A LONG-TERM SAFETY AND EFFICACY STUDY OF CD5789 50 μg/g CREAM IN SUBJECTS WITH ACNE VULGARIS

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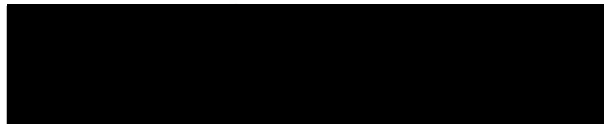**STATISTICAL ANALYSIS PLAN**
RD.06.SPR.18250

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Document History

Version No.	Description of Edits	Justification	Date
Amendment x			
Amendment y			

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1 STUDY OBJECTIVES AND ENDPOINTS

The purpose of this statistical analysis plan (SAP) is to describe the safety, tolerability, efficacy and pharmacokinetic to be included in the Clinical Study Report for Protocol RD.06.SPR.18250.

1.1 Study Objective (s)

1.1.1 Primary objective (s)

The primary objective of this study is to determine the safety of CD5789 50 μg/g cream in the long-term treatment (up to 52 Weeks) of subjects with acne vulgaris.

1.1.2 Secondary objective (s)

Efficacy will be evaluated as a secondary objective.

2 STUDY DESIGN

This is a multi-center, open-label, non-comparative safety and efficacy study with 52 Weeks of treatment on the face and trunk for acne vulgaris.

Male and female subjects, 9 years of age or older, with an IGA of 3 and a minimum of 20 inflammatory lesions and 25 non-inflammatory lesions on the face, with a PGA of 3 and a minimum of 20 inflammatory lesions and 20 non-inflammatory lesions

on the trunk will be enrolled in the study (PGA and truncal lesions are optional inclusion criteria for children between 9-11 years old).

Approximately 450 subjects will be enrolled worldwide (Europe, USA). The total number of sites is expected to be approximately 30 to 40 with a minimal of 10 subjects per site.

3 EFFICACY AND SAFETY ASSESSMENT

Refer to Protocol Section 7 "Clinical Trial Assessment" for details.

3.1 Efficacy assessment

Efficacy will be evaluated as a secondary objective in this study.

3.1.1 IGA (Investigator's global assessment) of facial acne

The areas defined for IGA assessment are forehead, each cheek, chin and nose. IGA will be confined to a global assessment of each area. The Investigator's Global Assessment (IGA) is a snapshot static assessment.

Investigators will evaluate the facial acne at Screening, Baseline, and at Week 12, Week 20, Week 26, Week 38 and Week52/ET visits or any unscheduled visit, according to the following scale:

Investigator's Global Assessment Scale (IGA) Face		
0	Clear	Clear skin with no inflammatory or non-inflammatory lesions.
1	Almost Clear	A few scattered comedones and a few small papules.
2	Mild	Easily recognizable; less than half the surface is involved. Some comedones and some papules and pustules.
3	Moderate	More than half of the surface is involved. Many comedones, papules and pustules. One nodule may be present.
4	Severe	Entire surface is involved. Covered with comedones, numerous papules and pustules. Few nodules may be present.

Note: IGA assessment is to be done prior to lesion counts

3.1.2   PGA (Physician Global Assessment) of truncal acne

The areas defined PGA assessment are shoulders, upper back and anterior chest which are accessible to self-application by the subject, i.e. the regions that the subject can easily reach and apply the study drug by himself or herself. PGA will be confined to a global assessment. The PGA is a snapshot static assessment.

Investigators will evaluate the upper truncal acne at Screening, Baseline, and Weeks 12, Week 20, Week 26, Week 38 and Week 52/ET visits or any unscheduled visit, according to the following scale.

Physician Global Assessment Scale (PGA) Trunk		
0	Clear	Clear skin with no inflammatory or non-inflammatory lesions.
1	Almost Clear	A few scattered comedones and a few small papules.
2	Mild	Easily recognizable; less than half the surface is involved. Some comedones and some papules and pustules.
3	Moderate	More than half of the surface is involved. Many comedones, papules and pustules. One nodule may be present.
4	Severe	Entire surface is involved. Covered with comedones, numerous papules and pustules. Few nodules may or not be present.

Specific requirements for children between 9 and 11 years old who do not have moderate acne on the upper truncal region at Baseline (i.e. who do not have PGA of 3, at least 20 inflammatory lesions on the trunk and at least 20 non-inflammatory lesions on the trunk):

The PGA scale will be completed at all visits (including Week 1, 2, 4 and 8 visits), and used by the investigators to decide if they want to start the treatment for truncal acne. However, the PGA data from these subjects will not be analyzed.

Note: PGA assessment is to be done prior to lesion counts.

3.1.3 Subject self-assessment of facial acne improvement

Subject self-assessment should occur prior any investigator assessment in order to not influence the subject. Subjects will evaluate his/her facial acne improvement by comparing what they recall on their disease at the start of the study at Weeks 12, 26 and 52/ET visits by completing the following scale:

Subject's Assessment of Acne Improvement	
0	Complete Improvement
1	Marked Improvement
2	Moderate Improvement
3	Minimal Improvement
4	No Change
5	Worse

3.2 Safety assessment

A safety assessment will be conducted for all subjects at the Screening visit (from the Informed consent signature) and every subsequent visit. The safety parameters are the recording of adverse events, laboratory safety tests, physical examination, vital signs and local tolerability scores on the face and on the trunk (0 [none] to 3 [severe]) for erythema, scaling, dryness, and stinging/burning.

3.2.1 Local tolerability assessment

Local tolerability (erythema, scaling, dryness, and stinging/burning) will be assessed on the face (forehead, each cheek, nose, chin) and trunk (upper trunk; middle and lower trunk will be captured if subject applied study drug on these areas) separately and will be graded separately at Baseline and at each post-baseline visit. Refer to protocol section 7.2.3 and 7.2.4 for more details.

Specific requirements for children between 9 and 11 years old who do not have moderate acne on the trunk at Baseline (i.e. do not have PGA of 3, at least 20 inflammatory lesions on the trunk and at least 20 non-inflammatory lesions on the trunk):

If the investigators decide to start the treatment for truncal acne in these subjects during the study, then the local tolerability scales (for trunk) will be completed and data will be evaluated in the safety analysis.

3.2.2 Adverse events

Adverse events (AEs) are to be monitored throughout the course of the clinical trial. All AEs are to be reported on the Adverse Event Form of the eCRF with complete information as required, including onset/end dates of AEs, severity of AEs, relationship to the study drug, serious AEs and AEs of special interest.

3.2.3 Laboratory safety tests

The laboratory analyses will be based on Central laboratory results. The following laboratory safety tests will be performed at the Screening visit, Week 26 andWeek 52/ET visits. Abnormal laboratory results will be evaluated by the investigator as clinically significant or non-clinically significant.

- Hematology: White blood cell (WBC) count with differential, red blood cell (RBC) count, hemoglobin(Hb), hematocrit (Hct), mean cell volume (MCV), and platelet count (Plt)

- Blood chemistry: Creatinine, uric acid, urea nitrogen, gamma glutamyl transferase (GGT or γGTP), alkaline phosphatase (ALP), aspartate aminotransferase (ASAT=SGOT [AST in US]), alanine aminotransferase (ALAT=SGPT [ALT in US]), and bilirubin (total, direct & indirect).

- Urinalysis: blood, proteins, leukocytes, glucose

3.2.4 Vital signs

Evaluation of vital signs will be performed after approximately 5 minutes rest in the sitting

position at the Screening visit, Baseline visit and at Weeks 12, 26 and 52 /ET/Unscheduled visits. It will include measurement of systolic and diastolic blood pressure and pulse rate.

3.2.5 Physical examination

The investigator should evaluate following body systems as "normal" or "abnormal" and should also evaluate abnormal values as "clinically significant/not clinically significant" at the Screening visit, Baseline visit and at Weeks 12, 26 and 52 /ET and Unscheduled visit:

- Skin
- Lungs
- Abdomen
- Eyes/ears/nose/throat
- Neurological function
- Musculoskeletal system
- Lymph nodes
- Cardiovascular system

3.3 PK assessment (at selected sites)

In selected sites only, a PK (pharmacokinetic) assessment will be performed only in 9 to 11 year old subjects who have agreed in the parents/guardian ICF and Assent form to have a PK sample taken. Systemic exposure to CD5789 will be assessed at Week 4 visit in a single sample PK time point.

The following PK parameters will be determined for each subject if sufficient CD 5789 plasma concentrations are detectable (above the limit of quantification):

- C 4 hours
- Extrapolated AUC0-24h using the linear correlation between AUC0-24h and C 4 hours

3.4   Other assessment

3.4.1   Lesions counts on the face and on the trunk

At Screening and Baseline visits, lesion counting will be performed separately on the face and on the upper truncal region.

Specific requirements for children between 9 and 11 years old who do not have moderate acne on the trunk at Screening and/or Baseline (i.e. who do not have PGA of 3, at least 20 inflammatory lesions on the trunk and at least 20 non-inflammatory lesions on the trunk):

The truncal lesion counts will not be performed.

3.4.2   Photographs (at selected sites)

Facial and truncal photos will be taken according to a standardized procedure guideline at

selected sites at Baseline, Week 12, Week 26 and Week 52/ET visits to document the effect observed on efficacy areas.

3.4.3   Dermatology Life Quality Index (DLQI) / Children's Dermatology Life Quality Index (C-DLQI)

The Dermatology Life Quality Index (DLQI, designed for use in adults, i.e. subjects over the age 16 years old) and Children's Dermatology Life Quality Index (C-DLQI, designed for 16 years or younger at the date of Baseline visit) will be completed at Baseline and Week 12, Week 26 and Week 52/ET visits.

The DLQI/ C-DLQI will measure the dermatology-related limitations of functional ability and the frequency, severity and impact of acne symptoms on subjects' lives and acne-related quality of life. The six areas addressed in the questionnaire are: symptoms and feelings; daily activities; leisure; work/school; personal relationships; and treatment. The score on the DLQI/ C-DLQI has a possible range of 0 to 30 and can also be presented as a percentage of the maximum possible score of 30.

4 EFFICACY AND SAFETY ENDPOINTS

4.1 Efficacy endpoints

Efficacy endpoints include:

1. Success rate of IGA (defined as 0=clear or 1=almost clear) at each time point

2. Success rate of PGA (defined as 0=clear or 1=almost clear) at each time point

3. Grade change from baseline of IGA at each time point

4. Grade change from baseline of PGA at each time point

5. Subject's assessment of facial acne improvement at each time point

4.2 Safety endpoints

Safety endpoints include:

1. Local tolerability (erythema, scaling, dryness, and stinging/burning) on the face and trunk,

2. Adverse event,

3. Laboratory parameters

4. Vital signs and physical examination

4.3 PK parameters

PK(Pharmacokinetic) parameters include:

1. C 4 hours

2. Extrapolated AUC0-24h using the linear correlation between AUC0-24h and C 4 hours

4.4 Other endpoints

Other endpoints include:

1. Dermatology Life Quality Index (DLQI) / Children's Dermatology Life Quality Index(CDLQI)

5 POPULATIONS ANALYZED

As this study is a long-term safety study, only the safety population will be used for all statistical analyses.

The safety (SAF) population will be used for the analyses of IGA data and all safety data except for the local tolerability on the trunk.

The safety population on the trunk (SAFT) will be used for the analyses of the local tolerability on the trunk.

The safety population for the PGA (SAFP) will be used for the analyses of the PGA data.

In the case that the SAFT turns out to be identical to the SAF population, then all safety analyses will be based on the SAF population. In the case that the SAFP turns out to be identical to the SAF population, then the analyses of all IGA and PGA data will be based on the SAF population.

PK evaluable subjects in the SAF population will be used for the analysis of PK data.

5.1 Safety (SAF) Population

The SAF Population is defined as subjects who applied the study drug(s) at least once.

5.2 Safety (SAFT) Population on the Trunk

The SAFT population is defined as any subjects in the SAF population who also applied the study medication on the upper truncal region and /or on the middle and lower back at least once.

5.3   Safety (SAFP) Population for the analysis of PGA

The SAFP population is defined as any subjects in the SAF population with moderate truncal acne at Baseline visit. In practice, this excludes from the SAF population the children between 9 and 11 years old who do not have PGA of 3, at least 20 inflammatory lesions on the upper truncal region and at least 20 non-inflammatory lesions on the upper truncal region at study entry.

6   SAMPLE SIZE CONSIDERATION

Approximately 600 subjects will be screened to enroll 450 subjects worldwide, including the United States of America and Europe.

The exposure of subjects to CD5789 50 μg/g cream follows internationally accepted guidelines for the assessment of clinical safety for products intended for chronic use. The International Conference on Harmonization E1a Guideline suggests that 300 subjects for six months or 100 subjects for one year should be evaluated for safety. This study was designed to ensure that at least 300 subjects will be exposed to CD5789 50 µg/g cream for 6 months, and 100 subjects exposed for 1 year.

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7 STATISTICAL METHODS AND DATA CONSIDERATIONS

For statistical analyses purpose, baseline is defined as the last measurement prior to the first application of the study drug.

No inferential statistical analysis is planned. Data to be collected will be summarized as observed.

For the summary statistics, the categorical variables will be summarized by frequency and percentage for each response category (N, %); and the continuous variables will be summarized using means, medians, minimum, maximum, and standard deviations.

All efficacy variables, DLQI/ C-DLQI, local tolerability, laboratory tests and vital signs will be summarized and analyzed by analysis visit. The methodology for defining analysis visit is provided in Section 7.9 "Analysis visit definition".

SAS version 9.3 or above will be used for all statistical analyses.

7.1 Study subjects

7.1.1 Disposition of subjects

Disposition of subjects will be summarized based on SAF population. Number and percentage of subjects screened, enrolled, completed, discontinued, and the primary reason for discontinuation based on the CRF exit form will be displayed.

In addition, the number and percentage of subjects in each study population (i.e., SAF, SAFT, SAFP) will be summarized.

7.1.2 Demographic and baseline characteristics

The following demographics variables will be summarized for SAF population: Age, Ethnicity, Race, Skin phototype, and Gender. Age will be analyzed as a continuous variable and will be tabulated by age groups of "<18years" ("9-11 years", "12-14 years", "15-17 years"), "18-64 years" ("18-25 years", "26-35 years", "36-45 years", "46-64 years") and "≥65 years".

Baseline IGA, PGA and Acne presence on back (middle/lower) will be summarized using SAF population. Facial lesion counts (inflammatory and non-inflammatory) will be summarized using SAF population and truncal lesion counts (inflammatory and non-inflammatory) will be summarized using SAFP population.

7.2 Protocol deviations

Not applicable.

7.3 Medical history, previous and concomitant therapies and procedures

For statistical analysis purposes, previous therapies/procedures are defined as those ending at or before the date of first dose; and concomitant therapies/procedures are defined as those ongoing at the date of first dose or starting after the date of first dose.

Previous and concomitant therapies will be coded using WHODRUG dictionary. Previous and concomitant procedures will be coded using MedDRA dictionary.

A summary table will be provided for each of the following in the SAF population:

1. number and percentage of subjects who had previous therapies/medications by ATC text and WHO drug name

2. number and percentage of subjects who had concomitant therapies/medications by ATC text and WHO drug name

3. number and percentage of subjects who had previous procedures by System organ class and preferred term

4. number and percentage of subjects who had concomitant procedures by System organ class and preferred term

7.4 Efficacy analysis

The safety population for the PGA (SAFP) will be used for the analyses of the PGA data. All other efficacy data will be analyzed based on the SAF population.

7.4.1 Success rate of IGA at each time point

A subject will be considered a success if they achieve an IGA score of 'clear' or 'almost clear'. The success rate will be calculated as the number of successes divided by the number of subjects in the SAF population. The descriptive statistics will be summarized by visit.

7.4.2 Success rate of PGA at each time point

A subject will be considered a success if they achieve a PGA score of 'clear' or 'almost clear'. The same summary statistics as section 7.4.1 will be provided using SAFP population.

7.4.3 Grade change from baseline of IGA at each time point

Raw grade at each visit and grade change from baseline at each post-baseline visit will be summarized as both categorical and continuous variables. In the grade change from baseline analysis, only subjects with both baseline and post-baseline will be included.

7.4.4 Grade change from baseline of PGA at each time point

The same summary statistics as section 7.4.3 will be provided using SAFP population.

7.4.5 Subject's assessment of facial acne improvement at each time point

Subject's assessment of facial acne improvement at each time point will be summarized as both categorical and continuous variables.

7.4.6 Statistical and analytical issues

7.4.6.1 Handling of dropouts or missing data

In this study, summary statistics will be based on the observed data and no missing data imputation will be performed.

7.4.6.2 Interim analyses and data monitoring

No interim analysis is planned for this study.

7.4.6.3 Examination of Subgroups

Subgroup summaries will be provided by descriptive statistics for success rate of IGA (using SAF) and PGA (using SAFP), within each category of the following classification variables:

- Age Group [<18 years ("9-11 years", "12-14 years", "15-17 years"), 18-64 years("18-25 years", "26-35 years", "36-45 years", "46-64 years") and ≥65 years")]
- Gender (female, male)
- Race (white, non-white)
- Country (Europe, USA)
- Skin Phototype (I-III, IV-VI)

7.5 Safety analysis

All safety data will be analyzed based on the SAF population except for the local tolerability on the trunk. The SAFT population will be used for the analyses of the local tolerability on the trunk.

7.5.1 Extent of exposure

7.5.1.1 Study Duration

Study duration (day) is defined as the date of the last visit minus the date of the baseline visit plus one. Study duration will be summarized by descriptive statistics.

7.5.1.2 Treatment Duration

Treatment duration (day) is defined as "the date of the last application on face or the trunk, whichever is later, minus the date of the first application on face or the trunk, whichever is earlier, plus one". If the date of the last application is not available, the date of the last visit will be used in calculation. If the date of the first application is not available, the date of the Baseline visit will be used in calculation.

Treatment duration will be summarized by descriptive statistics.

7.5.1.3 Study Medication Usage and Treatment Compliance

The study medication usage will be assessed based on CRF data in terms of the number of applications applied.

Number of applications applied is calculated as the expected number of applications minus the total number of missed applications during the treatment. If the number of missed applications is unknown, then 50% doses will be assumed to be missed between two adjacent visits. The expected number of applications is defined as the planned total number of applications during the exposed period. Number of applications applied and the daily average applications applied will be summarized.

Treatment compliance (%) is defined as (the Number of applications applied over the expected number of applications) *100%.

Study medication usage based on number of applications may also be summarized for the face using SAF population and for the trunk using the SAFT population separately.

Additionally, the study medication usage will be assessed based on the returned tubes. Total medication usage weight (g) and daily medication weight (g/day) will be calculated for each subject and be summarized by descriptive statistics.

Total medication usage (g) = total dispensed weight (g) - total returned weight (g);

Daily medication usage (g/day) = total medication usage (g) / study duration (day).

The tubes that were dispensed but not returned will be considered no information and will not be included in the calculation. If all dispensing tubes for a subject are not returned, the subject's total returned weight and daily medication usage will be considered missing.

7.5.2   Cutaneous safety

Analyses of the local tolerability on the face will be based on SAF population; and the analyses of the local tolerability on the trunk will be based on SAFT population.

Local tolerability variables (erythema, scaling, dryness, stinging/burning) will be summarized at Baseline, each post-baseline visit, "Worst" score, and "Final" score. "Worst" score is the highest severity score observed during post-baseline period for a subject. "Final" score is the last data observed during the post-baseline period for a subject. In addition, the number and percentage of subjects with a local tolerability score worsened from baseline will be summarized descriptively at each post-baseline visit, "Final" scores, and "Worst" score.

Additionally, subjects with a local tolerability score worse than the Baseline score will be summarized graphically at each post-Baseline visit including "Final" scores and "Worst" score.

Summary statistics by treating the severity scale as continuous outcome will also be presented.

Subgroup analyses by Age Group (<18 years, >=18 years), Race (white, non-white), Gender (female, male), Country (Europe, USA), and Skin Phototype (I-III, IV-VI) will be provided.

7.5.3   Adverse events

A treatment-emergent adverse event (TEAE) is defined as an adverse event that occurred on or after the first study drug application.

TEAEs will be tabulated in frequency tables by System Organ Class (SOC) and Preferred Term (PT) based on the MedDRA dictionary. In addition, incidence of TEAE by quarter will be summarized for "Baseline to < Month 3" (1 to 89 days), "Month 3 to <Month 6" (90 to179 days), "Month 6 to < Month 9" (180 to 269 days), "Month 9 to 1 Year" ($\geq$270 days). The AE incidence for each time period will be calculated by the number of subjects with AE onset dates within each period divided by the number of subjects at risk at the start of each period. Additional summary tables and listings will be provided for adverse events that are considered serious (SAEs), related to the study drug, severe, leading to discontinuation and of special interest. For a given TEAE, a subject will be counted once even if he or she has experienced multiple episodes for that particular TEAE.

The AEs of Special Interest for this protocol are pre-defined as follows:

- Out-of-range laboratory results that are identified as clinically significant and related to the study drug(s) are AESIs.
- Related cutaneous AEs which lead to permanent treatment discontinuation.
- Suspicion of allergic reaction suspected to be related to the study drug.

The following TEAE summaries will be provided:

- Summary of overall AE(s)
- Frequency and percentage of subjects with AE(s) by System Organ Class (SOC) and Preferred Term (PT)
- Frequency and percentage of subjects with serious AE(s) by System Organ Class (SOC) and Preferred Term (PT)
- Frequency and percentage of subjects with related AE(s) by System Organ Class (SOC) and Preferred Term (PT)
- Frequency and percentage of subjects with related AE(s) by Preferred Term (PT)
- Frequency and percentage of subjects with AE(s) leading to discontinuation by System Organ Class (SOC) and Preferred Term (PT)
- Frequency and percentage of subjects with severe AE(s) by System Organ Class (SOC) and Preferred Term (PT)
- Frequency and percentage of subjects with AE(s) of special interest by System Organ Class (SOC) and Preferred Term (PT)

Summaries of overall Adverse Events and summaries of Adverse Events by System Organ Class (SOC) and Preferred Term (PT) will be presented by Age Group (<18 years, ≥18 years), Race (white, non-white), Gender (female, male), Country (Europe, USA) and Skin Phototype (I-III, IV-VI).

Furthermore, the chronology of TEAE will be assessed with respect to AE onset and AE duration. Descriptive statistics (N, minimum, medians and maximum) will be presented by Preferred Term for the following:

- Duration from the first dose date to AE onset date,
- Duration of AE from AE start date to AE stop date.

7.5.4 Laboratory parameters

The descriptive statistics for laboratory data collected at each visit and changes from Baseline will be provided.

A summary table of the categorical grade shift changes using the normal ranges from baseline to the last post-baseline visit will be presented for each laboratory parameter. Only SAF subjects with both baseline and post-baseline assessments will be included in this analysis.

For each laboratory test, a complete data listing will be provided for subjects who have any laboratory results outside the reference ranges, and for subjects who have any laboratory results with clinical significance.

7.6 Vital Signs and Physical Exam

The descriptive statistics for Vital Signs collected at each visit and changes from Baseline will be provided. Nominal eCRF visit will be used as analysis visit.

Physical exam will be provided in a subject-by-subject listing.

7.7 Pharmacokinetic Analysis

Quantifiable PK profiles of CD5789 from previous PK studies 18237 and 40182 were used to investigate the relationship between AUC_{0-24h} and selected plasma points. A strong correlation was found between AUC_{0-24h} and C_{4h} using linear regression. The extrapolated AUC0-24h will be calculated using the following equation. For more details, refer to the document *CD5789 Limited sampling strategy for estimation of the AUC0-24h in the 9 to 11 years old subjects*.

$$AUC_{0-24h} = 34.26 + 7.90 * C_{4h}$$

The PK parameters C_{4h} and extrapolated AUC_{0-24h} will be summarized by descriptive statistics. Coefficient of variation (CV), geometric mean (GEO Mean), geometric standard deviation (GEO SD) and geometric coefficient of variation (GEO CV) will be presented as well.

For C_{4h}, the BLQ (below limit of quantification) values will be imputed using the LOQ (limit of quantification: 5pg/mL). Summaries with imputation and with no imputation will be both provided.

7.8 Other analyses (quality of life Questionnaire)

The DLQI/ C-DLQI will be summarized descriptively. Only SAF subjects with both baseline and post-baseline visit assessments using the same age-appropriate questionnaire will be included in the analyses.

Total Scores and Change from Baseline at Week 12, 26, and 52/Early Termination for DLQI/C-DLQI, DLQI only, and C-DLQI only will be summarized. In addition, number and percent of subjects will be reported for each of the following categories of the effect of disease on the quality of life as specified in Table 1:

Table 1   DLQI/C-DLQI Categories

DLQI		C-DLQI	
DLQI Category	Range of Total Score	C-DLQI Category	Score Maximum
No effect	0 - 1	No effect	0 - 1
Small effect	2 - 5	Small effect	2 - 6
Moderate effect	6 - 10	Moderate effect	7 – 12
Very large effect	11 – 20	Very large effect	13 – 18
Extremely large effect	21 - 30	Extremely large effect	19 - 30

Summaries of DLQI only and C-DLQI only by each dimension as defined in Table 2 below will also be provided.

Table 2   DLQI/C-DLQI Dimensions

DLQI		C-DLQI	
DLQI dimensions	Score Maximum	C-DLQI dimensions	Score Maximum
Total Score	**30**	**Total Score**	**30**
Symptoms and feelings	6	Symptoms and feelings	6
Daily Activities	6	Sleep	3
Leisure	6	Leisure	9
Work and School	3	School or holidays	3
Personal relationships	6	Personal relationships	6
Treatment	3	Treatment	3

7.9   Analysis visit definition

For efficacy, DLQI/ C-DLQI and local tolerability data, analysis visit will be assigned according to the algorithm in Table 3 below to summarize the data by proper visit window interval. Study day is calculated as visit date minus the date of first application plus 1. If multiple measurements are taken in the same interval, the one closest to the target study day will be used for the analysis. If two measurements are taken with equal differences in timing compared with the target date, the nominal visit number (recorded on the CRF page) will be used. If there is missing measurement at Baseline, Screening data will be used to impute the missing baseline data, i.e. Baseline will be the last available data prior to first application of study drug.

Table 3   Analysis Visit and Visit Window

Analysis Visit	Analysis Visit Number in Derived Dataset	Target Study Day	Visit Window (Study Day)
Baseline	1	1	[≤1]
Week 1	2	8	[2 – 11]
Week 2	3	15	[12 – 21]
Week 4	4	29	[22 – 42]
Week 8	5	57	[43 – 70]
Week 12	6	85	[71 – 112]
Week 20	7	141	[113 – 161]
Week 26	8	183	[162 – 224]
Week 38	9	267	[225 – 315]
Week 52	10	365	> 315

When assigning the analysis visits for vital signs, no visit window will be applied; Nominal eCRF visit will be used as analysis visit for summaries. Only data from schedule visit will be summarized.

When assigning the analysis visits for laboratory data, no visit window will be applied, however, the following rules will be applied:

1. If sample date is at or prior to date of first application, the data will be considered as screening visit. If multiple measurements of screening due to rescreening, retest or other unexpected reasons, the data closest to date of first application will be chosen.

2. Lab data from scheduled visit will be considered first when assigning analysis visit of each scheduled visit. If there is no data from scheduled visit available, the last of those corresponding unscheduled visit will be considered for assignment of analysis visits.

3. When assigning Final visit, the lab data from the last post-baseline scheduled visit during treatment period will be considered first. If the last scheduled visit during treatment period have missing lab data due to any reason and there are subsequent unscheduled lab data available, the last of those corresponding unscheduled lab data will be assigned as Final visit. Otherwise, the previous visit lab data will be considered in the same manner.

8   CHANGES FROM THE PROTOCOL ANALYSIS PLAN

There are no changes from the planned analyses on Protocol.

9 TABLE SHELLS AND REPORTING OUTPUT (GENERAL FEATURES)

The tentative list of tables to be produced in the reporting of this study is shown below. All eCRF data will also be available as subject listings and the eCRF data will be available in CDISC compliant data set.

Demographic and Baseline Characteristics tables

- Summary of Subject Enrollment
- Summary of Subject Enrollment by Analysis Center/Site, SAF Population
- Summary of Subject Disposition, SAF Population
- Summary of Subject Disposition by Analysis Center/Site, SAF Population
- Summary of Subject Disposition by Study Duration, SAF Population
- Listing of Discontinued Subjects, SAF Population
- Summary of Subject Demographics and Baseline Characteristics, SAF Population
- ATC Class, WHO Drug and Drug Name, SAF Population
- Summary of Previous Therapy, SAF Population
- Summary of Concomitant Therapy, SAF Population
- System Organ Class, Preferred Term and Procedure/Non-drug Therapy, SAF Populations
- Summary of Previous Procedure / Non-Drug Therapy, SAF Population
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