NCT04992546

STATISTICAL ANALYSIS PLAN

Protocol title:	**A randomized, intra-patient, double-blind, placebo-controlled study to evaluate the safety, tolerability, and pharmacokinetics of topically administered PRN473 (SAR444727) in patients with mild to moderate atopic dermatitis**
Protocol number:	**ACT17131 (PRN473-0005)**
Compound number (INN/Trademark):	**SAR444727 (PRN473)** **Not applicable**
Study phase:	**2a**
Short title:	**Phase 2a study of the safety, tolerability, and pharmacokinetics of topically administered PRN473 (SAR444727) in patients with mild to moderate atopic dermatitis**
Statistician:	[redacted]
Statistical Project Leader:	[redacted]
Date of issue:	**14-Sep-2022**

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VERSION HISTORY

This statistical analysis plan (SAP) for study ACT17131 is based on the Amended Clinical Trial Protocol 02 dated 01 March 2022.

This SAP is approved before the database lock or before the first interim analysis.

Major changes in statistical analysis plan

SAP Version	Approval Date	Changes	Rationale
1	14-Sep-2022	Not applicable	Original version

1 INTRODUCTION

1.1 STUDY DESIGN

PRN473 is also known as SAR444727 and both terminologies are used in an interchangeable way in this document. For the reporting "SAR444727" will be used.

Study ACT17131 is a Phase 2a that consists of a randomized, double-blind, intra-patient placebo-controlled treatment period and an open-label uncontrolled treatment period.

The objective of the study is to evaluate the safety, tolerability, pharmacokinetics (PK) and preliminary efficacy of topically administered SAR444727 in up to 40 participants with mild to moderate atopic dermatitis (AD).

On Day 1 (Baseline) of the Blinded Period, 2 target lesions of 100 cm^2 area each with a difference no greater than 1 point in lesional Total Sign Score (TSS) are randomly assigned to treatment in an intra-participant 1:1 manner, with one lesion assigned to SAR444727 Gel 5% and the other to matching placebo (ie, same inactive ingredients). SAR444727 Gel 5% and matching placebo (ie, same inactive ingredients) are applied twice a day (BID, morning and evening) at a quantity of 2.5 mg/cm^2 to a 100 cm^2 area of each target lesion on Days 1-14 (Blinded Period). On Days 15-42 (Open-Label Period), participants are instructed to apply SAR444727 Gel, 5% BID to all AD-affected areas in a thin layer (excluding the scalp, palms, soles and genitals), and should continue to treat the assigned areas throughout the Open-label Period.

Participation will take approximately 13 weeks, including up to a 5-week screening period, a 6-week treatment period (2-week blinded and 4-week open label), end of study assessments 1 day after last dose, and a safety follow-up phone call 2 weeks after last dose.

1.2 OBJECTIVE AND ENDPOINTS

Table 1 - Objectives and endpoints

Objectives	Endpoints
Primary	
Safety: To assess the safety and tolerability of PRN473 Gel, 5% versus placebo administered BID up to 6 weeks in participants with mild to moderate AD	Safety: • Incidence and severity of AEs • Changes in vital signs, ECGs, and laboratory tests • Assessment of local cutaneous tolerability: incidence and severity of application-site events such as burning/stinging, itching, and erythema
Secondary	
PK: To evaluate the plasma PK of PRN473 following administration of multiple topical doses of PRN473 Gel, 5% for 42 days in participants with mild to moderate AD	• PK: Plasma PRN473 concentrations at specified timepoints

Objectives	Endpoints
Exploratory	
• Biomarker: To evaluate blood and skin changes in protein expression, lymphocyte infiltration, and epidermal thickness following treatment with PRN473 Gel, 5% at Days 8 and 15	• Biomarker: Change from Baseline in biomarkers using blood samples, skin tape stripping, and skin biopsy
• Efficacy: To assess the preliminary efficacy following double-blind treatment with PRN473 Gel, 5% compared to placebo at Days 8 and 15	Efficacy During Blinded Period: • Change from Baseline in lesion TSS at Days 8 and 15 • Change from Baseline in daily lesional PP-NRS score up to Day 15 • Change from Baseline in lesional validated IGA score at Days 8 and 15 • Lesional validated IGA response (proportion of participants with a validated IGA score of 0 or 1 and ≥2-grade improvement from Baseline) at Days 8 and 15
• Efficacy: To assess the preliminary efficacy following open-label treatment with PRN473 Gel, 5% at Days 29 and 43	Efficacy During Open-Label Period • Change from Baseline in TSS for the 2 target lesions at Days 29 and 43. For EASI: • Percent change from Baseline in EASI at Days 29 and 43 • Percent change from Day 15 in EASI to Days 29 and 43 • Proportion of patients with EASI 50, EASI 75, and EASI 90 from Day 15 to Days 29 and 43 For PP-NRS: • Change in PP-NRS from Day 15 to Days 29 and 43 • Proportion of participants achieving at least 3-point reduction from Day 15 in PP-NRS at Days 29 and 43 • Proportion of participants achieving at least a 4-point reduction from Day 15 in PP-NRS at Days 29 and 43 • Change from Day 15 in weekly mean of PP-NRS at Days 29 and 43 For vIGA-AD: • Proportion of participants achieving at least 2 grade reduction in vIGA-AD to clear (vIGA-AD 0) or almost clear (vIGA-AD 1) from Day 15 to Days 29 and 43 Other endpoints: • Change from Day 15 in SCORAD at Days 29 and 43 • Change from Day 15 in percentage of treatable BSA at Days 29 and 43 • Change from Baseline in POEM at Days 15, 29, and 43 • Proportions of participants with a reduction in POEM ≥4 from Baseline at Days 15, 29 and 43 in participants with POEM≥4 at Baseline • Proportions of participants with a reduction in POEM ≥4 from Day 15 at Days 29 and 43 in participants with POEM≥4 at Baseline • Change from Baseline in DLQI at Days 15, 29, and 43

2 ANALYSIS POPULATIONS

The following populations for analyses are defined:

Table 2 - Populations for analyses

Participants Analysis Set	Description
Screened	All participants who signed the informed consent form (ICF).
Enrolled/Randomized	All participants from the screened population who have been allocated to a randomized intervention for each target lesion by interactive response technology (IRT) regardless of whether the intervention was received.
Safety	All randomized participants who receive any amount of study drug (SAR444727 or placebo) will be included in the Safety population. The Safety population will be based on the intervention actually received and will be used for the summaries of all safety assessments.
Pharmacokinetic	All participants who received any amount of active study drug (SAR444727) and have at least one pharmacokinetics (PK) sample taken will be included in the PK population. The PK population will be used for the summaries of all PK data.
Efficacy	- For double blind period All randomized participants who did actually receive at least 80% of prescribed study drug in the Blinded Period (for both lesion) and with at least 1 post-study drug administration efficacy (TSS) measurement. - For open label period All randomized participants who did actually receive at least 80% of prescribed study drug in the Blinded Period (for both lesion) and at least 80% of prescribed study drug in the Open-Label Period and at least 1 post-study drug administration efficacy (TSS) measurement. Participants will be analyzed according to the intervention they actually received.
Biomarker	All randomized participants with no important deviations impacting Biomarker measurements, for whom the Biomarker data are considered sufficient and interpretable.

Note: "Screened" means a participant's, or their legally acceptable representative's, agreement to participate in a clinical study following completion of the informed consent process.

Participants exposed to study intervention before or without being randomized will not be considered randomized and will not be included in any analysis population. The safety experience of these participants will be reported separately.

3 STATISTICAL ANALYSES

3.1 GENERAL CONSIDERATIONS

In general, unless otherwise specified, continuous data will be summarized using the number of observations available, mean, Standard Deviation (SD), median, range (minimum and maximum). Categorical and ordinal data will be summarized using the count and percentage of participants, as appropriate.

The baseline value is defined as the last available value before the first dose of Investigational Medicinal Product (IMP). For participants randomized but not treated, the baseline value is defined as the last available value before randomization.

Unless otherwise specified, analyses will be performed by intervention group (and overall, for baseline and demographics characteristics).

Observation period

The observation period will be divided into 3 segments:

- The **pre-treatment period** is defined as the period up to first IMP administration.
- The **treatment-emergent (TE) period** is defined as the period from the first IMP administration to the end of study (EOS) visit (EOS day included).
- The **post-treatment period** is defined as the period from the end of the TE period (starting the day after date of EOS visit).

Double blind analysis period is defined as the period from the date of first IMP up to the Day 15 (administration of first open label IMP) Visit or date of IMP discontinuation which ever comes first.

3.2 PRIMARY ENDPOINT(S) ANALYSIS

The primary endpoints detailed in this section are safety and tolerability of SAR444727 in participants with mild to moderate AD. Details are given in Section 3.6.

3.2.1 Definition of endpoint(s)

The primary endpoints are incidence and severity of the adverse events (AEs) defined in Section 3.6.2, the standard clinical parameters (vital signs and electrocardiograms [ECGs]), the laboratory parameters defined in Section 3.6.3.1 and the assessment of local cutaneous tolerability defined in Section 3.6.3.2.

3.2.2 Main analytical approach

All the safety analyses will be performed based on the safety population defined in Table 2.

The safety evaluation will be based upon the review of the individual values (clinically significant abnormalities), descriptive statistics (summary tables and figures). No statistical significance tests will be performed on safety data. No imputation will be performed.

Safety measures include AEs, Treatment-Emergent AEs (TEAEs), Serious AEs (SAEs), AEs leading to study intervention, treatment discontinuation (permanent or not), study discontinuation, and death. Overall AEs, TEAEs, and SAEs incidence tables will be presented by System Organ Class (SOC), high level group term (HLGT), high level term (HLT), and preferred term (PT for each study period and overall, showing the number (n) and percentage (%) of participants experiencing an AE. They will be described according to maximum intensity and relation to the study intervention.

Proportion of participants with at least 1 TEAE, treatment emergent SAE, TEAE leading to death, and TEAE leading to definitive treatment discontinuation will be tabulated by study period and overall.

For the changes in vital signs, ECGs and laboratory tests, the incidence of potentially clinically significant abnormalities (PCSAs) occurring during the TE period will be summarized overall and by baseline status.

For analysis local cutaneous tolerability see Section 3.6.3.2.

3.2.3 Sensitivity analysis

Not applicable.

3.2.4 Supplementary analyses

Not applicable.

3.3 SECONDARY ENDPOINT(S) ANALYSIS

The secondary endpoints are the Plasma SAR444727 concentrations at specified timepoints defined in Section 3.7.1.1.

3.4 TERTIARY/EXPLORATORY ENDPOINT(S) ANALYSIS

There are two type of exploratory endpoints. The first exploratory endpoint is biomarker to evaluate changes in blood samples, skin tape strippings, and skin biopsies. Details are given in Section 3.7.1.2.

The second exploratory endpoints are efficacy endpoints during double-blind period and Open-label period based on the efficacy population. For the double-blind period, treatment differences or ratios will be assessed for SAR444727 Gel, 5% versus placebo at Day 8 and Day 15, and data will be presented by treatment for the blinded period, for scores assessed per lesion, and overall otherwise. During the Open-Label Period, efficacy will be assessed mainly at Days 29 and 43,

overall. For TSS, data will be described over the full course of the study presented by treatment received during the double-blind Period.

More specifically, the following endpoints will be assessed:

During double-blind period

- Change from Baseline in lesional TSS for the 2 target lesions at Day 8 and Day 15
- Change from Baseline in daily lesional Peak Pruritus Numeric Rating Scale (PP-NRS) score for the 2 target lesions up to Day 15 and at Day 15
- Change from Baseline in lesional validated Investigator Global Assessment for AD (v-IGA-AD) score for the 2 taget lesions at Days 8 and 15
- Lesional v-IGA-AD response (proportion of participants with a lesional v-IGA-AD score of 0 [clear] or 1 [almost clear] and ≥2-grade improvement from Baseline) at Days 8 and 15

During Open-label period

- For lesional TSS
  - Change from Baseline in lesional TSS for the 2 target lesions at Days 29 and 43
  - Change from Day 15 in lesional TSS for the 2 target lesions at Days 29 and 43
- For PP-NRS
  - Change in daily global PP-NRS from Day 15 to Days 29 and 43
  - Change in weekly average of PP-NRS from Day 15 to Days 29 and 43
  - Proportion of participants achieving at least 3-point reduction from Day 15 in daily global PP-NRS at Days 29 and 43 in participants with PP-NRS≥3 at Day 15
  - Proportion of participants achieving at least a 4-point reduction from Day 15 in daily global PP-NRS at Days 29 and 43 in participants with PP-NRS≥4 at Day 15
- For Eczema Area and Skin Severity Index (EASI)
  - Percent change from Baseline in EASI at Days 29 and 43
  - Percent change from Day 15 in EASI at Days 29 and 43
  - Proportion of participants with at least a reduction ≥50% in EASI (EASI-50), with at least a reduction ≥75% in EASI (EASI-75), with at least a reduction ≥90% in EASI (EASI-90), and with at least a reduction ≥100% in EASI (EASI-100), from Baseline to Days 15, 29 and 43
  - Proportion of participants with EASI-50, EASI-75, EASI-90, and EASI-100 from Day 15 to Days 29 and 43
- For v-IGA-AD
  - Proportion of participants achieving vIGA-AD of 0 (clear) or 1 (almost clear) at Day 29

  - Proportion of participants achieving a vIGA-AD of 0 (clear) or 1 (almost clear) at Day 43
  - Proportion of participants achieving vIGA-AD of 0 (clear) or 1 (almost clear) and a reduction of ≥2 points from Day 15 to Day 29
  - Proportion of participants achieving vIGA-AD of 0 (clear) or 1 (almost clear) and a reduction of ≥2 points from Day 15 to Day 43
- For Body Surface Area (BSA)
  - Change from Day 15 in percentage of treatable BSA at Days 29 and 43
- For Scoring Atopic Dermatitis (SCORAD)
  - Percent change from Day 15 in SCORAD index at Days 29 and 43
- For Patient Oriented Eczema Measure (POEM)
  - Change from Baseline in POEM at Days 15, 29, and 43
  - Change from Day 15 in POEM at Days 29 and 43
  - Proportions of participants with a reduction in POEM ≥4 from Baseline at Days 15, 29 and 43 in participants with POEM≥4 at Baseline
  - Proportions of participants with a reduction in POEM ≥4 from Day 15 at Days 29 and 43 in participants with POEM≥4 at Day 15
- For Dermatology Quality of Life Index (DLQI)
  - Change from Baseline in DLQI at Days 15, 29, and 43.
  - Change from Day 15 in DLQI at Days 15, 29, and 43
  - Proportions of participants with a reduction in DLQI ≥4 from Baseline at Days 15, 29 and 43 in participants with DLQI≥4 at Baseline
  - Proportions of participants with a reduction in DLQI ≥4 from Day 15 at Days 29 and 43 in participants with DLQI≥4 at Day 15

Analyses for binary endpoints

The binary endpoints will be descriptively summarized using number, percentage and 95% confidence interval (CI) of percentage at each time point.

The proportion of subjects meeting the binary endpoint during the Open label period and corresponding exact 95% and 80% CI (95% CI and 80% CI respectively calculate with Wilson score method) will be summarized.

For the intra-participant comparison of SAR444727 vs placebo during the double blind period, binary endpoints (only for lesional v-IGA-AD response) will be analyzed for Day 8 and Day 15 separately, using a logistic regression model with intervention (SAR444727, placebo) as fixed effects. Odds ratio and difference in proportions as well as the corresponding 95% CI will be provided.

Analyses for continuous endpoints

The descriptive statistics (mean, SD, SEM, median, Q1, Q3, and range) for all continuous endpoints collected will be provided by treatment and time point on raw data, absolute changes or percent changes from baseline using the baseline efficacy population. Boxplots will also be provided by treatment and time point. Absolute or percent change from baseline and ratio from Baseline (mean ± SEM and/or median with interquartile range) will also be produced by treatment for the double blind period.

For the intra-participant comparison of SAR444727 vs placebo, a linear mixed model (using restricted maximum likelihood) with repeated measurements will be fitted to estimate the difference in mean change in lesional TSS from Baseline to Day 15; and from Baseline to Day 8.

In addition to the visit, treatment, and visit-by-treatment interaction terms, the model includes the participant-specific baseline lesional TSS score covariate. Repeated measurements for visit are taken within participant and an unstructured covariance matrix will be used to model the within-subject variance-covariance errors. Baseline lesional TSS will be defined as the mean TSS from the two treated lesions at Baseline.

Change from baseline TSS= Intercept + TSS_{base} + VISIT + TRT + VISIT*TRT + Error

Least square means will be calculated for change from Baseline to Day15 for both treatments and differences of means for SAR444727 versus placebo with two-sided 95% CI will be derived from the model framework.

The model may be simplified if there are convergence issues.

SAS Statement

```
proc mixed data= method=reml;
        class VISITNUM USUBJID TRT;
        model CHGSC=BASESC TRT VISITNUM TRT*VISITNUM/solution ddfm=kr ;
        repeated VISITNUM*TRT/type=UN subject=USUBJID;
        lsmeans VISITNUM*TRT /slice=VISITNUM  cl;
        estimate "SAR versus Plbo D15" TRT -1 1 VISITNUM*TRT 0 0 -1 1 /cl;
        estimate "SAR versus Plbo D8" TRT -1 1 VISITNUM*TRT -1 1 0 0 /cl;

run;
```

Participants with missing data at Baseline will not be included in the analysis. Participants with one or more post-dose timepoints will be included. Mixed model for repeated measures (MMRM) to account for missing data is used for the primary analysis under the missing at random (MAR) framework. Parameters will be estimated using restricted maximum likelihood method with the Newton-Raphson algorithm. Denominator degrees of freedom will be estimated using Kenward-Roger adjustment. All efficacy data after discontinuation of treatment will not be considered.

The same analysis will be conducted for lesional v-IGA-AD score at Days 8 and 15 and lesional PP-NRS. For the other efficacy parameters, only descriptive analyses will be provided.

The weekly average PP-NRS scores will be defined as the average of daily non-missing scores within the week preceding the given visit and will be calculated if there is a minimal amount of 4 non-missing scores.

The POEM score is a 5-point scale: 0 (“No days”), 1 (“1-2 days”), 2 (“3-4 days”), 3 (“5-6 days”) and 4 (“Every day”). The POEM score is calculated by summing the values for the 7 items.

If two or more questions are left unanswered the questionnaire is not scored.

The DLQI is a 4-point scale: 0 (“Not relevant”/“Not at all”), 1 (“A little”), 2 (“A lot”), 3 (“Very much”). For Question 7, “Prevented work or studying” is scored at 3. The DLQI is calculated by summing the score of each question.

The EASI-50/75/95/100 response is defined as a participant achieved a decrease by at least 50%/ 75%/ 95%/100% of EASI from Day 15.

Change in lesional TSS, PP-NRS (daily global and weekly average), EASI, BSA, SCORAD, POEM, DLQI during the Open label period will be analyzed descriptively. Estimations with 95% and 80% CIs may be derived. Sub-score of EASI by localization will also be provided.

Supplemental analyses

Where appropriate, supplemental analyses may be presented excluding observations after administration of rescue medication. No imputation will be made.

3.5 MULTIPLICITY ISSUES

No adjustment will be made for multiple analyses.

3.6 SAFETY ANALYSES

All safety analyses will be performed on the safety population as defined in Section 2, during double blind and Open-label period separately and overall unless otherwise specified, using the following common rules:

- The analysis of the safety variables will be essentially descriptive, and no testing is planned.
- Safety data in participants who do not belong to the safety population (eg, exposed but not randomized) will be provided separately.

Safety data will be assigned to study phase as following:

- Blinded Period, if the TEAE onset was between the first administration (Day 1) of any study intervention in the Blinded Period and the first administration of study intervention (SAR444727 Gel, 5%) in the Open-Label Period (scheduled Day 15 morning).

- Open-Label Period, if the TEAE onset was after the first administration of study intervention (SAR444727 Gel, 5%) in the Open-Label Period (scheduled Day 15 morning).

3.6.1 Extent of exposure

The extent of IMP exposure will be assessed by the duration of IMP exposure and compliance and will be summarized in the safety population for the double-blind period and the Open-label period.

Duration of IMP exposure

For each study period, duration of IMP exposure is defined as last IMP administration date – first IMP administration date + 1 days, regardless of unplanned intermittent discontinuation(s). If the date of the last dose of IMP is missing, the duration of IMP will be left as missing.

For each study period, duration of IMP exposure will be summarized quantitatively and categorically:

- Double-blind period: 1 day to ≤7 days, > 8 to <15 days, and ≥15 days
- Open-label period: 15 days to ≤29 days, > 29 to ≤43 days, and >43 days

Additionally, the cumulative duration of treatment exposure defined as the sum of the duration of treatment exposure over each study period for all participants will be provided.

Treatment compliance

Percentage of treatment compliance for a participant will be defined as the number of administrations/days that the participant was compliant divided by the total number of administrations/days that the participant was planned to take from the first administration of IMP up to the actual last administration of IMP.

Treatment compliance will be summarized over each study period, quantitatively and categorically: <80%, ≥80% by treatment (SAR444727 Gel, 5% or placebo) and overall for the Open-label phase.

3.6.2 Adverse events

General common rules for adverse events

All AEs will be coded to a LLT, PT, HLT, HLGT, and associated primary SOC using the Medical Dictionary for Regulatory Activities (MedDRA) version currently in effect at Sanofi at the time of database lock.

The AEs will be analyzed in the following 3 categories:

- Pre-treatment AEs: AEs that developed, worsened or became serious during the pre-treatment period.

- TEAEs: AEs that developed, worsened or became serious during the TE period
- Post-treatment AEs: AEs that developed, worsened or became serious during the post-treatment period

Similarly, the AE leading to deaths will be analyzed in the pre-treatment, TE and post-treatment periods.

The primary focus of AE reporting will be on TEAEs. Pre-treatment and post-treatment AEs will be described separately. Main summary will be per study period (Blinded Period, Open-Label Period) and overall.
If selected TEAEs from the Blinded Period can be clearly assigned to one of the study interventions treated lesions, they may be presented additionally assigned to the treatment of the corresponding lesion.

An AE with incomplete or missing date/time of onset (occurrence, worsening, or becoming serious) will be classified as a TEAE unless there is definitive information to determine it is a pre-treatment or a post-treatment AE.

If the assessment of the relationship to IMP is missing for an AE, this AE will be assumed as related to IMP. If the severity/grade is missing for an AE, the severity/grade will be left as missing. AEs which are possibly related to study intervention and have onset date after the first dose of SAR444727 will be considered possibly related to SAR444727, unless they are documented as possibly related to the study intervention formulation of the placebo-treated lesion and not possibly related to the study intervention formulation of the SAR4447272 Gel, 5%-treated lesion.

The AE tables will be sorted as indicated in Table 3.

Table 3 - Sorting of AE tables

AE presentation	Sorting rules
SOC and PT	By the internationally agreed SOC order and decreasing frequency of PTs[a, b]
PT	By decreasing frequency of PTs[a]

a Sorting will be based on the overall incidence
b The table of all TEAEs presented by SOC and PT will define the presentation order for all other tables (eg, treatment-emergent SAE) presented by primary SOC and PT, unless otherwise specified.

Analysis of all adverse events

The overview of TEAEs with the details below will be generated:

- Any TEAE
- Any severe TEAE
- Any treatment emergent SAE
- TEAE leading to death, if any

- Any TEAE leading to permanent intervention discontinuation
- Any TEAE leading to permanent study discontinuation
- Any treatment emergent AE of special interest (AESI) (Expedited reports as described in section 8.3.7 of the protocol will be considered as AESIs)

The AE summaries of Table 4 will be generated with number (%) of participants experiencing at least one event and sorted by the internationally agreed SOC order and decreasing frequency of PTs. Sorting will be based on experimental study drug intervention group (see Table 3).

Table 4 - Analyses of adverse events

Type of AE	MedDRA levels
All TEAE	Primary SOC and PT
TEAE related to IMP as per Investigator's judgment	Primary SOC, and PT
Treatment emergent SAE	Primary SOC, and PT
Treatment emergent SAE related to IMP as per Investigator's judgment *[optional]*	Primary SOC, and PT
TEAE leading to permanent intervention discontinuation *[optional]*	Primary SOC, and PT
TEAE leading to death (death as an outcome of the AE as reported by the Investigator in the AE page) *[optional]*	Primary SOC and PT
AESI	Primary SOC and PT

In addition, the all TEAE summary by Primary SOC and PT will be performed by trial impact (disruption) due to COVID-19 (coronavirus disease 19). The number (%) of participants experiencing at least one treatment emergent COVID-19 related AE by primary SOC and PT, if applicable.

Optional tables mentioned in Table 4 are to be done in case of sufficient number of events.

Deaths, serious, and other significant adverse events

Deaths and SAEs will be listed.

Adverse events leading to intervention/study discontinuation

AE leading to intervention or study discontinuation will be listed.

Analysis of adverse events of special interest (AESIs)

AESIs will be selected for analyses as indicated in Table 5. Number (%) of participants experiencing at least one event will be provided for each event of interest, by PT if applicable. Tables will be sorted as indicated in Table 3.

Table 5 - Selections for AESIs

AESIs	Selection
Increase in alanine transaminase (ALT)	e-CRF specific tick box on the AE page
Pregnancy	Specific page
Symptomatic overdose (serious or nonserious) with IMP	Specific page

3.6.3 Additional safety assessments

3.6.3.1 Vital signs, electrocardiograms (ECGs) and laboratory variables

The following variables will be analyzed. They will be converted into standard international units.

- Vital signs (see Section 8.2.2 of the protocol): heart rate, systolic and diastolic blood pressure, weight, temperature
- ECG variables (see Section 8.2.3 of the protocol): heart rate, PR, QRS, QT, and corrected QTc (according to Bazett/Fridericia)
- Laboratory variables (see Section 8.2.4.1 of the protocol): hematology, clinical chemistry, coagulation, urinalysis

For laboratory parameters, out-of-normal range definitions will be listed.

Data below the Lower Limit Of Quantitation/detection limit (LLOQ) will be replaced by half of the LLOQ, data above the Upper Limit Of Quantification (ULOQ) will be replaced by ULOQ value.

Quantitative analyses

When relevant, vital signs, ECG variables above and for laboratory variables, descriptive statistics for results and changes from Baseline as appropriate will be provided for each planned visit and time/analysis window.

For vital signs, ECG and laboratory variables, mean changes from Baseline with the corresponding standard error deviation will be plotted over time.

Analyses according to PCSA

PCSA analyses will be performed based on the PCSA list currently in effect at Sanofi at the time of the database lock. For laboratory parameters for which no PCSA criteria are defined, similar analyses will be done using out-of-normal ranges, if applicable. For parameters defined as efficacy/pharmacodynamic endpoints, PCSA summaries will not be provided.

Analyses according to PCSA will be performed based on the worst value during the TE period, using all measurements (either local or central, either scheduled, nonscheduled or repeated).

For laboratory variables above, the incidence of participants with at least one PCSA during the TE period will be summarized regardless of the baseline level and according to the following baseline status categories:

- Normal/missing
- Abnormal according to PCSA criterion or criteria

Summary statistics (including number, mean, median, Q1, Q3, standard deviation, minimum and maximum) of all ECG variables (raw values and changes from Baseline) will be calculated for each planned visit by intervention group. In addition, mean changes from Baseline with the corresponding standard errors will be plotted over time in each intervention group.

For ECGs, the incidence of participants with at least one abnormal ECG during the TE period will be summarized regardless of the baseline level and according to the following Baseline status categories:

- Normal/missing
- Abnormal

Listing of participants with QTc >480 msec and/or change from baseline QTc >60 msec

If any, an intext listing of participants with QTc >480 msec and/or change from Baseline QTc >60 msec will be provided.

3.6.3.2 Local cutaneous tolerability

The local cutaneous tolerability is assessed by the incidence and severity (grade) of application-site events such as burning/stinging, itching, and erythema.

Grading of application site local tolerability symptoms will be recorded using the grading scale (cf Protocol Appendix 4, Section 10.4.1) following each dosing during the blinded period. During the Open Label period symptom grading will record worst symptom observed on the lesional areas treated within approximately 30 min after dosing.

For each lesion, number and proportion of participants with at least one application-site event (such as burning/stinging, itching, and erythema) over the 2-week double-blind period, the 4-week Open label period, overall and by type of sign will be summarized. For each lesion, and by type of sign, the distribution of corresponding worst grade (intensity) will be summarized. The localization of the lesion on the body with an application-site event of local untolerability will be reported.

Burning/stinging sub-score assessments over time by lesion during blinded period and overall during Open-label period will be also summarized.

Overview of AEs linked to local cutaneous tolerability will be presented by SOC, PT for each study period and overall.

No analysis of the total score will be performed.

3.7 OTHER ANALYSES

3.7.1 Other variables and/or parameters

3.7.1.1 PK analyses

For PK concentrations, the arithmetic mean, SD, median, minimum, maximum, percent coefficient of variation (CV%), geometric mean, geometric coefficient of variation (geometric CV%), and the number of observations below LLOQ values will be presented by timepoint. For the purpose of calculating summary statistics, plasma concentrations (and applicable metabolites) that are below the LLOQ will be set to 0 for both pre-dose and post-dose samples excepted for the geometric mean and associated coefficient of variation for which they will be considered as missing. Additional analyses will be performed as deemed necessary upon review of the data.

Graphical displays of concentrations over time may also be presented.

3.7.1.2 Biomarkers analyses

Statistical analyses of biomarkers (RNAseq data, proteomic data…) will be exploratory in nature and will be detailed in a Biomarker SAP and results may be analysed separately.

3.8 INTERIM ANALYSES

An interim analysis (IA) for internal decision making will be implemented when approximately 25 or more of the planned participants have completed the Blinded Period (Day 15). Available data of the Open Label Period may be included in the analysis as appropriate.

The outcome is meant for internal decision making and may lead to early termination of the study only in case of unfavorable signals, or continuation without any changes.

3.8.1 General considerations for the interim analysis

The Sponsor team that will analyze the data will include: a Medical Monitor, a biostatistician, a programmer, and a safety designee (global safety officer, [GSO]). Only the biostatistician and the programmer will have the access to unblinded individual data at the time of the analysis, which will not be provided to other Sponsor team members reviewing the data. Results will be provided in a restricted way following a dissemination plan, issued before any treatment code release for the analysis established upfront before the unblinding. The blinding will be preserved notably toward the Investigator, other site staff involved in the conduct of the trial, and participants.

The results of this IA will be considered preliminary results as they will not be based on final data. Final analysis will be conducted after database lock for the clinical study report.

Analyses methods and conventions described in the other sections of this SAP will be applied for all analyses as applicable.

3.9 CHANGES TO PROTOCOL-PLANNED ANALYSES

No major statistical changes were included in the protocol amendment(s).

One major statistical change in SAP to the current amended protocol has been made and is summarized in the section below:

Major statistical changes in SAP to (current) amended protocol

Current Amended Protocol Number	Section	Changes	Rationale
	2- Analysis Populations	Delete ITT population Redefine Efficacy population	ITT population is not used in the analysis Efficacy population has been redefined to take into account compliance durin both periods (double-blind and open-label period)

4 SAMPLE SIZE DETERMINATION

No sample size calculations were performed due to the exploratory nature of this study.

The sample size of up to 40 for this study with participants receiving both SAR444727Gel, 5% and placebo is based upon empirical clinical consideration. The sample size is considered adequate to evaluate the safety, tolerability, and PK of topically administered SAR444727.

This study is signal seeking and neither aimed nor powered to provide formal inferential statistical analyses.

5 SUPPORTING DOCUMENTATION

5.1 APPENDIX 1 LIST OF ABBREVIATIONS

AD:	atopic dermatitis
AE:	adverse event, adverse event
AESIs:	adverse events of special interest
AUC:	area under the curve
BID:	twice daily
BLQ:	below the limit of quantification
BSA:	body surface area
CI:	confidence interval
Cmax:	maximum plasma concentration
COVID-19:	coronavirus disease 19
CV%:	percent coefficient of variation
DLQI:	dermatology life quality index
EASI:	eczema area and skin severity index
ECG:	electrocardiogram
EOS:	end of study
HLT:	high level term
ICF:	inform consent form
IMP:	investigational medicinal product
IRT:	interactive responses technology
LLOQ:	lower limit of quantification
LLT:	lower-level term
MedDRA:	medical dictionary for regulatory activities
PCSA:	potentially clinically significant abnormality
PK:	pharmacokinetics
POEM:	patient oriented eczema measure
PP-NRS:	peak pruritus numeric rating scale
PT:	preferred term
SAE:	serious adverse event
SAP:	statistical analysis plan
SCORAD:	scoring atopic dermatitis
SD:	standard deviation
SEM:	standard error of the mean
SOC:	system organ class
TE:	treatment-emergent
TEAE:	treatment-emergent adverse event
TSS:	total sign score
vIGA-AD:	validated Investigator Global Assessment – Atopic Dermatitis
WHO-DD:	World Health Organization-drug dictionary

5.2 APPENDIX 2 PARTICIPANT DISPOSITION

The number (%) of participants included in each of the analysis populations listed in Table 2 will be provided.

Screen failures are defined as participants who consent to participate in the study (ie, signed the informed consent form [ICF]) but are not subsequently randomized. The number (%) of screen failures and reasons for screen failures will be provided in the screened population.

The number (%) of participants in the following categories will be provided:

- Screen / screen-failed
- Randomized participants
- Randomized but not exposed participants
- Randomized and exposed participants (ie, having a randomization number assigned and who received at least one administration of IMP
- Participants who did not complete the study treatment period as per protocol and main reason for permanent intervention discontinuation
- Participants who completed the study period as per protocol
- Participants who did not complete the study period as per protocol and main reason for study discontinuation
- Reason for study period withdrawal by subject

Reasons for permanent study intervention and study discontinuation “AE” and “other reasons” will be split as related versus not related to COVID-19.

The number (%) of exposed and not randomized participants will also be summarized, if applicable.

Listings of participants with permanent study intervention discontinuation or with premature end of study (i.e. who did not complete the study period as per protocol) will be provided for the safety population along with the main reason of discontinuations and related to COVID-19 or not, respectively.

A summary of visits impacted by COVID-19 pandemic will be provided along with the description of the impact (visit not done, visit partially done on site / by phone, visit done but delayed), if applicable. In addition, the number (%) for reasons for exclusion from COVID-19 non-impacted population will be provided, if applicable. A listing of participants excluded from this population will be provided.

Protocol deviations

Critical and major protocol deviations (automatic or manual) will be listed in the randomized population. They will be displayed separately as related versus not related to COVID-19. The list of predefined protocol deviations can be found in the eTMF (Trial management Section).

5.3 APPENDIX 3 DEMOGRAPHICS AND BASELINE CHARACTERISTICS, PRIOR OR CONCOMITANT MEDICATIONS

Demographics, baseline characteristics, medical surgical history

The following demographics and baseline characteristics, medical and surgical history and disease characteristics at baseline will be summarized using descriptive statistics in the randomized population.

Demographic and baseline characteristics

- age in years as quantitative variable and in categories (18 to <65, ≥65)
- gender (Male, Female)
- race (White, Black or African American…)
- ethnicity [(Hispanic or Latino, not Hispanic or Latino)]
- weight, height, body mass index screening v-IGA-AD score
- screening %BSA
- EASI

Target lesion baseline (lesional TSS, lesional PP-NRS, lesional v-IGA-AD) characteristics data will be summarized by treatment.

Baseline safety and efficacy parameters (apart from those listed above) will be presented along with the safety and efficacy summaries.

Specific disease history includes time from diagnosis, severity of the disease (v-IGA-AD) will be summarized.

Medical and surgical history

Additionally, all medical and surgical history will be coded to a LLT, PT, HLT, HLGT, and associated primary SOC using the MedDRA version currently in effect at Sanofi at the time of database lock. All medical history will be summarized by primary SOC and PT using a frequency table (number and % of participants) by study intervention group.

Prior or concomitant medications

All medications will be coded using the World Health Organization-Drug Dictionary (WHO-DD) using the version currently in effect at Sanofi at the time of database lock.

- Prior medications are those the participant used prior to first IMP intake. Prior medications can be discontinued before first administration or can be ongoing during study intervention period.
- Concomitant medications are any medications received by the participant during the TE period.

- Post-treatment medications are those the participant took after the TE period.

A given medication can be classified as a prior medication and/or as a concomitant medication and/or as post-treatment medication. If it cannot be determined whether a given medication was taken prior or concomitantly or post, it will be considered as prior, concomitant, and post-treatment medication.

The prior and concomitant medications will be summarized for the safety population, by anatomic and therapeutic level. The summaries will be sorted by decreasing frequency of anatomic category (ATC) based on incidence in SAR444727 group. In case of equal frequency, alphabetical order will be used. Participants will be counted once in each ATC category (anatomic or therapeutic) linked to the medication.

5.4 APPENDIX 4 DATA HANDLING CONVENTIONS

Double blind analysis period is defined from the date of first IMP up to Day15 or date of IMP discontinuation which ever comes first.

Day15 of Open label period is defined as the first day the placebo is not used.

For parameters with evaluations before administration and in cases of rechecked value(s) for one participant, only the last observation will be used as baseline in descriptive statistics and derivations of other parameter values. After baseline, only observations planned in the protocol will be used in descriptive statistics.

For clinical laboratory parameters with non-numeric values, the imputed values used for the descriptive statistics and/or the flags will be determined by considering the following rules:

- If database value is ‘ <X’, the value used will be X/2
- If database value is ‘ >X’, the value used will be X
- If database value is a range (eg, ‘X – Y’), the values used will be (Y + X)/2

Pharmacokinetic analysis

For ease of presentation, mean values will be arithmetic mean unless specified. Concentration values below the plasma assay limit will be treated as zero in all summary statistics. Mean values below LLOQ will be reported as LLOQ in the tables and not plotted in the figures if after maximal plasma concentration (C_{max}). Mean calculations and their associated statistics will be generated from unrounded numbers and may differ slightly from those values that would be determined using the rounded numbers displayed in the tables. Values expressed in all tables will before ease of presentation and will not be meant to imply accuracy to more than 3 significant figures.

Area under the curve (AUC) values extrapolated by more than 30% will be excluded from any pharmacokinetic statistical analysis.

Analysis windows for time points

The following analysis windows will decide how the scheduled and/or unscheduled visits will be used in the by-visit analyses of efficacy. For participants with premature study discontinuation, follow-up measurements will be reallocated to the corresponding analysis window and reported together with other measurements.

A measurement (scheduled or unscheduled) will be used if it is available and measurement date is within the analysis window.

After applying these time windows, if multiple assessments are associated to the same time point, the closest from the targeted study day will be used. If the difference is a tie, the value after the targeted study day will be used. If multiple valid values exist within a same day, then the first value of the day will be selected when time is available, otherwise the scheduled exam will be used.

If there is no measurement for a given parameter in an analysis window, data will be considered missing for the corresponding visit.

Table 6 - Analyses window definition

Study period	Scheduled visit post baseline	Targeted study day	Analysis window in study days
Double blind period	Day 8	8	7 to 9
Open label period	Day 15	15	13 to 18
	Day 29	29	25 to 33
	Day 43	43	39 to 47

Study days are calculated considering Day 1 as the day of first administration of intervention in blinded period.

Unscheduled and end of treatment (EOT)/EOS visits

Unscheduled visit measurements of efficacy, laboratory data, vital signs, PK and biomarkers will be used, in particular for computation of Baseline, the last on-treatment value, analysis according to PCSAs, and the shift summaries for safety. They will also be included in the by-visit summaries if they are re-allocated to scheduled visits.

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