TITLE PAGE

Protocol Title:

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.

Protocol Number: DMB-3115-2

Amendment Number: 01

Product: Ustekinumab

Short Title:

Efficacy, Safety, and Immunogenicity of Subcutaneous DMB-3115 Versus EU Sourced Stelara® in Patients with Moderate to Severe Chronic Plaque Psoriasis.

Study Phase: Phase III

Sponsor Name: Dong-A ST Co. Ltd., Republic of Korea

Legal Registered Address:

64 Cheonho-daero, Dongdaemun-gu, Seoul, 02587, Republic of Korea

Regulatory Agency Identifying Number(s):

IND Number: [redacted]

EudraCT number: [redacted]

Date of Protocol: 04 June 2021 (Final)

Sponsor Signatory:

I have read this protocol in its entirety and agree to conduct the study accordingly:

[redacted]

Medical Monitor name and contact information can be found in Appendix 2.

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

Table A Document History

Document	Date	Substantial	Region
Amendment 01	04-Jun-2021	Yes	Global
Original Protocol	07-Dec-2020		Global

Amendment 01

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

The overall rationale for this amendment is to implement changes following regulatory authorities/ethic committees' recommendations/feedback. Additional clarifications and corrections are added. Details on the changes and rationale are provided in Table B Description of Changes in Amendment.

Table B Description of Changes in Amendment

Section # and Name	Description of Change	Brief Rationale
Section 1.1: Synopsis Section 1.3: Schedule of Activities Section 3.0: Objectives and Endpoints	The pharmacokinetic endpoint was updated to include 'post dose for 24 hours' timepoint.	Wording updated to clarify timepoints.
Section 1.1: Synopsis 1.3: Schedule of Activities Section 4.1: Overall design Section 7.1: Discontinuation of Study Treatment	Overall design (Period 1) has been updated to include: Patients who do not achieve Psoriasis Area and Severity Index (PASI) 50 response by Week 12 will be discontinued from the study treatment with ustekinumab (either DMB-3115 or Stelara).	To implement Food and Drug Administration (FDA) recommendation "Only patients who achieve at least PASI 50 at Week 12 be eligible for continued treatment".
Section 1.1: Synopsis 1.3: Schedule of Activities	Checking (✓) mark for Non-responder evaluation Week 12 Visit 8.	Added in line with new discontinuation criteria PASI 50 at Week 12.
Section 1.1: Synopsis Section 4.1: Overall Design	In Period 2, the text has been added regarding the re-stratification of the patients based on the body weight at Week 28 (≤100 kg or >100 kg). The following text has also been added to Period 2: The doses at re-randomization	To clarify process in line with Interactive Response Technology (IRT) system specifications.

Section # and Name	Description of Change	Brief Rationale
	(Week 28) for both DMB-3115 and Stelara would be re-assigned based on the 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 in order to maintain blinding.	
Section 1.1: Synopsis	Number of Investigators and Study Sites updated from 90 to 124.	The change was made to be in alignment with an actual plan.
Section 1.3: Schedule of Activities Appendix 3: Clinical Laboratory Tests	Laboratory blood tests row was revised to include the erythrocytes sedimentation rate (ESR), which will be done locally with the kits provided by the central laboratory.	Correction of original protocol wording due to error.
	Glucose updated to Glucose (fasting status not mandatory).	In alignment with the Schedule of Activities and Informed Consent.
	'Direct bilirubin' has been included in the Chemistry panel.	Added as per the inclusion criteria 10 and as per central laboratory set-up.
Section 5.2: Exclusion Criteria	Notes added for Exclusion criteria #5 and #6.	To clarify the wash-out period for the treatments that falls under Exclusion criteria #4, #5, and #6.
	Exclusion criteria number 19 has been revised to exclude active malignancy patients.	To clarify that current malignancy is also to be excluded.
	Exclusion criteria number 24 has been clarified for patients with evidence of latent infection (at baseline positive TB test but negative chest X-ray).	To implement FDA recommendation "Screening all subjects for TB at baseline. Subjects with a positive TB test should be evaluated for presence of active TB. Subjects with a baseline positive TB test but negative chest X-ray may be enrolled into the trial following initiation of appropriate treatment for latent tuberculosis."
Section 6.1.2: Drug Delivery Device Component Section 8.3.7: Medical Device Deficiencies	The following text has been added: The regulatory considerations regarding the device component are governed by applicable directives and regulations and/or country legislation. The pre-filled syringe (PFS) does not fall under the current definition of a medical device in the European Union (EU).	To clarify that PFS is not a medical device in the EU. As per medical devices and in vitro diagnostic medical devices Regulations (EU) 2017/745 and (EU) 2017/746.
Section 6.3: Measures to Minimize Bias: Randomization and Blinding	Assignment of 6-digit number as Subject Number or Subject ID at screening visit, has been added to delete 'randomization number' assigned on screening visits.	Updated in line with other study documents.

Section # and Name	Description of Change	Brief Rationale
	Following text has been updated: Patients who achieve at least PASI 50 response by Week 12 and PASI 75 response at Week 28 will continue on the study.	Updated the text to be consistent with the new added criteria of 'discontinuation criteria PASI 50 at Week 12'
Section 6.5: Concomitant Therapy	The concomitant therapy has been updated to include following points: This includes topical products such as moisturizing creams, emollients, and dressings as part of wound care with an exception of salicylic acid, lactic acid, urea, alpha-hydroxy or fruit acids.	Text added to clarify that topical products as part of wound care are allowed during the study, following questions from the ethics committees/regulatory authorities.
	Text has been added to include the COVID-19 vaccines.	Text added to clarify on the use of the COVID-19 vaccines.
Section 7.1: Discontinuation of Study Treatment	Discontinuation criteria has been updated to include 'any female patient who becomes pregnant while participating in the study'.	Added in alignment with Appendix 6.
Section 7.1: Discontinuation of Study Treatment Section 8.2.5: Tuberculosis Evaluation	Discontinuation criteria has been updated to include, 'the patient diagnosed with active TB during study participation'.	Added clarification following FDA recommendation.
Section 7.1: Discontinuation of Study Treatment Section 2.3 Benefit/Risk Assessment Table 2	Word 'treatment' has been added at the end of the sentence (Study **treatment**) in criteria 9i in the list of 'Patients who will be removed from the study treatment by the Investigator'.	Text updated to clarify that the patient will be discontinued from the study treatment only and will not be discontinued from the study.
Section 7.1: Discontinuation of Study Treatment	List of 'Patients who can be removed from the study treatment by the Investigator', has been updated to include, 'the patient diagnosed with latent TB during the study participation'.	Text updated in line with Section 8.2.5.
Section 8.2.1: Physical Examinations	Assessment of 'dermatology' has been included in complete physical examination.	Added as per the eCRF set-up.
Section 8.3.6: Adverse Events of Special Interest	Modification to the hepatic injury: An elevation of AST and/or ALT≥3-fold upper limit of normal (ULN) combined with an elevation of total bilirubin ≥2-fold ULN measured in the same blood draw sample Following hepatic injury criteria has been added: An elevation of AST and/or ALT ≥3 fold ULN combined with an	To maintain the consistency between the Section 8.3.6 and Appendix 3.

Section # and Name	Description of Change	Brief Rationale
	elevation of international normalized ratio (INR) >1.5, if INR measured,	
Section 8.3.7: Medical Device Deficiencies	Updated the form name 'Medical Device Deficiency Report form'.	The Medical Device Deficiency Report Form is not the form included in the CRF, so the name was revised.
Section 8.3.7.3: Prompt Reporting of Medical Device Deficiencies to Sponsor	The timeline was updated for the prompt reporting of Medical Device Deficiencies. 3rd point has been added to apply the timeline specified in original 1st point to the device malfunction/deficiency associated with an SAE. 4th point regarding the timelines of the other cases of medical device malfunction/deficiency has been added.	To correct reporting timelines for device malfunction/deficiencies.
Section 8.3.8: Serious Adverse Device Effect Reporting	The 1st point has been revised as follows: Any device malfunction/deficiency associated with an SAE should be reported to Sponsor or designee within 24 hours after the Investigator determines that the event meets the protocol definition of a device deficiency. (In addition, eCRF must be completed within 24 hours of the Investigator being aware of the SAE).	To add the timeline for the completion of the eCRF.
Section 10: References	Details of the references for Stelara EU Summary Product Characteristics and the product IB's were updated in the reference list.	Updated the reference list with latest available updated.
Appendix 3	Footnote 'a' to the Table 10 has been revised to include the following to Severe liver hepatic criteria: All events of (1) AST and/or ALT ≥3 × ULN combined with total bilirubin ≥2 × ULN or (2) AST and/or ALT ≥3 × ULN combined with international normalized ratio (INR) >1.5, if INR measured and (3) Marked peak aminotransferase (ALT, and/or AST) elevations ≥10-fold ULN, which may indicate severe hepatic injury (possible Hy's Law), must be reported as an SAE.	To maintain consistency with Section 8.3.6.
Throughout the document	Minor editorial changes (e.g., deletion of duplicate sentence in Section 8.0).	Minor changes.

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1.0 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: 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.

Short Title: Efficacy, Safety and Immunogenicity of Subcutaneous DMB-3115 Versus EU Sourced Stelara® in Patients with Moderate to Severe Chronic Plaque Psoriasis.

Rationale:

Ustekinumab is a human Immunoglobulin G1kappa monoclonal antibody and a human interleukin-12 and -23 antagonist.

DMB-3115 is being developed by Dong-A ST (co-development partner: Meiji Seika Pharma) as a proposed biosimilar to Stelara® marketed by Janssen-Cilag in the United States (US) and European Union (EU).

This study is designed to evaluate efficacy, safety, pharmacokinetics (PK) and immunogenicity of subcutaneously (SC) administered DMB-3115 in comparison with EU sourced Stelara® (hereafter referred to as Stelara) for treatment of moderate to severe chronic plaque psoriasis.

Objectives and Endpoints

Objectives	Endpoints
Primary Objective	Primary Endpoints
• To evaluate efficacy of DMB-3115 in comparison with Stelara sourced from the EU.	• 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).
Secondary Objective	Secondary Endpoints
• To evaluate safety, tolerability, PK, and immunogenicity of DMB-3115 in comparison with Stelara sourced from the EU.	• 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. • 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. • 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. • 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. • Percentage change in Area under the effect curve (AUEC) for the PASI score from baseline at Weeks 4, 8, 12, 16, 28, 40, and 52. • Percent change in the PASI score from baseline at Weeks 4, 8, 12, 16, 28, 40, and 52.

	• 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. • Change from baseline in Dermatology Life Quality Index (DLQI) at Weeks 4, 8, 12, 16, 28, 40, and 52. Safety Endpoint: • Incidence of AEs, SAEs, including incidence of injection site reactions, changes in vital signs, laboratory abnormalities. Immunogenicity Endpoint: • Incidence of anti-drug antibodies (ADA) (binding and/or neutralizing). Pharmacokinetic Endpoint: • Drug concentrations at Weeks 0 (Pre dose and 24 hours post dose [±12 hours]), 1, 2, 4, 8, 12, 16, 28, 40, and 52. • Pharmacokinetic parameters after the first dose (maximum observed serum concentration [C_{max}], time from dosing to maximum measured concentration [t_{max}], area under the concentration-time curve from Week 0 to Week 4 [AUC_{w0-w4}] and other PK parameter, as appropriate).

Abbreviations: AE = adverse event; EMA = European Medicines Agency; EU = European Union; PK = pharmacokinetic; SAE = Serious Adverse Event; US FDA = United States Food and Drug Administration.

Overall Design:

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

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 and re-stratified based on the body weight at Week 28 (≤100 kg or >100 kg) 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 re-assigned based on the 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 in order to maintain blinding. Blinding will be maintained throughout the study.

Only those patients who achieve at least 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 as per Section 7.1 will remain in the study and be followed up to Week 52 for safety monitoring, including immunogenicity.

Any patients who are prematurely withdrawn from the study at any time post IP administration at Visit 2, will be required to have an early termination (ET) visit. Early termination visit will be performed within 12 weeks from the last IP administration. If ET visit occurs before 12 weeks, a phone call for safety follow-up will be performed at 12 weeks from the last IP administration.

Efficacy, safety, and immunogenicity assessments will be done periodically.

Blood samples for PK and ADA assessments will be collected prior to IP administration (in case a dose is scheduled for the same visit).

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

The patients will visit the clinical site for screening and then at baseline (Week 0/Day 1), Week 0/Day 2, Week 1, Week 2, Week 4, and then every 4 weeks up to Week 16. Thereafter, the patients will visit the clinical site every 12 weeks up to Week 52. The last visit at Week 52 will be End of Study (EOS) visit. There are total 12 scheduled visits planned, including the screening and EOS visit.

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 and an interim clinical study report will be generated for submission to the regulatory agencies.

Number of Investigators and Study Sites:

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

Number of Patients:

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 European Medicines Agency (EMA) (N=100), 590 patients (a minimum of 400 completed patients) will be necessary in total.

Thus, 590 patients (295 patients per treatment group at baseline) 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.

Statistical methods:

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.

Primary Efficacy Analysis (for European Medicines Agency [EMA])

- Percent change in PASI at Week 8 will be analyzed with a 95% confidence interval (CI) for the difference in means using estimates from an Analysis of Covariance (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 Intent-to-Treat (ITT) and Per Protocol Set (PPS). The PPS is the primary efficacy analysis population.
- Missing values for primary efficacy variable in the ITT set will be imputed by multiple imputation (MI) method.

Primary Efficacy Analysis (for United States Food and Drug Administration [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 ITT set will be imputed by MI method.

Sensitivity Analysis

Percent change in PASI will be analyzed for each PPS and ITT set (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.

Secondary Efficacy Analysis

Endpoints 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. Percentage change from baseline will be analyzed using ANCOVA 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. Change from baseline in Dermatology Life Quality Index (DLQI) will be analyzed using ANCOVA 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. All the secondary efficacy endpoints are summarized by the 90% CI (for US FDA) and 95% CI (for EMA).

Supportive Analysis to Secondary Endpoint for Period 2

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.

Safety Analysis

The number and proportion of patients experiencing AEs and Serious Adverse Events will be tabulated and compared by treatment group. Adverse events will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA).

Vital signs and clinical laboratory parameters being monitored for safety will be summarized by treatment and scheduled time point using descriptive statistics of number of observations, mean, SD, minimum, median, and maximum. Data listings of clinically significant abnormalities/outliers will be presented.

Immunogenicity Analyses

The incidence of ADAs and neutralizing antibodies will be summarized by treatment group and visit and listed.

Pharmacokinetic Analysis

Pharmacokinetic data will be summarized descriptively. Pharmacokinetic parameters after the first dose (e.g., C_{max}, t_{max}, area under the concentration-time curve from Week 0 to Week 4 [$AUC_{w0\text{-}w4}$] and other PK parameters, as appropriate) will be determined using an appropriate analysis methodology.

Additional details about the statistical methods including, but not limited, analysis sets, missing data strategies, etc. will be provided in the body of the protocol and the Statistical Analysis Plan (SAP) which will be prepared as a separate document prior to database lock.

Statistical Hypotheses

Statistical hypotheses and testing utilized will be defined in the SAP, including the null and alternative hypotheses. Primary and secondary endpoint analyses will be included in the SAP.

Sample Size Determination

The sample size required for the primary endpoint has been calculated based on the following assumptions; two-sided alpha of 0.05 (for EMA) or 0.10 (for US FDA), power of 90%, the difference between Stelara and DMB-3115 is 0, and the SD is 0.3. One to one (1:1) randomization rate of Period 1 is assumed. Equivalence margins of 15% and 10% were recommended by the EMA and US FDA, respectively. The SD assumption was derived from the observed SD of the mean improvement in PASI score in studies PHOENIX 1 and PHOENIX 2. Sample size was calculated using the Two one-sided t-tests (TOST) procedure as implemented in the R package power TOST. The overall sample size will be based on the larger sample size calculated through EMA and US FDA's recommendation.

Sample Size scenarios based on parameters suggested by the US FDA and the EMA		
	US FDA	**EMA**
Test Significance Level, α (two-sided)	0.1	0.05
Lower Equivalence Limit for μ_0-μ_1, Δ(L)	-0.1	-0.15
Upper Equivalence Limit for μ_0-μ_1, Δ(U)	0.1	0.15
Expected Difference, μ_0-μ_1	0	0
Common Standard Deviation, σ	0.3	0.3
Power (%)	90	90
Evaluable Sample Size per Group, n	**196**	**105**
Total	**392**	**210**
Total with Dropout 20% in Period 1 for Primary Efficacy Analysis	**490**	**264**
Abbreviations: EMA = European Medicines Agency; n = evaluable sample size per group; US FDA = United States Food and Drug Administration.		

As shown in above table, for primary efficacy analysis, the US FDA sample size of 490 patients in total (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.

On the other hand, for safety analysis, a minimum of 400 completed patients (at least 100 patients per treatment group for long-term data) will be necessary to meet the minimum requirement by EMA considering 1:1 re-randomization for Stelara arm. To achieve 400 completed patients, 590 patients (295 patients per treatment group at baseline) need to be enrolled assuming both dropout rate of 20% in Period 1 and 15% in Period 2.

The total number of patients needed for the safety analysis is larger than that needed for the primary efficacy analysis. Thus, 590 patients (295 patients per treatment group) in total need to be enrolled (randomized).

Populations for Analyses

For the purpose of analysis, the analysis sets are defined.

- Intent-to-Treat set: All patients who have been randomized.
- Per protocol set (for EMA): Patients who complete the study up to Week 8 and have no major protocol deviations. All decisions to exclude the patients from the per protocol population dataset will be made prior to the unblinding of the study.
- Per protocol set (for US FDA): Patients who complete the study up to Week 12 and have no major protocol deviations. All decisions to exclude patients from the per protocol population dataset will be made prior to the unblinding of the study.
- Safety set: Patients who randomize and receive at least 1 dose of the IP. The safety analysis will be conducted according to the treatment that a patient actually receives.
- PK analysis set: Patients who receive at least 1 dose of IP, have at least one measured concentration at a scheduled post dose PK time point, and have no major protocol deviations/events that may significantly affect the PK assessment.

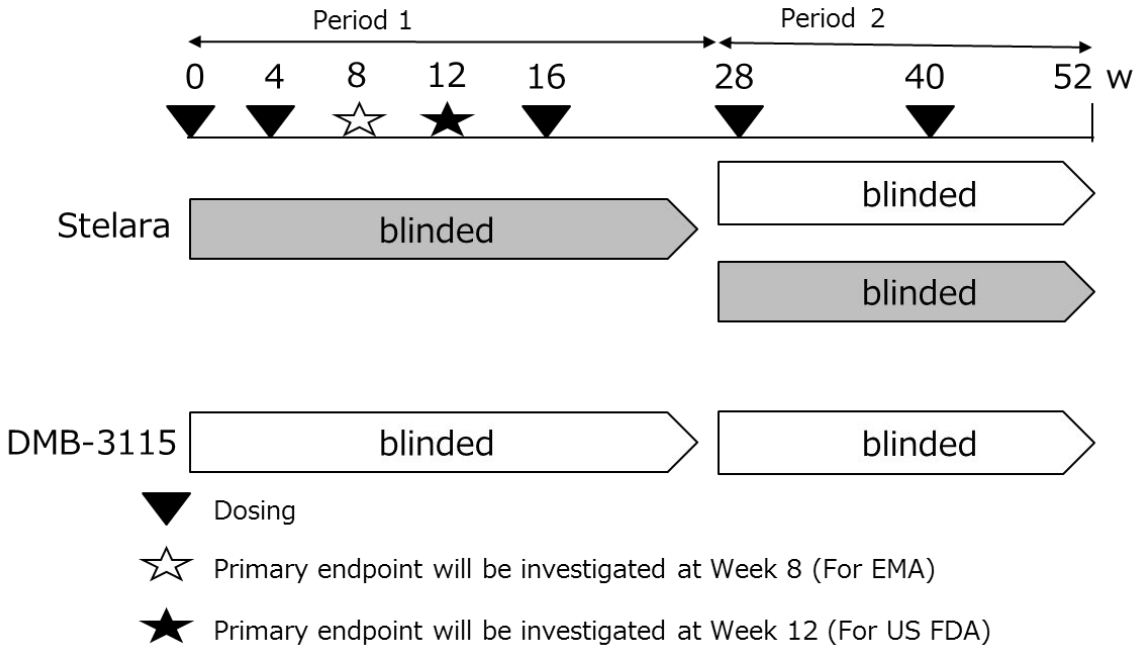
Data Monitoring Committee:

An independent Data Safety Monitoring Board (DSMB) will be constituted by the study Sponsor to oversee the safety aspects of this study. The DSMB will include physicians with relevant clinical expertise, none of

whom is affiliated with the Sponsor. The DSMB will operate as per a written charter. The DSMB would periodically examine the safety data emerging from the study and provide its recommendations to the Sponsor. Based on its review, the DSMB may advise for the study to be continued as is, or for the protocol to be modified, or for the study to be terminated.

1.2 Schema

Figure 1 Treatment design schematic



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

1.3 Schedule of Activities

Table 1 Schedule of Activities

Visit purpose/Assessments	Screening	Treatment										ET[r]/End of Study Follow-Up
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Week	**Up to 4 weeks**	**Wk 0/Day 1**	**Wk 0/Day 2 (24 ±12 hours)**	**Wk 1 (±2 days)**	**Wk 2 (±3 days)**	**Wk 4 (±3 days)**	**Wk 8 (±3 days)**	**Wk 12 (±3 days)**	**Wk 16 (±5 days)**	**Wk 28 (±5 days)**	**Wk 40 (±5 days)**	**Wk 52 (±7 days)**
Informed consent	✓											
Eligibility evaluation	✓	✓										
Non-responder evaluation								✓		✓		
Demographics	✓											
Medical history	✓											
Physical examination[a]	✓	✓			✓	✓	✓	✓	✓	✓	✓	✓
Chest X-Ray[b]	✓											
Vital signs[c]	✓	✓			✓	✓	✓	✓	✓	✓	✓	✓
Tuberculosis evaluation[d]	✓	✓			✓	✓	✓	✓	✓	✓	✓	✓
QuantiFERON Gold test[d]	✓											
HBsAg, HBcAb, HCVAb, HIV	✓											
Laboratory blood tests[e]	✓	✓				✓		✓	✓	✓	✓	✓

(Central lab; ESR locally with Central Lab Kits)												
Urinalysis[f]	✓	✓				✓		✓	✓	✓	✓	✓
Pregnancy Test[g]	✓	✓				✓			✓	✓	✓	✓
12-lead ECG[h]	✓								✓			✓
PK blood Sampling[i]		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
ADA blood Sampling[j]		✓	✓		✓	✓	✓	✓	✓	✓	✓	✓
Randomization[k]		✓								✓		
IP administration[k, l, m,n]		✓				✓			✓	✓	✓	
Injection site reaction examination		✓			✓	✓	✓	✓	✓	✓	✓	✓
PASI[o]	✓	✓				✓	✓	✓	✓	✓	✓	✓
PGA[o]	✓	✓				✓	✓	✓	✓	✓	✓	✓
DLQI[o]		✓				✓	✓	✓	✓	✓	✓	✓
Concomitant and previous medications[p]	✓	✓			✓	✓	✓	✓	✓	✓	✓	✓
Adverse events[q]	✓	✓			✓	✓	✓	✓	✓	✓	✓	✓

Abbreviations: ADA = Anti-Drug Antibody; DLQI = Dermatology Life Quality Index; ECG = Electrocardiogram; EOS = End of Study; ESR = Erythrocyte sedimentation rate; ET = Early Termination; HBcAb = Hepatitis B core antibody; HBsAg = Hepatitis B surface antigen; HCVAb = Hepatitis C virus antibody; HIV = human immunodeficiency virus; IP = Investigational Product; PASI = Psoriasis Area and Severity Index; PGA = Physician's Global Assessment; PK = Pharmacokinetics; SAE = Serious Adverse Event; Wk = Week.

a. Complete physical examination, including height and weight, will be performed at screening visit, Weeks 0, 28, and ET/EOS (height: at screening only); at other visits only brief physical examination will be performed (see Section 8.2.1).

b. Chest X-ray (posterior-anterior and lateral view) is required unless available within 12 weeks prior to the first administration of IP (see Section 8.2.4 and Section 5.4).

c. Vital signs include pulse rate, blood pressure and oral/axillary body temperature (see Section 8.2.2).

d. Tuberculosis evaluation and QuantiFERON Gold test will be performed as detailed in Section 8.2.5.

e. Laboratory blood tests: Hematology = hemoglobin, hemoglobin A1c, hematocrit, platelet count, Red Blood Cell (RBC) Count, white blood cell count (total and differential), Mean corpuscular volume (MCV), Mean corpuscular hemoglobin (MCH), and erythrocytes sedimentation rate (ESR). ESR test will be done locally with kits provided by central laboratory.
Biochemistry = sodium, potassium, creatinine, glucose (fasting status not mandatory), calcium, phosphorus, total bilirubin, direct bilirubin, albumin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, blood urea nitrogen, total protein, and C-reactive protein.
Other = Follicle stimulating hormone (as needed in women of non‑childbearing potential only at screening visit), prothrombin time, activated partial thromboplastin time, and international normalized ratio (see Section 8.2.6 and Appendix 3).

f. Urinalysis: Color, Clarity/Appearance, protein, blood, leucocytes, nitrite, glucose, ketone, pH, specific gravity, bilirubin, urobilinogen, microscopic examination (if blood or protein is abnormal).

g. Serum pregnancy test must be performed at screening visit for all females of childbearing potential only. Thereafter, from randomization onwards, a urine pregnancy test will be performed at Weeks 0, 4, 16, 28, 40, and 52 and should be negative before each IP administration. Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected (see Appendix 6).

h. 12-lead ECG will be performed as detailed in Section 8.2.3.

i. Blood samples for PK analysis will be collected at Weeks 0 (Pre dose and 24 hours post dose [±12 hours]), 1, 2, 4, 8, 12, 16, 28, 40, and 52. At visits when IP is to be administered, the PK sample will be collected prior to IP administration.

j. Blood samples for ADA analysis will be collected at Weeks 0 (Pre dose and 24 hours post dose [±12 hours]), 2, 4, 8, 12, 16, 28, 40, and 52. At visits when IP is to be administered, the ADA sample will be collected prior to IP administration.

k. At Week 28, patients who achieved a PASI 75 response will enter the study transition period. Patients receiving Stelara will be re-randomized in a 1:1 ratio to either continue to receive Stelara or be transitioned to DMB-3115. Patients receiving DMB-3115 will continue to receive DMB-3115 up to Week 40 but they will also follow the re-randomization procedure in order to maintain blinding.

l. Patients who do not achieve at least PASI 50 response by Week 12 will be discontinued from further treatment with ustekinumab. These patients will remain in the study and will be followed up to Week 52 for safety monitoring, including immunogenicity.

m. Patients who do not achieve at least PASI 75 response by Week 28 will be discontinued from further treatment with ustekinumab (either DMB-3115 or Stelara). These patients will remain in the study and will be followed up to Week 52 for safety monitoring, including immunogenicity.

n. Appropriate medical personnel must be in attendance at the time of the injection and for at least 30 minutes after the SC injection.

o. The PASI, PGA, and DLQI assessments shall be completed using the electronic devices provide by the site.

p. Previous and concomitant medication at screening and concomitant medication only at visits from randomization onwards (see Section 6.5).

q. Safety data reporting period begins from the time of signing the informed consent (even if this is prior to randomization visit) until Week 52 (±7 days). Note: Related SAEs should be collected irrespective of the time elapsed since the last dose of IP. For detailed instructions on safety reporting (see Appendix 4).

r. Patients who are prematurely withdrawn from the study at any time post Visit 2, will be required to have an ET visit. The ET visit will be performed within 12 weeks from the last IP administration. If ET visit occurs before 12 weeks, a phone call for safety follow-up will be performed at 12 weeks from the last IP administration.