# STATISTICAL ANALYSIS PLAN

## DMB-3115-2

## A Randomized, Double-Blind, Multicentric, Parallel Group Therapeutic Equivalence Study Comparing Efficacy, Safety and Immunogenicity of Subcutaneous DMB-3115 and EU Sourced Stelara® in Patients with Moderate to Severe Chronic Plaque Psoriasis.

**AUTHOR:** [redacted]
**VERSION NUMBER AND DATE:** V1.0 21APR2022

# STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

Statistical Analysis Plan V1.0 (Dated 21 APR 2022) for Protocol DMB-3115-2

[redacted]

Upon review of this document, the undersigned approves this version of the, authorizing that the content is acceptable for the reporting of this study.

[redacted]

**Modification History**

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# 1. INTRODUCTION

This document describes the rules and conventions to be used in the presentation and analysis of safety, immunogenicity, pharmacokinetic (PK) data and efficacy data.

Current SAP has been generated based on Protocol No (DMB-3115-2)-Amedment-01 dated 04JUN 2021.

# 2. STUDY OBJECTIVES

## 2.1. PRIMARY OBJECTIVE

- To evaluate efficacy of DMB-3115 in comparison with Stelara sourced from the EU.

## 2.2. SECONDARY OBJECTIVES

- To evaluate safety, tolerability, PK, and immunogenicity of DMB-3115 in comparison with Stelara sourced from the EU.

## 2.3. EXPLORATORY OBJECTIVES

- Not Applicable.

# 3. STUDY DESIGN

## 3.1. GENERAL DESCRIPTION

This is a randomized, double-blind, multicentric, parallel group, and active controlled study comparing efficacy, safety and immunogenicity of subcutaneous administration of DMB-3115 and EU sourced Stelara in patients with moderate to severe chronic plaque psoriasis.

The study includes a screening period of up to 4 weeks followed by IP administration of up to Week 40 and last (EOS) assessment at Week 52.

After a screening period of up to 4 weeks, the eligible patients will be randomly assigned in a 1:1 ratio to receive treatment with either DMB-3115 or Stelara. Randomization will be stratified according to patient's body weight at baseline (≤100 kg or >100 kg), geographic region (EU, US or Rest of the World [ROW]) and the number of previous systemic therapies for psoriasis (<3 or ≥3).

The study will have 2 periods:

**Period 1**: In the Period 1 (from Week 0 to Week 28), patients will receive the assigned treatment (either DMB-3115 or Stelara) at Weeks 0, 4, and 16.

Patients who do not achieve at least Psoriasis Area and Severity Index (PASI) 50 response by Week 12 will be discontinued from further treatment with ustekinumab (either DMB-3115 or Stelara).

**Period 2**: In the Period 2 (from Week 28 to Week 52), patients randomized to receive DMB-3115 at the beginning of the study will continue to receive the same treatment up to Week 40 while patients randomized to receive Stelara at the beginning of the study will be re-randomized at Week 28 in a 1:1 ratio to either continue on Stelara or will be transitioned to receive DMB-3115 every 12 weeks up to Week 40 (i.e., 2 doses of investigational product [IP] after re-randomization).

The Doses at re-randomization (Week 28) for both DMB-3115 and Stelara would be reassigned based on body weight at Week 28 (≤100 kg or >100 kg). Patients receiving DMB-3115 will continue to receive DMB-3115 up to Week 40 but they will also follow the re-randomization procedure to ensure blinding. Blinding will be maintained throughout the study.

Only those patients who achieve at least Psoriasis Area and Severity Index (PASI) 75 response at Week 28 will be eligible for inclusion into the Period 2 of the study (Transition period: from Week 28 to Week 52).

Patients who do not achieve at least PASI 50 response by Week 12 or PASI 75 response by Week 28 will be discontinued from further treatment with Ustekinumab. These patients will remain in the study and be followed up to Week 52 for safety monitoring, including immunogenicity. For safety monitoring and immunogenicity in non-responders the following should be completed at follow-up visits: physical examination, vital signs, hematology and biochemistry laboratory tests, urine analysis, tuberculosis evaluation, anti-drug antibodies (ADA) blood sampling, electrocardiogram, pregnancy testing, and adverse events (AEs). All patients who discontinue treatment including non-responders will remain in the study and be followed up to Week 52 for safety monitoring, including immunogenicity.

Safety will be evaluated through an assessment of AEs, vital signs, electrocardiograms, and immunogenicity, along with clinical laboratory testing.

Number of Investigators and Study Sites:

Approximately 124 Investigators and sites are expected to participate in this study.

Number of Patients:

For primary efficacy analysis, the US FDA sample size of 490 patients in total, or 245 patients per treatment group at baseline, is selected

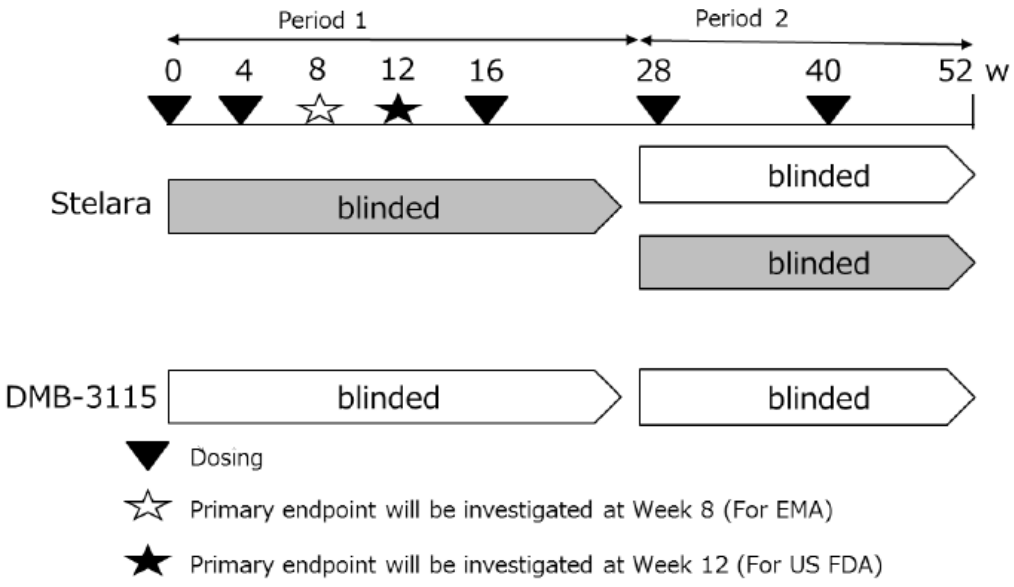
to achieve 392 evaluable patients to have a 90% CI for the difference in primary endpoint fall entirely within the 10% equivalence margin with more than 90% power.

Assuming a dropout rate of 20% in Period 1, 15% in Period 2, and considering the 1:1 re-randomization rate for Stelara arm in Period 2 and to meet the minimum requirement of safety analysis by EMA (N=100), 590 patients (a minimum of 400 completed patients) will be necessary in total.

Thus, 590 patients (295 patients per treatment group) will be enrolled.

Treatment Groups and Duration:

Two treatment groups (DMB-3115, and Stelara) in Period 1 and 3 treatment groups (DMB-3115, Stelara, and Stelara switched to DMB-3115) for Period 2. Patients who weigh ≤100 kg will receive an initial dose of 45 mg ustekinumab administered subcutaneously (either DMB-3115 or Stelara as assigned), followed by another 45 mg dose 4 weeks later, and then every 12 weeks thereafter (up to 40 weeks after randomization). Patients who weigh >100 kg will receive 90 mg doses as per same schedule. The doses at re-randomization (Week 28) would be assigned on the body weight at that time. The total duration of patient participation in the study will be up to 56 weeks.




Abbreviation: EMA = European Medicines Agency; US FDA = United States Food and Drug Administration; w = weeks

## 3.2. SCHEDULE OF EVENTS

Schedule of events can be found in Section 1.3 of the protocol.

## 3.3. CHANGES TO ANALYSIS FROM PROTOCOL

There will be additional sensitivity analysis conducted for COVID-19 affected subjects for which protocol will not be updated. COVID-19 analysis: As the pandemic started at the time of recruitment and as per regulatory requirement sensitivity analysis e.g. extended window, is planned for COVID-19 patients, if any.

Definition of Per Protocol set (EMA and USFDA) has been modified to indicate impact on primary efficacy analysis. Additional reasons which may impact primary endpoint has been added. Modifications for the same can be found in section 5.3 and 5.4.

Subgroup analyses of treatment group differences for assessing Percent change in PASI will be presented for the primary endpoint based on imputed data.

# 4. PLANNED ANALYSIS

## 4.1. INTERIM ANALYSIS

An interim analysis will be performed when all active patients complete the Week 28 assessment visit. The efficacy endpoints up to week 28 and all available safety, ADA and PK data will be analyzed using the analysis methods described in this plan and an interim clinical study report will be generated for submission to the regulatory agencies. A limited number of identified individuals of the Sponsor or CRO will be unblinded for the interim analysis. However, patients, Investigators, and other study personnel will remain blinded throughout the entire study period.

## 4.2. FINAL ANALYSIS

Final analysis will be performed when all active patients complete the Week 52 assessment visit. The efficacy endpoints up to week 52 and all available safety, ADA and PK data will be analyzed using the methods described in the analysis plan and a final CSR report will be generated for submission to the regulatory agencies.

# 5. ANALYSIS SETS

Agreement and authorization of subjects included/excluded from each analysis set will be conducted prior to the unblinding of the study.

## 5.1. SCREENED SET (SCR)

Consists of all subjects who provide informed consent for this study

## 5.2. INTENT-TO-TREAT SET (ITT)

All patients who have been randomized.

## 5.3. SAFETY SET (SAF)

Patients who randomize and receive at least one dose of the IP. The safety analysis will be conducted according to the treatment that a patient actually receives.

## 5.4. PER PROTOCOL ANALYSIS SET (PPS-EMA)

Patients who complete the study up to Week 8 and have no critical/major protocol deviations which may have a significant impact on primary endpoint analysis. All decisions related to exclusion of patients from the analysis set will be made prior to unblinding to the study.

Below are critical/major protocol deviations which may have a significant impact on primary endpoint analysis which are mentioned below and is not limited to:

- Missing PASI score (primary endpoint data) at Baseline or Week 8
- Not receiving at least one dose of IP (Compliance issue)
- Randomization error
- Subject does not meet any of inclusion criteria
- Subject meets any of the exclusion criteria
- Use of Prohibited medication/vaccine
- Other major protocol deviations which may have a significant impact on primary endpoint analysis

## 5.5. PER PROTOCOL ANALYSIS SET (PPS-US FDA)

Patients who complete the study up to Week 12 and have no critical/major protocol deviations which may have a significant impact on primary endpoint analysis. All decisions related to exclusion of patients from the analysis set will be made prior to unblinding to the study.

Below are critical/major protocol deviations which may have a significant impact on primary endpoint analysis which are mentioned below and is not limited to:

- Missing PASI score (primary endpoint data) at Baseline or Week 12
- Not receiving at least one dose of IP (Compliance issue)
- Randomization error
- Subject does not meet any of inclusion criteria
- Subject meets any of the exclusion criteria
- Use of Prohibited medication/vaccine
- Other major protocol deviations which may have a significant impact on primary endpoint analysis

## 5.6. PHARMAKOKINETIC SET (PK SET)

Patients who receive at least one dose of IP, have at least 1 measured concentration at a scheduled post dose PK time point, and have no major protocol deviations/events that may significantly affect the PK assessment. Pharmacokinetic data will be summarized based on the treatment a patient actually receives.

# 6. GENERAL CONSIDERATIONS

The following descriptive statistics will be presented in summary tables for non-PK data:

For continuous variables: the number of contributing observations (n), mean, standard deviation (SD), median, minimum, and maximum.

For categorical variables: the number and percentage of subjects in each category.

If the original data has N decimal places, then the summary statistics will have the following decimal places:

Minimum and maximum: N;

Mean, median, lower and upper bounds of two-sided CI: N + 1;

Percentage of subjects in each category, SD: N + 2

p-values will be presented with 4 decimal places

See Section 20 for descriptive statistics of PK data.

## 6.1. REFERENCE START DATE AND STUDY DAY

Study Day will be calculated from the reference start date and will be used to show start/stop day of assessments and events.

Reference start date is defined as the day of the first dose of study medication, (Day 1 is the day of the first dose of study medication) and will appear in every listing where an assessment date or event date appears.

If the date of the event is on or after the reference start date, then:

Study Day = (date of event – reference start date) + 1.

If the date of the event is prior to the reference start date, then:

Study Day = (date of event – reference start date).

In the situation where the event date is partial or missing, study day, and any corresponding durations will appear partial or missing in the listings.

## 6.2. BASELINE

Unless otherwise specified, baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments). In the case where the last non-missing measurement and the reference start date/time coincide, that measurement will be considered pre-baseline, but Adverse Events (AEs) and medications commencing on the reference start date will be considered post-baseline.

## 6.3. RETESTS, UNSCHEDULED VISITS AND EARLY TERMINATION DATA

In general, for by-visit summaries, data recorded at the nominal visit will be presented. Unscheduled measurements will not be included in by-visit summaries.

In the case of a retest (same visit number assigned), the latest available measurement for that visit will be used for by-visit summaries.

Early termination data will be mapped to the ET/End of Study Follow-Up visit for by-visit summaries.

Listings will include scheduled, unscheduled, retest and early discontinuation data.

## 6.4. STATISTICAL TESTS

Primary efficacy endpoint will be analyzed using an Analysis of Covariance (ANCOVA) at Week 8 (for EMA) and Week 12 (for US FDA).

Secondary efficacy endpoints will be analyzed using ANCOVA and logistic regression for protocol specified visits and supportive analysis to secondary efficacy endpoint for Period 2 will be performed using ANCOVA with Welch's test.

Primary and secondary efficacy endpoints will be analyzed with 95% CI (for EMA) and 90% CI (for US FDA). using ANCOVA and Logistic Regression. Confidence Interval, Standard Errors and P values will be provided based on ANCOVA Model Results.

Sensitivity and supportive analyses will be analyzed with 95% CI (for EMA) and 90% CI (for US FDA).

Subgroup analyses of treatment group differences for assessing Percent change in PASI will be analyzed using an ANCOVA for the primary endpoint at Week 8 (for EMA) and Week 12 (for US FDA).

## 6.5. COMMON CALCULATIONS

Unless otherwise specified, for quantitative measurements, change from baseline will be calculated as:

Test Value at Visit X – Baseline Value

## 6.6. SOFTWARE VERSION

Non-compartmental PK parameter calculations will be performed using Phoenix® WinNonlin® Version 8.3 or higher (Certara L.P., Princeton, New Jersey, USA. All other analyses will be conducted using SAS® software (version 9.4 or higher).

# 7. STATISTICAL CONSIDERATIONS

All data listings, summaries, and analyses will be performed under the guidance and approval of the Sponsor. Descriptive statistics will

be used for all variables, as appropriate. Continuous variables will be summarized by the number of observations, mean, standard deviation (SD), median, minimum, and maximum. Categorical variables will be summarized by frequency counts and percentages for each category. Unless otherwise stated, percentages will be calculated out of the total population for each treatment group.

## 7.1. ADJUSTMENTS FOR COVARIATES AND FACTORS TO BE INCLUDED IN ANALYSES

The following stratification factors are used in the analysis.

- Baseline body weight (≤100 kg or >100 kg).
- Geographic regions (EU, US or ROW).
- Number of previous systemic therapies for psoriasis (<3 or ≥3).

The following covariates are used in the analysis.

- Visit, and the treatment-by-visit interaction will be used as Fixed effects.
- Baseline PASI Score, Baseline PGA Score, Baseline DLQI Score will be used as Covariates.

For details of their inclusion in the models, see the specific analysis.

## 7.2. MISSING DATA

Missing values for primary efficacy variable and subgroup analysis (for Primary efficacy) in the ITT will be imputed by multiple imputation (MI) method. Additional details are provided under missing data methods for primary efficacy variables. Safety, missing PK or immunogenicity data will not be imputed. Missing PK concentrations will be handled as described in Section 20.

## 7.3. MULTIPLE COMPARISONS/ MULTIPLICITY

Not Applicable

# 8. DISPOSITION AND WITHDRAWALS

All subjects who provide informed consent will be accounted for in this study.

## 8.1. DISPOSITION

Subject disposition including the number of subjects screened, randomized, treated, completed as well as the number of dropouts along with the reasons for discontinuation will be tabulated for Screened Set (SCR).

A listing will be presented to describe date of screening, assigned treatment, completion or early withdrawal, and the reason for early discontinuation, if applicable, for each subject.

A disposition plot in terms of flowchart would be presented to capture all information pertaining to disposition.

# 9. DERIVATIONS

- BMI (kg/ $m^2$) = weight (kg)/ height $(m)^2$
- Percent change of PASI score (%) at visit x = (PASI score at visit baseline– PASI score at visit X)/ PASI score at baseline x* 100
- Coefficient of Variation (%)= (SD/Mean)*100

In case of baseline value equal to 0 and non-missing post-baseline value recorded, then the change is set to 0% for the corresponding visit.

- PASI50 at visit X:
  - Yes if percent change of PASI score at visit X ≥ 50
  - No if percent change of PASI score at visit X < 50
- PASI75 at visit X:
  - Yes if percent change of PASI score at visit X ≥ 75
  - No if percent change of PASI score at visit X < 75
- PASI90 at visit X:
  - Yes if percent change of PASI score at visit X ≥ 90
  - No if percent change of PASI score at visit X < 90
- PASI100 at visit X:
  - Yes if percent change of PASI score at visit X = 100

- No if percent change of PASI score at visit X < 100

# 10. PROTOCOL DEVIATIONS

Protocol deviations are the deviations from the procedure outlined in the protocol. All the Protocol Deviations (PDs) will be summarized using the ITT analysis set as obtained from Clinical Trial Management System (CTMS) logs. PDs will be identified and discussed with the Investigator/Sponsor in PD review discussion to categorize them, and to finalize analysis set assignment.

Any PDs will be categorized into critical, major and minor protocol deviations and will be summarized based on severity categories. Critical and Major protocol deviations having impact on primary analysis will be considered while finalizing the Per Protocol (PP) Analysis set. PDs log will be used for reporting purpose in tables. PDs will be summarized based on period 1 and period 2

# 11. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic data and other baseline characteristics will be summarized using the ITT and per-protocol set (EMA and US FDA).

No statistical testing will be carried out for demographic or other baseline characteristics.

Summary statistics will be provided for:

- Age (years)
- Weight (kg)
- Height (cm)
- BMI ($kg/m^2$)

Frequency and percentages will be provided for:

- Gender
- Ethnicity
- Race
- Patients body weight at baseline [≤100 kg or >100 kg]
- Geographic region [EU, US or ROW]

- Number of previous systemic therapies for psoriasis [<3 or ≥3]
- Number of subjects with PGA Score of 3 or more [3 or 4] at Baseline

Summary statistics under baseline characteristics will be provided for:

- PASI Score
- PGA Score
- DLQI Score
- Duration of plaque-type psoriasis (years)
- Percentage of Body surface area (BSA) affected by plaque-type psoriasis

Similarly, count and percentages will be provided for:

- HIV Status
- Hepatitis B Surface Antigen, Hepatitis B Core Antibody, Hepatitis C Virus Antibody
- Quantiferon Gold Test.
- Diagnosed with active or latent tuberculosis

Results collected at Baseline.

A listing of subject demographic data and other baseline characteristics will be presented.

# 12. MEDICAL HISTORY AND CONCOMITANT ILLNESS

Medical History and concomitant illness information will be summarized using the ITT analysis set. A listing of medical history and concomitant illness will be provided.

- Medical History and concomitant illness will be coded using the latest version of MedDRA Dictionary, according to the Data Coding Guidelines.
- Medical History conditions are defined as those conditions which stop prior to screening or at screening.
- Concomitant conditions/illnesses are defined as any medical conditions/illnesses that started before screening and were ongoing at screening or ended after screening.

- Presented by SOC and PT.

# 13. MEDICATIONS

All medications will be coded using the latest version of WHODrug Global B3. Each medication will be classified as prior medication if it is stopped prior to the first dose of IP, or concomitant medications defined as started prior to, on or after the first dose of study drug and started before the end of study drug and ended on or after the date of first dose of study drug or were ongoing at the end of the study drug.

Prior and concomitant medication will be summarized by Anatomical Therapeutic Chemical level 1 (ATC 1) and Anatomical Therapeutic Chemical level 2 (ATC 2) categories, and preferred name. Prior medications will be summarized using the ITT, and concomitant medications will be summarized using the SAF.

See Appendix 2 for handling of partial dates for medications, in the case where it is not possible to define a medication as prior, or concomitant, the medication will be classified by the worst case; i.e. concomitant.

# 14. STUDY MEDICATION EXPOSURE

Treatment groups in study listed as below:
Two treatment groups (DMB-3115, and Stelara) in Period 1 and 3 treatment groups (DMB-3115, Stelara, and Stelara switched to DMB-3115) for Period 2.

Exposure to study medication will be summarized by body weight (≤100kg and >100kg) for duration exposure, average dose at week and cumulative average dose (mg) for all weeks for the SAF. A listing will also be provided.

Duration of medication exposure (weeks)= (Date of last study medication administration – Date of first study medication administration+1)/7.

Duration of exposure (days)=Date of last dose of study drug -Date of first dose of study drug +1.

# 15. STUDY MEDICATION COMPLIANCE

- Compliance with trial medication will be based on the eCRF page “IP Administration”. An administered injection is considered when the question “Was Dose administered?” is answered “Yes”. Study medication compliance will be based on SAF.
- Compliance will be based on the comparison of actual administered injections and the planned usage. Compliance will include visits until treatment discontinuation.
- ‘Per visit’ compliance will be calculated as:

  Compliance at visit N = Yes if the question “Was Dose administered?” is answered “Yes”.

No else

Per visit compliance (%) = (Number of administered injections at visit x) *100/ (Planned number of injections at visit x)

- Overall' compliance will be calculated as follows:

  Overall compliance (%) = (Total Number of administered injections) *100/ (Total Planned number of injections)

# 16. ESTIMANDS

| Estimand | Definition | Attributes | | | |
|---|---|---|---|---|---|
| | | **Population** | **Variable/Endpoint** | **Intercurrent event handling strategy** | **Population-level summary measure** |
| Primary | DMB-3115/Stelara Dose | Population 1-Subjects who qualify under PPS Analysis set with Week 8 Assessments Regulatory Authority-EMA | Percent change in the Psoriasis Area and Severity Index (PASI) score from baseline to Week 8 (For EMA). | Not Applicable | [For EMA] 95% confidence interval of the difference (DMB-3115 - Stelara) in percent change in PASI at Week 8. |
| Primary | DMB-3115/Stelara Dose | Population 1-Subjects who qualify under ITT Analysis set with Week 12 Assessments Regulatory Authority-US FDA | Percent change in the Psoriasis Area and Severity Index (PASI) score from baseline to Week 12 (For US FDA). | Missing outcome at Week 12 will be imputed, using the Multiple Imputation at Week 12 | [For US-FDA] 90% confidence interval of the difference (DMB-3115 - Stelara) in percent change in PASI at Week 12. |

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# 17. EFFICACY OUTCOMES

## 17.1. PRIMARY EFFICACY

To evaluate efficacy of DMB-3115 in comparison with Stelara sourced from the EU.

### 17.1.1. PRIMARY EFFICACY VARIABLE(S)

The primary efficacy variable is

- Percent change in the Psoriasis Area and Severity Index (PASI) score from baseline to Week 8 (For EMA).
- Percent change in the PASI score from baseline to Week 12 (For US FDA).

### 17.1.2. MISSING DATA METHODS FOR PRIMARY EFFICACY VARIABLE(S)

Missing efficacy data for the primary endpoint will be handled using a Multiple Imputation (MI) procedure as follows:

Step 1- Creation of monotone missing data structure using 50 interactions (M), to ensure that the results do not suffer from a relative efficiency loss.

Intermediate (non-monotone) missing data (where some subjects may have missing records) will be imputed using the Markov Chain Monte Carlo (MCMC) method including treatment arm, PASI_Baseline, PASI_Week4, PASI_Week8, PASI_Week12, and assuming that the joint distribution of these variables is multivariate normal and the pattern for missing data is arbitrary. For this step the SAS procedure PROC MI with the MCMC option will be used

Step 2- Further imputations:

The datasets, now with monotone missing data, will be imputed further, in a stepwise manner to impute each week's PASI from Week 1 to Week 12 using the regression method (assuming missing at random). The model for each week will include terms for all the previous weeks and follow the structure of the following model for each visit.

### 17.1.3. PRIMARY ANALYSIS OF PRIMARY EFFICACY VARIABLE(S)

The primary objective of this study is to test the hypothesis that

$H_0$: $|\text{Treatment}_{(\text{DMB-3115})} - \text{Treatment}_{(\text{Stelara})}| \geq \delta$

Vs

$H_1$: $|Treatment_{(DMB\text{-}3115)} - Treatment_{(Stelara)}| < \delta$

Whereas $\delta$ is an equivalence margin which is defined as for EMA regulatory submission as [-15%, 15%] and for US FDA consider as [-10%, 10%].

The primary efficacy analysis will be performed for the PPS and the ITT analysis set for both regulatory submission (EMA at 8 week and US FDA at 12 week).

Primary Efficacy Analysis (for EMA)

- Percent change in PASI at Week 8 will be analyzed with a 95% CI for the difference in means using estimates from an ANCOVA model adjusted for baseline PASI score and the stratification factors (patient's body weight at baseline (≤100 kg or >100 kg), geographic region (EU, US or ROW) and the number of previous systemic therapies for psoriasis (<3 or ≥3)).
- Equivalence between the 2 treatment groups will be declared if the 95% CI of the mean difference is entirely contained within the pre-specified equivalence margin of (-15%, 15%).
- Analysis will be performed in the ITT and PPS. The PPS is the primary efficacy analysis population.
- Missing values for primary efficacy variable in the ITT will be imputed by MI method.

Primary Efficacy Analysis (for US FDA)

- Percent change in PASI at Week 12 will be analyzed with a 90% CI for the difference in means using estimates from an ANCOVA model adjusted for baseline PASI score and the stratification factors (patient's body weight at baseline (≤100 kg or >100 kg), geographic region (EU, US, or ROW) and the number of previous systemic therapies for psoriasis (<3 or ≥3).
- Equivalence between the 2 treatment groups will be declared if the 90% CI of the mean difference is entirely contained within the pre-specified equivalence margin of (-10%, 10%).
- Analysis will be performed in the ITT and PPS. The ITT is the primary efficacy analysis population.
- Missing values for primary efficacy variable in the ITT will be imputed by MI method.

# 17.2. SECONDARY EFFICACY

## 17.2.1 SECONDARY EFFICACY VARIABLES

**THE SECONDARY EFFICACY ANALYSES WILL BE PERFORMED FOR THE ITT.**

17.2.1.1. Percentage of patients with a PASI 50 (a 50% reduction in the PASI score) response at Weeks 4, 8, 12, 16, 28, 40, and 52.

17.2.1.2. Percentage of patients with a PASI 75 (a 75% reduction in the PASI score) response at Weeks 4, 8, 12, 16, 28, 40, and 52.

17.2.1.3. Percentage of patients with a PASI 90 (a 90% reduction in the PASI score) response at Weeks 4, 8, 12, 16, 28, 40, and 52.

17.2.1.4. Percentage of patients with a PASI 100 (a 100% reduction in the PASI score) response at Weeks 4, 8, 12, 16, 28, 40, and 52.

17.2.1.5. Percentage change in AUEC for the PASI score from baseline at Weeks 4, 8, 12, 16, 28, 40, and 52.

17.2.1.6. Percent change in the PASI score from baseline at Weeks 4, 8, 12, 16, 28, 40, and 52.

17.2.1.7. Percentage of patients with a Physician's Global Assessment (PGA) score of Cleared or Minimal at Weeks 4, 8, 12, 16, 28, 40, and 52.

17.2.1.8. Change from baseline in Dermatology Life Quality Index (DLQI) at Weeks 4, 8, 12, 16, 28, 40, and 52.

## 17.2.2. ANALYSIS OF SECONDARY EFFICACY VARIABLES

For Period 1 (Weeks 4, 8, 12, 16 and 28), analysis will be performed as mentioned below sections.

For Period 2 the descriptive statistics will be provided for each treatment group.

17.2.2.1. Analysis of Secondary Efficacy Endpoint- Psoriasis Area and Severity Index (PASI) Response

The analysis of secondary endpoint based on proportions will be analyzed using a logistic regression test with the baseline value, baseline body weight (≤100 kg or >100 kg), geographic region (EU, US or ROW), and the number of previous systemic therapies for psoriasis

(<3 or ≥3) as covariates.

An estimate of odds ratio of achieving PASI response of treatment group comparisons corresponding p-value and 90% CI (for US FDA) 95% CI (For EMA) for the odds ratio of treatment group comparisons will be given using Wald's test.

Then CI criteria is decided and calculated on the basis of regulatory submission (for US FDA-90% CI) and (for EMA - 95% CI).

#### 17.2.2.2. Analysis of Secondary Efficacy Endpoint- Area under effect curve (AUEC) for Psoriasis Area and Severity Index (PASI) score

Percentage change from baseline will be calculated at each timepoint based on PASI score and then below mentioned trapezoidal formula will be applied for AUEC calculation

$AUEC=\sum_{i=2} 1/2\ (M_{i-1}+M_i)*(t_i-t_{i-1})$; where i=2, …, k, $t_1=0$, and $M_1=0$

Each Trapezoidal value is added cumulatively and last observation at a given timepoint will be its AUEC value

Percent change of PASI value (%) at visit x = (PASI value at baseline – PASI score at visit X)/ PASI value at baseline x 100

Where m is the percent change of PASI Score and **t** is the timepoints for PASI Score. As per the above formula (trapezoidal rule) calculate the trapezoidal values for each timepoint.

The analysis of secondary endpoint will be analyzed using ANCOVA at Weeks 4, 8, 12, 16, 28, 40, and 52 with baseline PASI value, body weight (≤100 kg or >100 kg), geographic region (EU, US or ROW), and the number of previous systemic therapies for psoriasis (<3 or ≥3) as covariates.

Then Confidence Interval criteria is decided and calculated on the basis of regulatory submission (for US FDA-90% CI) and (for EMA - 95% CI).

#### 17.2.2.3. Analysis of Secondory Efficacy Endpoint -Psoriasis Area and Severity Index (PASI) Score

The analysis of secondary endpoint based on percentage change from baseline will be analyzed using ANCOVA at Weeks 4, 8, 12, 16, 28, 40, and 52 with baseline PASI score, body weight (≤100 kg or >100 kg), geographic region (EU, US or ROW), and the number of previous systemic therapies for psoriasis (<3 or ≥3) as covariates.

Then CI criteria is decided and calculated on the basis of regulatory submission (for US FDA-90% CI) and (for EMA - 95% CI).

#### 17.2.2.4. Analysis of Secondory Efficacy Endpoint- Physicians Global Assessment (PGA) .

Percentage of patients with a Physician's Global Assessment (PGA) score of Cleared or Minimal at Weeks 4, 8, 12, 16, 28, 40, and 52will be analyzed based on proportions using a logistic regression test with the baseline value, baseline body weight (≤100 kg or >100 kg), geographic region (EU, US or ROW), and the number of previous systemic therapies for psoriasis (<3 or ≥3) as covariates.

Then CI is decided and calculated on the basis of regulatory submission (for US FDA-90% CI) and (for EMA - 95% CI).

#### 17.2.2.5. Analysis of Secondory Efficacy Endpoint- Dermatology Life Quality Index (DLQI) .

Change from baseline in Dermatology Life Quality Index (DLQI) will be analyzed using ANCOVA at Weeks 4, 8, 12, 16, 28, 40, and 52 with baseline DLQI score, body weight (≤100 kg or >100 kg), geographic region (EU, US or ROW), and the number of previous systemic therapies for psoriasis (<3 or ≥3) as covariates.

Then CI criteria is decided and calculated on the basis of regulatory submission (for US FDA-90% CI) and (for EMA - 95% CI).

### 17.2.3. SENSITIVITY ANALYSIS OF PRIMARY EFFICACY VARIABLES

Percent change in PASI will be analyzed for each PPS and the ITT (EMA and US FDA) using a mixed linear model with treatment group, baseline body weight (≤100 kg or >100 kg), geographic region (EU, US or ROW), the number of previous systemic therapies for psoriasis (<3 or ≥3), visit, and the treatment-by-visit interaction as fixed effects and baseline PASI score as a covariate. The treatment mean difference at Week 8 (for EMA) and Week 12 (for US FDA), along with CI are calculated.

The variance-covariance matrix of unstructured form is used to model the correlation within each patient. If the Mixed Model with unstructured covariance fails to converge, a simpler covariance structure will be used selected by the AIC criterion.

Then Confidence Interval criteria is decided and calculated on the basis of regulatory submission (for US FDA-90% CI) and (for EMA - 95% CI).

### 17.2.4. SENSITIVITY ANALYSIS OF PRIMARY VARIABLES FOR SUBJECTS IMPACTED BY COVID-19

Percent change in PASI for COVID-19 confirmed subjects till Week 8 (for EMA) and Week 12 ( For US FDA) and subjects identified under COVID-19 impact log whose visit till Week 8 (for EMA) and Week 12 (For US FDA) will be analysed for each PPS and the ITT with a 95% CI (for EMA) and 90% CI (for US FDA) for the difference in means using estimates from an ANCOVA model adjusted for baseline PASI score and the stratification factors (patient's body weight at baseline (≤100 kg or >100 kg), geographic region (EU, US or ROW) and the number of previous systemic therapies for psoriasis (<3 or ≥3)).

Similar Analysis will be conducted for subjects excluding subjects impacted by COVID-19

Confidence Interval criteria is decided and calculated on the basis of regulatory submission (for US FDA-90% CI) and (for EMA - 95% CI).

### 17.2.5. SUPPORTIVE ANALYSIS TO SECONDARY ENDPOINT FOR PERIOD2

Percentage change in PASI score from baseline to Weeks 40 and 52 will be analyzed using ANCOVA with Welch's test with baseline PASI score, body weight (≤100 kg or >100 kg), geographic region (EU, US, or ROW), and the number of previous systemic therapies for psoriasis (<3 or ≥3) as covariates.

Then Confidence Interval criteria is decided and calculated on the basis of regulatory submission (for US FDA-90% CI) and (for EMA - 95% CI).

### 17.2.6. EXAMINATION OF SUBGROUPS

Subgroup analyses of treatment group differences for assessing Percent change in PASI will be presented for the primary endpoint based on imputed data.

The following subgroups will be assessed for endpoints which are specified above:

1. body weight at baseline (≤100 kg or >100 kg)
2. geographic region (EU, US or Rest of the World [ROW])
3. number of previous systemic therapies for psoriasis (<3 or ≥3)

Percent change in PASI will be analyzed for each PPS and ITT (EMA and US FDA).

Percent change in PASI will be analyzed with a 95% CI (for EMA) at Week 8 and 90% CI (for US FDA) at Week 12 for the difference in means using estimates from an ANCOVA model adjusted for baseline PASI score and the stratification factors (patient's body weight at baseline [≤100 kg, or >100 kg], geographic region [EU, US, or ROW] and the number of previous systemic therapies for psoriasis [<3 or ≥3]) except the subgroup factor being analyzed.

# 18. SAFETY OUTCOMES

There will be no statistical comparisons between the treatment groups for safety data, unless otherwise specified with the relevant section.

## 18.1. ADVERSE EVENTS

Adverse Events (AEs) will be coded using the latest version of MedDRA Dictionary.

Treatment emergent adverse events (TEAEs) are defined as:

- A new event that occurs during or after first dose of study treatment or,
- Any event present at baseline that worsens in either intensity or frequency after first dose of study treatment.

See Appendix 2 for handling of partial dates for AEs. In the case where it is not possible to define an AE as treatment emergent or not, the AE will be classified by the worst case; i.e. treatment emergent.

All Adverse Events started on the date of Week 28 dosing should be included in the Period 2.

Only TEAEs will be summarized on Safety Analysis Set (SAF).

An overall summary of number of subjects along with number of events within each of the categories described in the sub-section below, will be provided as specified in the templates.

Listings will include TEAEs and Non-TEAEs.

Adverse events will be presented for Period 1, Period 2 and Overall period (Week 0 ~Week 52)

### 18.1.1. ALL TEAEs

Incidence of TEAEs will be presented by System Organ Class (SOC) and Preferred Term (PT) and broken down further by relationship to study medication.

Incidence of Non-TEAEs will be presented by System Organ Class (SOC) and Preferred Term (PT)

#### 18.1.1.1. Intensity

Intensity will be classified according to CTCAE Grading V5.0 as (Grade1-Grade5).

If a subject report a TEAE more than once within that SOC/ PT, the AE with the worst-case severity will be used in the corresponding severity summaries.

• Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
• Grade 2: Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL).
• Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
• Grade 4: Life-threatening consequences; urgent intervention indicated.
• Grade 5: Death related to AE.
Adverse Events falling under Grades 3 to 5 are considered as Severe Adverse events.

#### 18.1.1.2. Relationship to Study Medication

Relationship as indicated by the Investigator, is classified as “Unrelated”, “Unlikely to be related”, “Possibly related”, “Probably related” or, “Not applicable”.

Probably related and Possibly related are considered as Related to study medication, Unlikely and Unrelated are considered as Unrelated to study medication.

- “Unrelated” is used if there is not a reasonable possibility that the study treatment caused the AE.
- “Unlikely to be related” suggests that only a remote connection exists between the study treatment and the AE. Other conditions, including chronic illness, progression or expression of the disease state or reaction to concomitant therapy, appear to explain the reported AE.
- “Possibly related” suggests that the association of the AE with the study treatment is unknown. However, the AE is not reasonably

supported by other conditions.

- "Probably related" conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

All efforts should be made to classify the AE according to the above categories.

- The category "not applicable" may be used for SAEs which happen prior to any procedures/dosing.

If a subject report the same AE more than once within that SOC/ PT, the AE with the maximum intensity to study medication will be used in the corresponding relationship summaries.

### 18.1.2. TEAEs Leading to Discontinuation of Study Medication

For TEAEs leading to permanent discontinuation of study medication, summaries of incidence rates (frequencies and percentages) by SOC and PT will be prepared.

TEAEs leading to permanent discontinuation of study medication will be identified by using the AE page ("Drug Withdrawn" chosen for "Action Taken with Study Treatment") of the (e)CRF.

### 18.1.3. TEAEs Leading to Withdrawal of Patients from Study

For TEAEs leading to withdrawal from study, summaries of incidence rates (frequencies and percentages) by SOC and PT will be prepared.

TEAEs leading to withdrawal of patients from study will be identified by using the AE page ("Drug Withdrawn" chosen for "Action Taken with Study Treatment", at the same time, "Yes" chosen for "Caused Study Discontinuation") of the (e)CRF.

### 18.1.4. Serious Adverse Events

Serious adverse events (SAEs) are those events recorded as" Serious" on the Adverse Events page of the (e)CRF. A summary of serious TEAEs by SOC and PT will be prepared. Listing for SAEs will also be provided.

### 18.1.5. Adverse Events Leading to Death

TEAEs leading to death are those events which are recorded as "Results in Death" on the Adverse Events page of the (e)CRF. A summary of TEAEs leading to death by SOC and PT will be prepared. Listing will also be provided.

### 18.1.6. ADVERSE EVENTS RELATED TO COVID-19

Adverse events occurring due to COVID-19 will be summarized by system organ class and preferred term. Adverse events occurring for COVID-19 patients also will be summarized by system organ class and preferred term.

AEs related to COVID-19: includes TEAEs, where the verbatim term contains key text “COVID”. TEAEs related to COVID-19 vaccine, where the verbatim term contains “disease related to COVID-19 vaccine” will not be included. Listing will also be provided.

### 18.1.7. ADVERSE EVENTS RELATED TO DEVICES DEFICIENCY

Adverse events occurring due to Device deficiency will be summarized based on relationship category recorded as the response to the question “Is this event associated/related with device(prefilled syringe) deficiency?” on the AE eCRF page, which is classified as Unrelated, Unlikely, Possible, Probable and Not applicable.

Listing related to adverse events due to device deficiency will be provided.

### 18.1.8. ADVERSE EVENTS OF SPECIAL INTEREST

Adverse Events of Special Interest (AESIs) are to have “Yes” recorded as the response to the question “Is the AE an Adverse event of special interest (AESI)?” on the AE eCRF page.

The following are considered as AESIs:

- Acquired immunodeficiency syndrome;
- Autoimmune disease;
- Cerebrovascular accident;
- Confirmed myocardial infarction;
- Congestive heart failure;
- Depression;
- Erythrodermic psoriasis;
- Facial palsy;
- Hematologic events (e.g., pancytopenia, aplastic anemia, or agranulocytosis);

- Hepatic injury: A hepatic injury is defined by the following alterations of hepatic laboratory parameters:
- An elevation of AST and/or ALT ≥3-fold ULN combined with an elevation of total bilirubin ≥2-fold ULN measured in the same blood draw sample, or
- An elevation of AST and/or ALT ≥3-fold ULN combined with an elevation of international normalized ratio (INR) >1.5, if INR measured, or
- Marked peak aminotransferase (ALT, and/or AST) elevations ≥10-fold ULN.
- These laboratory findings constitute a hepatic injury alert and the patients showing these laboratory abnormalities need to be followed up. In case of clinical symptoms of hepatic injury (icterus, unexplained encephalopathy, unexplained coagulopathy, right upper quadrant abdominal pain, etc.) without laboratory results (ALT, AST, and total bilirubin) available, the Investigator should make sure these parameters are analyzed, if necessary, in an unscheduled blood test. Hypersensitivity reactions；
- Injection Site Reactions: An injection site reaction is any unfavorable or unintended sign that occurs at the IP injection site. Any adverse reaction (e.g., pain, erythema, and/or induration) should be recorded on the AE page of the eCRF;
- Malignancies;
- Neurologic or demyelinating events (e.g., progressive multifocal leukoencephalopathy; peripheral demyelination; posterior reversible encephalopathy syndrome [reversible Posterior Leukoencephalopathy Syndrome, RPLS]); have been reported with the administration of Stelara. Reversible Posterior Leukoencephalopathy Syndrome is a neurological disorder, which is not caused by demyelination or a known infectious agent. Reversible Posterior Leukoencephalopathy Syndrome can present with headache, seizures, confusion and visual disturbances. Conditions with which it has been associated include preeclampsia, eclampsia, acute hypertension, cytotoxic agents, and immunosuppressive therapy. Fatal outcomes have been reported (Prescribing Information for Stelara). In case RPLS is suspected, the treatment with the IP should be discontinued and the patient should be referred to neurologist for full evaluation and appropriate treatment.
- Opportunistic infections;
- Pustular psoriasis;
- Transient ischemic attack ;
- Tuberculosis;
- Unexpected reaction to a vaccine (e.g., active infection by live-attenuated vaccine)

Summaries of Treatment emergent AESI incidence rates (number and percentage of patients) by AESI Category will be prepared. Listing

will also be provided.

## 18.2. DEATHS

If any subjects die during the study as recorded on the "deaths" page of the (e)CRF, the information will be presented in a summary table and a data listing.

Following summaries will be generated.

Number (%) of patients who died during study period (TEAE, on-study) and reasons for death summarized for the SAF by treatment received.

Death in nonrandomized patients or randomized and not treated patients will be listed.

## 18.3. LABORATORY EVALUATIONS

Results from the central laboratory and local laboratory will be included in the reporting of this study for Hematology, Blood Chemistry, Coagulation and Urinalysis.

Quantitative laboratory measurements reported as "< X", i.e. below the lower limit of quantification (BLQ), or "> X", i.e. above the upper limit of quantification (ULQ), will be converted to X for the purpose of quantitative summaries, but will be presented as recorded, i.e. as "< X" or "> X" in the listings.

The following summaries and plot will be provided for laboratory data:

- Actual and change from baseline by visit (for quantitative measurements)
- Laboratory shift from Baseline
- Boxplot for Actual and change from baseline by visit for Hematology, Biochemistry and Coagulation (for quantitative measurements)
- Listing of subjects meeting clinically abnormal criteria
- Spaghetti plot for Hepatic Injury (Liver Enzyme Profile) for Subjects with Treatment-Emergent Abnormalities. Treatment Emergent abnormalities for hepatic injury is defined as below:
- An elevation of AST and/or ALT ≥3-fold ULN combined with an elevation of total bilirubin ≥2-fold ULN measured in the same blood draw sample or

- An elevation of AST and/or ALT ≥3-fold ULN combined with an elevation of international normalized ratio (INR) >1.5, if INR measured, or
- Marked peak aminotransferase (ALT, and/or AST) elevations ≥10-fold ULN
- eDish Plot for total bilirubin versus ALT will be presented for possible Hy's Law cases.

### 18.3.1. LABORATORY REFERENCE RANGES CRITERIA

Quantitative laboratory measurements will be compared with the relevant laboratory reference ranges in SI units and categorized as:

- Low: Below the lower limit of the laboratory reference range.
- Normal: Within the laboratory reference range (upper and lower limit included).
- High: Above the upper limit of the laboratory reference range.

## 18.4. ECG EVALUATIONS

Results from the central ECG (Electrocardiogram) Reading Centre will be included in the reporting of this study. Results for ECG will be presented under SAF.

The following ECG parameters will be reported for this study:

- PQ Interval (PR) (msec)
- QRS Interval (msec)
- QT Interval (msec)
- QTc Interval (msec)
- QTcF Interval (msec) [derived]
- QTcB Interval (msec) [derived]
- HR (bpm)
- Overall assessment of ECG (Investigator's judgment):
- Normal

- Abnormal, Not Clinically Significant (NCS)
- Abnormal, Clinically Significant (CS)
- The following summaries will be provided for ECG data:
- Actual and change from baseline by visit (for quantitative measurements)
- Listing of subjects meeting markedly abnormal criteria

### 18.4.1. ECG MARKEDLY ABNORMAL CRITERIA

All ECG data results (normal/abnormal) will be summarized using frequency and percentages for discrete variables. Clinically significant abnormalities will be presented in by-patient listings.

## 18.5. VITAL SIGNS

Results for Vital Signs will be presented under SAF. The following Vital Signs measurements will be reported for this study:

- Systolic Blood Pressure (mmHg)
- Diastolic Blood Pressure (mmHg)
- Pulse Rate (beats/min)
- Body Temperature (°C)
- Height (cm)
- Weight (kg)
- BMI ($kg/m^2$)

- Body temperature collected °F will be converted to °C as follows:
- °C = (°F − 32) * 5/9

The following summaries will be provided for vital signs data:

- Actual and change from baseline by visit
- Listing capturing vital signs of Patients.

## 18.6. PHYSICAL EXAMINATION

Physical examination findings as collected in eCRF and associated abnormalities, along with clinical significance will be tabulated and presented in the listings on SAF.

The following summaries will be provided for physical examination data:

- Incidence of abnormalities by visit.
- Shift from Baseline.

## 18.7. OTHER SAFETY ASSESSMENTS

Results for other safety assessments will be presented under SAF unless specified otherwise.

A chest X-ray (both posterior-anterior and lateral views) is required unless available within 12 weeks prior to the first administration of IP and should be read by a qualified radiologist or pulmonologist to evaluate signs of active TB or history of TB.

A summary table and listing of TB assessment will be presented, Similarly Listing for Chest X-Ray will also be provided. Listing of Injection site reaction indicating findings will be provided.

A listing of COVID-19 Impact log will be provided to indicate the assessment procedure, visit, type of impact. Reason of Impact and any additional information due to which assessment was affected would be provided. This listing will be based on ITT population.

A listing will be provided for female subjects for Pregnancy Test. Details indicating test type (Serum/Urine) and Test results would be provided.

# 19. IMMUNOGENICITY ANALYSIS

Venous blood samples of approximately 50 mL will be collected during the study for measurement of ADA (binding and/or neutralizing). Each serum sample will be divided into 10 aliquots (5 for ADA, 3 for neutralizing antibodies and 2 back-up). A tiered approach will be followed for assessing antibody formation in response to ustekinumab administration. All samples will be screened for occurrence of binding antibodies to ustekinumab.

Those samples that test positive will be subjected to a confirmatory assay. Samples that are positive on confirmatory assay will be further tested for neutralizing potential and subjected to titration analysis.

Results for Immunogenicity analysis will be presented under SAF. The following analyses will be performed: Number and frequency of subjects with ADA / neutralizing ADA sampling results by actual treatment arm and visit

- Negative
- Positive

The incidence of ADAs and neutralizing antibodies will be summarized by treatment group and visit and listed. Descriptive statistics for Binding and Neutralizing antibody titer will be provided for all available parameters at protocol specified visits using Number of subjects available at each assessment visit, Arithmetic Mean, Median, Minimum Maximum, quartiles and Geometric Mean. Summaries for both Actual and change from baseline will be presented. For geometric mean, the mean and the 95% CIs will be calculated on Log10 (titers/data), with subsequent antilog transformations applied.

Incidence of ADA and Nabs will be summarized based on Period 1, Period 2 and overall period (Week0 to Week 52).

# 20. PHARMACOKINETICS

Changes to the procedures or events which may impact the quality of the PK data will be considered important protocol deviations or events and will be described within the clinical study report body text. These changes or events will include any circumstances that will alter the evaluation of the PK. Examples of deviations/events for PK include but may not be limited to sample processing errors that lead to inaccurate bioanalytical results, use of disallowed medications affecting PK, and/or inaccurate or incomplete dosing. Important deviations/events may potentially affect as little as a single data record (e.g. sample processing error) or an entire concentration-time profile. In the case of a significant protocol deviation or event with impact on PK, the affected PK data will be excluded from PK analysis and/or descriptive statistics, as appropriate. Other changes to the procedures or events which do not impact the quality of the PK data will not be considered important protocol deviations. A common example of a protocol deviation which is not considered to be important is a missed blood sample or deviations from blood collection times at a non-critical time in the profile; such deviations may sometimes be adjusted for in the analysis, if appropriate, but will not result in exclusion of data from analysis.

All PK concentrations will be reported and analyzed with the same precision as the source data provided by the bioanalytical laboratory regardless of how many significant figures or decimals the data carry. Derived PK parameters will be rounded for reporting purposes in by-subject listings. Summary statistics of derived PK parameters will be performed by using the unrounded values and the statistical results will be rounded for reporting purposes.

For most derived PK parameters, 3 significant digits will be used as the standard rounding procedure for reporting, with the following exceptions:

- Parameters directly derived from source data (e.g. $C_{max}$) will be reported and analyzed with the same precision as the source data.
- Parameters derived from actual elapsed sample collection times (e.g. $t_{max}$) will be reported with a precision of 2 decimal places.

For the reporting of descriptive statistics, the means and SD will be presented to one digit more precision than the source data. The minimum, median, and maximum will be presented to the same precision as the source data. Coefficients of variation will always be reported to 1 decimal place.

## 20.1. SERUM CONCENTRATIONS

Subjects with partial data will be evaluated on a case-by-case basis to determine if sufficient data are available for reliable estimation of PK parameters.

A listing of PK blood sample collection times as well as derived sampling time deviations will be provided. Plasma concentrations will be summarized for each treatment and measurement time using descriptive statistics including n, mean, SD, coefficient of variation (CV%), median, minimum, and maximum. Concentration summaries by treatment and body weight category (Week 0 to Week 28 only) will also be provided. Concentration summaries by treatment and ADA status (binding and neutralizing) will also be provided. For these summaries, a subject's ADA status will be classified 2 ways: (1) An Overall categorization will be used where a subject's status will be classified as positive if they have a positive result at any time over 0- to 52-week measurement period; otherwise it will be classified as negative. (2) A by-time-point categorization will be used where a subject's status will be classified at each time point based on whether they have a positive or negative result at that time point; if there is no antibody measurement at a time point or if the antibody result is missing or inconclusive, the last reliable result will be carried forward to this time point.

Concentrations that are below the limit of quantitation (BLQ) will be treated as zero for the computation of descriptive statistics. Samples that are collected outside the protocol-specified windows (Table 1 of the protocol) will be excluded from descriptive statistics. A subject listing of all concentration-time data for each treatment will be presented. For subjects who switch from Stelara to DMB-3115 treatment at Week 28, concentrations up to and including Week 28 will be summarized under Stelara treatment, but post-Week 28 concentrations will be listed and summarized separately.

Figures of arithmetic mean concentration-time data (±SD on linear plot) will be presented for each treatment on linear and semi-logarithmic scales for the 0- to 4-week period. Figures of arithmetic mean (±SD) concentration-time data will also be presented for each treatment on linear scale for the 0- to 52-week period (separate figures will show subjects who switched from Stelara to DMB-3115 at Week 28 either included or excluded for time points beyond Week 28). Similar figures will also be included which further subset these treatments by ADA status (binding and neutralizing). Arithmetic mean figures by treatment and body weight category (Week 0 to Week 28) will also be provided. Individual subject concentration-time data will be graphically presented on linear and semi-logarithmic scales (0- to 4-week period) and linear scale (0- to 52-week period). Individual concentrations which are BLQ will be displayed as zero in the graphic presentations on linear scale, but will not be plotted on semi-logarithmic scale. Means which fall below the LLOQ will be

displayed as zero in the graphic presentations on linear scale, but will not be plotted on semi-logarithmic scale.

Handling of the concentration-time profiles for statistical summaries with anomalous predose concentrations of greater than 5.00% of $C_{max}$ prior to the first dose will follow the handling conventions of the PK parameters as described in Section 20.2.

## 20.2. SERUM PARAMETERS

Pharmacokinetic parameters will be calculated for the first dose. For PK parameter calculations, predose samples that are BLQ or missing will be assigned a numerical value of zero. Any other BLQ concentrations will be assigned a value of zero if they precede quantifiable samples in the initial portion of the profile. A BLQ value that occurs between quantifiable data points, especially prior to $C_{max}$, will be evaluated to determine if an assigned concentration of zero makes sense, or if exclusion of the data is warranted. Following $C_{max}$, BLQ values embedded between 2 quantifiable data points will be treated as missing when calculating PK parameters. If a BLQ value occurs at the end of the collection interval (after the last quantifiable concentration), it will be treated as zero. If consecutive BLQ concentrations are followed by quantifiable concentrations in the terminal portion of the concentration curve, these quantified values will be excluded from the PK analysis by setting them to missing, unless otherwise warranted by the concentration-time profile.

Any anomalous concentration values observed prior to the first dose will be identified in the study report and used for the computation of PK parameters. If the anomalous concentration is greater than 5.00% of $C_{max}$ (when rounded to 3 significant digits), the PK parameters for the affected subject profile will be calculated and reported in the listing but excluded from statistical summaries and analyses. Similarly, PK concentrations for the affected profile will be excluded from statistical summaries.

The following PK parameters will be estimated for the first dose (Week 0) by non-compartmental methods using actual elapsed time from dosing (rounded to 2 decimal places). A minimum of 3 quantifiable concentration-time data points will be required for calculation of PK parameters).

| | |
|---|---|
| $C_{max}$ | Maximum concentration, obtained directly from the observed concentration versus time data. |
| $t_{max}$ | Time of maximum concentration, obtained directly from the observed concentration versus time data. |
| $AUC_{(w0\text{-}w4)}$ | Area under the concentration-time curve from Week 0 (predose) to Week 4, calculated by linear up/log down trapezoidal summation. Actual elapsed time and associated concentration at Week 4 will be used for the calculation. If the Week-4 sample is collected outside the protocol-specified window (see Table 1 of protocol), the $AUC_{(w0\text{-}w4)}$ for the affected subject profile will be calculated and reported in the listing but excluded from statistical summaries and analyses. |

Pharmacokinetic parameters except $t_{max}$ will be summarized by treatment using descriptive statistics including n, mean, SD, CV%, median, minimum, maximum, geometric mean and geometric CV%. For $t_{max}$, only n, median, minimum, and maximum will be presented. Summaries by treatment and body weight category will also be provided. A subject listing of individual PK parameters for each treatment will be provided.

Box plots of $C_{max}$ and $AUC_{(w0\text{-}w4)}$ versus treatment will be presented. Figures by treatment and body weight category will also be provided.

# 21. DATA NOT SUMMARIZED OR PRESENTED

The other variables and/or domains not summarized or presented are:

- Comments
- These domains and/or variables will not be summarized or presented, but will be available in the clinical study database, SDTM and/or ADaM datasets.

# 22. REFERENCES

- http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/09/WC500096793.pdf

Little, R., & Yau, L. (1996). Intent-to-Treat Analysis for Longitudinal Studies with Drop-Outs. *Biometrics* , vol 52, 1324-1333.

- UZA82634-DMB-3115-2_Protocol_Amendment_v1_4Jun21-0001
- UZA82634_DMB-3115-2_CRF Finalt_V5.0.
- (Van Buuren, 2012 cited by Patricia Berglund and Steven Heeringa in Multiple imputation using SAS 2014.):

# APPENDIX 1. PROGRAMMING CONVENTIONS FOR OUTPUTS

[redacted]

## DATES & TIMES

Depending on data available, dates and times will take the DDMMMYYYY Thh:mm:ss.

## SPELLING FORMAT

English US (or English UK)

## LISTINGS

All listings will be ordered by the following (unless otherwise indicated in the template):

- Center-subject ID,
- Randomized treatment group (or treatment received if it's a safety output)
- Date (where applicable),
- For listings where non-randomized subjects are included, these will appear in a category after the randomized treatment groups labeled 'Not Randomized'.

## OUTPUT PRESENTATIONS

The templates provided with this SAP describe the presentations for this study and therefore the format and content of the summary tables, figures and listings to be provided by [redacted]

All visit assessments will be presented according to the nominal visit name.

# APPENDIX 2. PARTIAL DATE CONVENTIONS

Imputed dates will NOT be presented in the listings.

## ALGORITHM FOR TREATMENT EMERGENCE OF ADVERSE EVENTS:

| START DATE | STOP DATE | ACTION |
|---|---|---|
| Known | Known/Partial/ Missing | If start date < study med start date, then not TEAE<br>If start date ≥ study med start date, then TEAE |
| | | |
| Partial, but known components show that it cannot be on or after study med start date | Known/Partial/ Missing | Not TEAE |
| | | |
| Partial, could be on or after study med start date OR Missing | Known | If stop date < study med start date, then not TEAE<br>If stop date ≥ study med start date, then TEAE |
| | Partial | Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then:<br>If stop date < study med start date, then not TEAE<br>If stop date ≥ study med start date, then TEAE |
| | Missing | Assumed TEAE |
| | | |

## ALGORITHM FOR PRIOR / CONCOMITANT MEDICATIONS:

| START DATE | STOP DATE | ACTION |
|---|---|---|
| Known | Known | If stop date < study med start date, assign as prior<br><br>If stop date ≥ study med start date and start date ≤ end of treatment, assign as concomitant<br><br>If stop date ≥ study med start date and start date > end of treatment, assign as post treatment |
| | Partial | Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then:<br><br>If stop date < study med start date, assign as prior<br><br>If stop date ≥ study med start date and start date ≤ end of treatment, assign as concomitant<br><br>If stop date ≥ study med start date and start date > end of treatment, assign as post treatment |
| | Missing | If stop date is missing could never be assumed a prior medication<br><br>If start date ≤ end of treatment, assign as concomitant<br><br>If start date > end of treatment, assign as post treatment |
| | | |
| Partial | Known | Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then:<br><br>If stop date < study med start date, assign as prior<br><br>If stop date ≥ study med start date and start date ≤ end of treatment, assign as concomitant<br><br>If stop date ≥ study med start date and start date > end of treatment, assign as post treatment |

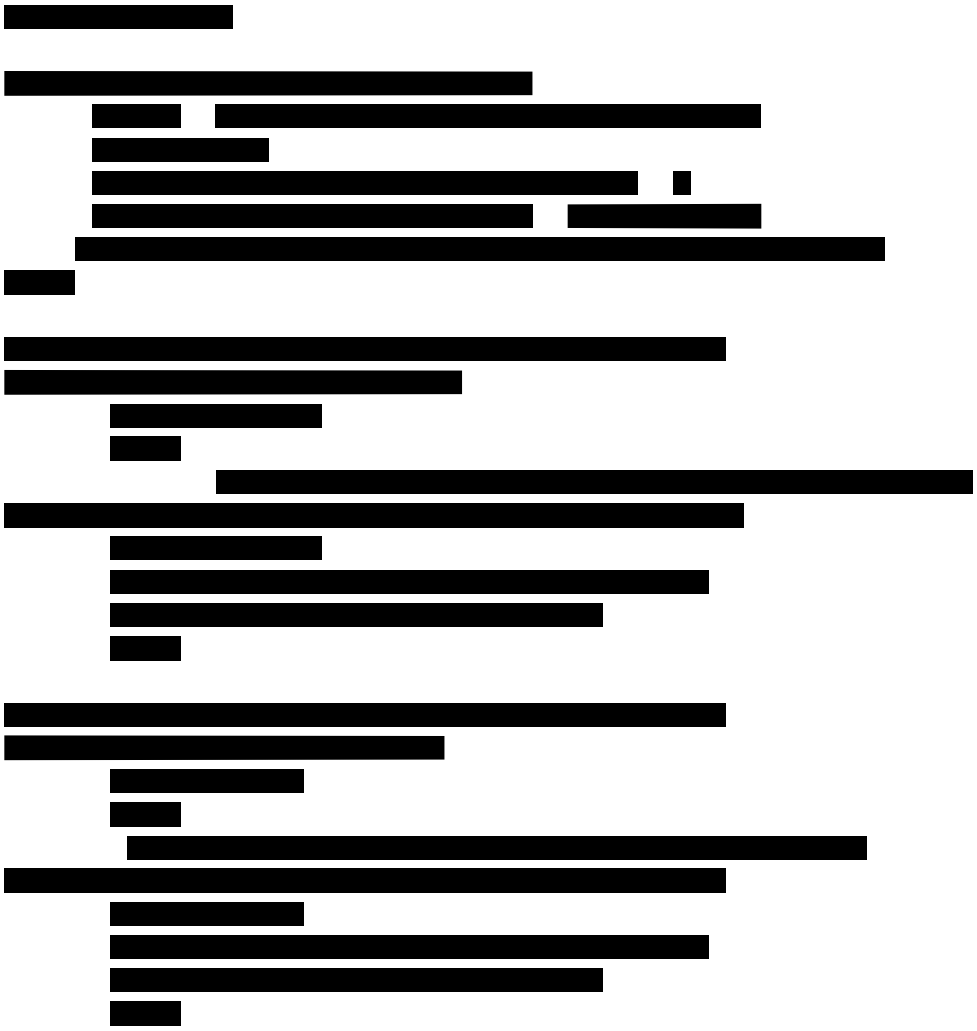
| START DATE | STOP DATE | ACTION |
|---|---|---|
| | Partial | Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown) and impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then:<br>If stop date < study med start date, assign as prior<br>If stop date ≥ study med start date and start date ≤ end of treatment, assign as concomitant<br>If stop date ≥ study med start date and start date > end of treatment, assign as post treatment |
| | Missing | Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then:<br>If stop date is missing could never be assumed a prior medication<br>If start date ≤ end of treatment, assign as concomitant<br>If start date > end of treatment, assign as post treatment |
| | | |
| Missing | Known | If stop date < study med start date, assign as prior<br>If stop date ≥ study med start date, assign as concomitant<br>Cannot be assigned as 'post treatment' |
| | Partial | Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then:<br>If stop date < study med start date, assign as prior<br>If stop date ≥ study med start date, assign as concomitant<br>Cannot be assigned as 'post treatment' |
| | Missing | Assign as concomitant |

# APPENDIX 3. SAMPLE CODES

## MULTIPLE IMPUTATIONS FOR DATASETS

[redacted]

# SAMPLE CODES FOR PRIMARY EFFICACY(MULTIPLE IMPUTATIONS)



Sample codes mixed model

[redacted]