate problems doing my usual activities; 4= I have severe problems doing my usual activities; 5= I am unable to do my usual activities. **Pain/Discomfort:** 1= I have no pain or discomfort; 2= I have slight pain or discomfort; 3= I have moderate pain or discomfort; 4= I have severe pain or discomfort; 5= I have extreme pain or discomfort. **Anxiety/Depression:** 1= I am not anxious or depressed; 2= I am slightly anxious or depressed; 3= I am moderately anxious or depressed; 4= I am severely anxious or depressed; 5= I am extremely anxious or depressed.

It should be noted that the numerals 1-5 have no arithmetic properties and should not be used as a cardinal score.

In addition to the descriptive system, respondents also assess their health today on a visual analogue scale, ranging from 0 (worst imaginable health) to 100 (best imaginable health). This score will be summarized separately using descriptive statistics for baseline, each study evaluation, and change from baseline to each evaluation.

12. EVALUATION OF EXPLORATORY OUTCOME MEASURES

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13. ANALYSIS SOFTWARE

All data processing, summarization, and analyses will utilize SAS® software package, Version 9.2. If the use of other software is warranted the final statistical report will detail what software was used.

14. GUIDANCE DOCUMENTS

DLQI Scoring: Finlay AY, Khan GK. Dermatology life quality index (DLQI): a simple practical measure for routine clinical use. *Clinical and Exp Dermatol* 194;19:210-6.

EQ-5D-5L User Guide Version 2.1 April 2015: <http://www.euroqol.org/eq-5d-publications/user-guides.html>

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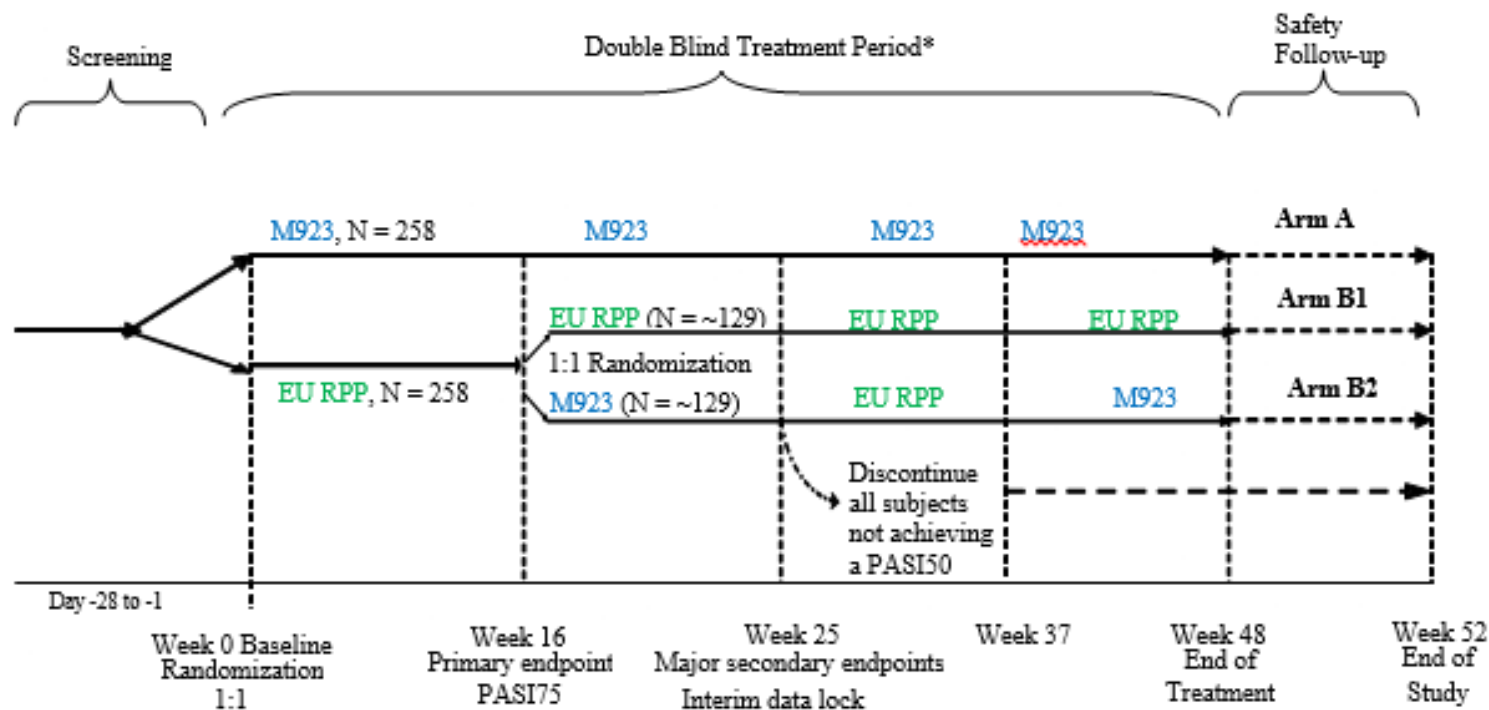


15. SUPPLEMENTS

15.1 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.

15.2 Schedule of Study Procedures and Assessments

Table 3
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
Informed consent	X																			
Medical history and prior medications (including prior therapy, psoriasis, and surgeries)	X																			
Inclusion/exclusion criteria	X	X ^a																		
Concomitant therapy ^b																				
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																				
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

Table 3
Schedule of Study Procedures and Assessments

Phase	Screen- ing	Double-Blind Period																		Safety Follow- up ^s
		0	1	4	8	12	16	17	19	21	25	27	29	33	37	39	41	45	48/ ETV	
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
Pregnancy test ^l	X	X		X	X	X	X	X		X	X		X	X	X		X		X	X
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.

Table 3
Schedule of Study Procedures and Assessments

Phase	Screen- ing	Double-Blind Period																		Safety Follow- up ^g
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

^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.

^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

Table 3
Schedule of Study Procedures and Assessments

Phase	Screen- ing	Double-Blind Period																		Safety Follow- up ^s
		0	1	4	8	12	16	17	19	21	25	27	29	33	37	39	41	45	48/ ETV	
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

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.

16. REFERENCES

Kim and Won, 2013

Adjusted proportion difference and confidence interval in stratified randomized trials.
PharmaSUG 2013 – Paper SP04.

17. REVISION HISTORY

Version	Issue Date	Summary of Changes
1.0	26APR2016	New Document
1.0	29JUN2016	Final Document Version 1