STATISTICAL ANALYSIS PLAN

Protocol title:	**A Phase 2, International, Multicenter, Randomized, Double-blind, Placebo-controlled, Dose-ranging study of Efficacy and Safety of SAR441566 in Adults with Moderate to Severe Plaque Psoriasis**
Protocol number:	**DRI17849**
Compound number (INN/Trademark):	**SAR441566** **Not applicable/Not applicable**
Study phase:	**Phase 2**
Short Title:	**A study to evaluate efficacy and safety of SAR441566 in adults with plaque psoriasis**
Statistician:	[redacted]**(contractor, Ividata)**
Biomarker statistician:	[redacted]
Statistical project leader:	[redacted]
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VERSION HISTORY

This statistical analysis plan (SAP) for study DRI17849 is based on the protocol dated 25-Apr-2024. This is the second version of the SAP.

The first participant was randomized on 14-Nov-2023. This SAP is approved before the database lock.

Major changes in statistical analysis plan

SAP Version	Approval Date	Changes	Rationale
1	25-Oct-2024	Not Applicable	Original version
2	Current version	• Section 2: Definiton of PDy population is updated	• To clarify the definition
		• Section 3.4.1: Clarification of FACIT-Fatigue definition has been added	• To clarify the definition
		• Section 3.7: Deletion of Concentration-ECG section	• Decide not to perform this analysis
		• Section 3.7.1.1: Clarification of PK analyses has been added	• To clarify how the PK analysis will be performed
		• Section 5.3: The prior systemic treatment use has been added in the baseline disease table.	• To clarify the prior treatment history
		• Section 5.4: The analysis window for PK has been added.	• To add more details for PK analysis.

1 INTRODUCTION

Major changes to the protocol-planned analyses are described in Section 3.9.

1.1 STUDY DESIGN

This is a parallel group, phase 2, randomized, double-blind, placebo controlled, dose-ranging study, international, multicenter, 12-week study. It is designed to assess the therapeutic dose, efficacy, and safety of treatment with SAR441566 in male and female adults with moderate to severe plaque psoriasis.

Study details include:

- Screening period (4 weeks and not less than 11 days before Day 1).
- Treatment period (12 weeks ±3 days).
- Post-treatment period (safety follow-up) (4 weeks ±3 days).
- The total number of study visits will be 7.

Participants who satisfy the inclusion and exclusion criteria will be randomized to either SAR441566 or matching placebo, administered orally for 12 weeks.

Visits during the 12-week treatment period will occur at Week 0 (baseline/randomization), 2, 4, 8, and 12 weeks, followed by a 4-week post-treatment period if enrolled under the protocol dated 04-Dec-2023 or after, otherwise by a 2-week post-treatment period.

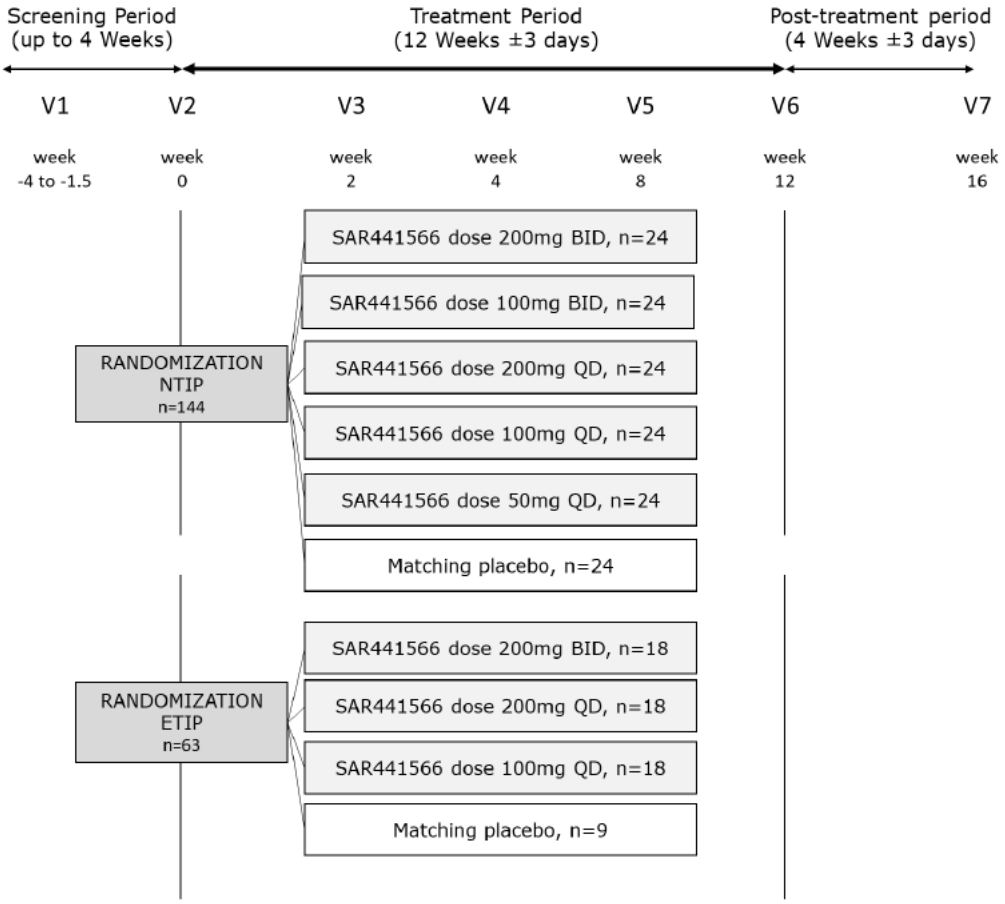
Approximately 207 adult participants who meet the inclusion/exclusion criteria will be randomized to either SAR441566 or matching placebo in two different strata, ie, Naive Targeted Immunotherapy Population (NTIP) and Experienced Targeted Immunotherapy Population (ETIP).

- NTIP: Approximately 144 participants will be randomized to either SAR441566 or matching placebo (120 in the five SAR441566 groups and 24 in the placebo group) in this stratum. This population is the primary population for efficacy analysis.
- ETIP: Approximately 63 participants will be randomized to either SAR441566 or matching placebo (54 in the three SAR441566 groups and 9 in the placebo group) in this stratum. This population is for exploratory purposes only.

In the NTIP, there are 6 arms in this stratum with parallel groups of 200 mg bis in die (BID) (n=24), 100 mg BID (n=24), 200 mg quaque die (QD) (n=24), 100 mg QD (n=24), 50 mg QD (n=24), or placebo (n=24), at a randomization ratio of 1:1:1:1:1:1. Duration of investigational medicinal product (IMP) treatment is 12 weeks. (See Figure 1 for schema).

In the ETIP, there are 4 arms in this stratum with parallel groups of 200 mg BID (n=18), 200 mg QD (n=18), 100 mg QD (n=18) or placebo (n=9), at a randomization ratio of 2:2:2:1. Duration of IMP treatment is 12 weeks. (See Figure 1 for schema).

Figure 1 - Graphical study design



Study primary analysis will be conducted after study completion.

1.2 OBJECTIVES AND ENDPOINTS

Table 1 - Objectives and endpoints

Objectives	Endpoints
Primary	
• To demonstrate the superiority of SAR441566 over placebo in participants with moderate to severe plaque psoriasis, in the NTIP.	• Proportion of participants with a 75% or greater PASI score (Psoriasis Area and Severity Index score) improvement (reduction) from baseline (PASI75) at Week 12.
Secondary	
• To evaluate the efficacy of SAR441566 in plaque psoriasis as compared to placebo in the NTIP.	• PASI percent change from baseline to Week 12. • Proportion of participants with static Psoriasis Global Assessment (sPGA) score 0 (complete clearance) or 1 (minimal disease) at Week 12.

Objectives	Endpoints
• To evaluate the safety of SAR441566.	• Incidence of TEAE, SAEs, and AEs of AESIs. • Incidence of study IMP permanent discontinuations and study withdrawals due to TEAEs. • Participants with medically significant changes in vital signs, ECG, and/or laboratory evaluations.
• To assess pharmacokinetics of SAR441566 in participants with moderate to severe plaque psoriasis.	• Plasma pre-dose and post-dose concentrations of SAR441566.
Tertiary/Exploratory	
• To evaluate the efficacy of SAR441566 in plaque psoriasis as compared to placebo change over time.	• PASI percent change from baseline to Week 4 and 8. [redacted] • The proportion of participants with a 90% or greater PASI reduction from baseline (PASI90) at Week 4, 8 and 12. [redacted] • The proportion of participants with PASI75 at Week 4, and 8. [redacted]
• To characterize the pharmacodynamic profile of SAR441566 in participants with plaque psoriasis.	• Change in peripheral blood soluble biomarkers (including but not limited to hsCRP, IL-17A, IL-17F, [redacted]

Objectives	Endpoints
[redacted]	
• To evaluate the impact of SAR441566 on health	• Change in Dermatology Life Quality Index (DLQI)
[redacted]	

1.2.1 Estimands

Primary estimands defined for main endpoints are summarized in Table 2 below. More details are provided in Section 3.

For all these estimands, the comparison of interest will be the comparison of SAR441566 vs. placebo.

Table 2 - Summary of primary estimand for main endpoints

Endpoint Category (estimand)	Estimands			
	Endpoint	**Population**	**Intercurrent event(s) (ICE) handling strategy**	**Population-level summary (Analysis and missing data handling)**
Primary objective: To demonstrate the superiority of SAR441566 over placebo in NTIP with moderate to severe plaque psoriasis.				
Primary endpoint (treatment policy/composite estimand)	Proportion of participants with	NTIP	Initiation of selected concomitant	Difference in the percentage of participants achieving

Endpoint Category (estimand)	Estimands			
	Endpoint	**Population**	**Intercurrent event(s) (ICE) handling strategy**	**Population-level summary (Analysis and missing data handling)**
	PASI75 response at Week 12.		medication[1]: It will be handled with the composite strategy, ie, participants will be considered as non-responders after such event.	PASI75 response at Week 12 between each active arm and placebo. Testing for odds ratio using the Cochran-Mantel-Haenszel test.
			Discontinuation of IMP: It will be handled with the treatment policy strategy. The primary endpoint will be assessed based on all assessments irrespective of the IMP discontinuation.	After applying the rules for the ICEs, the remaining missing data will be handled as follows: - Participants will be considered as non-responders
Secondary objective: To evaluate the efficacy of SAR441566 in plaque psoriasis as compared to placebo in the NTIP.				
Secondary endpoint (treatment policy/composite estimand)	PASI percent change from baseline to Week 12.	NTIP	Initiation of selected concomitant medication[1]: It will be handled with the composite strategy WOCF (Worst Observation Carried Forward), ie, data after the concomitant medication use will be assigned using the worst postbaseline value on or before the time of the medication usage.	Mean difference in PASI percent change from baseline to Week 12 between each active arm and placebo, using ANCOVA analysis.
			Discontinuation of IMP: It will be handled with the treatment policy strategy. The endpoint will be assessed based on all assessments irrespective of the IMP discontinuation.	After applying the rules for the ICEs, the remaining missing data will be handled as follows: - "Worst observation carried forward" (WOCF) approach will be used to impute missing data

Endpoint Category (estimand)	Estimands			
	Endpoint	**Population**	**Intercurrent event(s) (ICE) handling strategy**	**Population-level summary (Analysis and missing data handling)**
	Proportion of participants with sPGA score 0 or 1 at Week 12.	NTIP	Initiation of selected concomitant medication[1]: It will be handled with the composite strategy, ie, participants will be considered as non-responders after such event.	Difference in the percentage of participants with sPGA score 0 or 1 at Week 12 between each active arm and placebo. Testing for odds ratio using the Cochran-Mantel-Haenszel test.
			Discontinuation of IMP: It will be handled with the treatment policy strategy. The endpoint will be assessed based on all assessments irrespective of the IMP discontinuation.	After applying the rules for the ICEs, the remaining missing data will be handled as follows: - Participants will be considered as non-responders

[1]Selected concomitant medication are listed in Table 4.

2 ANALYSIS POPULATIONS

The following populations for analyses are defined.

Table 3 - Populations for analyses

Population	Description
Screened	All participants who signed the ICF.
Randomized	All participants from screened population who have been allocated to a randomized intervention by IWRS regardless of whether the intervention was received.
Intent-to-treat (ITT)*	All randomized participants. Participants will be analyzed according to the intervention allocated by randomization.
Safety	All randomized participants who have taken at least 1 dose of study intervention, regardless of the amount of treatment administered. Participants will be analyzed according to the intervention they received, ie, "as treated" group.
Pharmacokinetic (PK)	All participants from the safety population with at least one post-baseline PK result with adequate documentation of dosing and sampling dates and times. Participants having received only placebo will not be part of the PK population. Participants will be analyzed according to the intervention they received.
Pharmacodynamic biomarker (PDy) population	All randomized participants who (a) had at least one dose of study intervention (SAR441566 or placebo) and (b) had a sample drawn for biomarker measurement and successfully analyzed at baseline and at one or more post-baseline visits. The assignment of patients to interventions will be "as treated".
NTIP	All randomized participants who have never received targeted immunotherapy for psoriasis. Participants will be analyzed according to the intervention allocated by randomization.
ETIP	All randomized participants who previously received targeted immunotherapy for psoriasis. Participants will be analyzed according to the intervention allocated by randomization.

* Randomized population and ITT population are the same population in this study.

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.

Randomized participants for whom it is unclear whether they took the study intervention will be considered as exposed and will be included in the safety population as randomized.

For any participant randomized more than once, only the data associated with the first randomization (except if the first randomization is done by error) will be used in any analysis population. The safety experience associated with any later randomization will be reported separately.

For participants receiving more than one study intervention during the study, the intervention group for "as-treated" analyses will be the intervention group as randomized if the participant received at least one administration as randomized.

If a participant is stratified incorrectly at randomization, the participant will be analyzed as stratified per the ITT principle.

3 STATISTICAL ANALYSES

3.1 GENERAL CONSIDERATIONS

In general, continuous data will be summarized using the number of observations available, mean, standard deviation (SD), median, Q1, Q3, minimum, and maximum. Categorical and ordinal data will be summarized using the count and percentage of participants. The graphical plots will be presented for selected endpoints including primary, secondary and some exploratory endpoints.

The baseline value is defined as the last available value before the first dose of double-blind 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/dose level (and overall for baseline and demographics characteristics).

Observation period

The observation period will be divided into 4 segments:

- The **pre-treatment period** is defined as the period up to first double-blind investigational IMP administration.
- The **treatment-emergent (TE) period** is defined as the period from the first IMP administration to the last IMP administration + 5 days. The treatment-emergent period includes the following 2 periods:
  - The **on-treatment period** is defined as the period from the first IMP administration to the last administration of the IMP + 1 day.
  - The **residual treatment period** is defined as the period from the end of the on-treatment period to the end of the treatment-emergent period.
- The **post-treatment period** is defined as the period from the end of the treatment-emergent period.

3.2 PRIMARY ENDPOINT(S) ANALYSIS

The primary endpoint is the response in PASI75, which is defined by proportion of participants with a 75% or greater PASI improvement (reduction) from baseline at Week 12.

3.2.1 Definition of endpoint(s)

The primary endpoint is defined based on psoriasis area and severity index (PASI) as explained below.

Psoriasis area and severity index (PASI)

The PASI is an established measure of clinical efficacy for psoriasis medications. The PASI is a tool that provides a numeric scoring for participants' overall psoriasis disease state, ranging from 0 to 72. Higher scores indicated greater Psoriasis severity. It is a linear combination of percent of surface area of skin that is affected and the severity of erythema, induration, and desquamation over four body regions.

The endpoints used are based on the percent reduction from baseline, generally summarized as a dichotomous outcome based on achieving over an X% reduction (or PASIX), where X is 50, 75, 90 and 100. The primary endpoint is defined as the proportion of participants who achieve PASI75.

To calculate the PASI, the four main body areas are assessed: head (h), trunk (t), upper extremities (u) and lower extremities (l). These correspond to 10, 30, 20 and 40% of the total body area respectively.

The physician quantifies the percentage of the considered body area covered by plaque psoriasis. This percentage of psoriatic involvement is translated into a numerical value "Ax" for each body area: 0 = no involvement, 1 = <10%, 2 = 10 to <30%, 3 = 30 to <50%, 4 = 50 to <70%, 5 = 70 to <90%, and 6 = 90 to 100% involvement. These scores are noted Ah, At, Au, and Al in the formula below.

The signs of severity, erythema (E), induration (I) and desquamation (D) of lesions are assessed using a numeric scale 0-4 where 0 is a complete lack of cutaneous involvement and 4 is the severest possible involvement; scores are made independently for each of the areas, h, t, u and l and represents a composite score for each area. An illustration of judging erythema follows: 0 = no erythema, 1 = slight erythema, 2 = moderate erythema, 3 = striking erythema, and 4 = exceptionally striking erythema.

The PASI score is calculated according to the following formula:

$$PASI = 0.1(Eh+Ih+Dh)Ah + 0.3(Et+It+Dt)At + 0.2(Eu+Iu+Du)Au + 0.4(El+Il+Dl)Al$$

The PASI score will be set to missing if any severity score or degree of involvement is missing.

3.2.2 Main analytical approach

The individual statistical hypothesis for comparing each dose of SAR441566 vs. placebo on the primary endpoint at the two-sided significance level of 0.05 is as follows:

- Null hypothesis H0: The odds ratio between SAR441566 and placebo is equal to 1 when evaluating the primary endpoint,
- Alternative hypothesis H1: The odds ratio between SAR441566 and placebo is NOT equal to 1 when evaluating the primary endpoint.

The primary endpoint will be analyzed with the primary estimand defined according to the following attributes:

- Endpoint: Proportion of participants with a 75% or greater PASI score improvement from baseline at Week 12.
- Intervention condition: SAR441566 200 mg BID, 100 mg BID, 200 mg QD, 100 mg QD and 50 mg QD will be compared to placebo
- Analysis population: NTIP population
- Intercurrent events:
  - IMP discontinuation: it will be handled with the treatment policy strategy. The primary endpoint will be assessed based on all assessments irrespective of the IMP discontinuation.
  - Starting the selected concomitant medication (ie, prohibited/permitted/rescue) (see Table 4): It will be handled with the composite variable strategy. For primary endpoint, participants who receive selected concomitant medications will be considered as non-responders for time points after the medication usage. For other participants, all available data including those collected during the off-treatment period will be used to determine the responder/non-responder status. Imputation rules of partial start dates of medication are detailed in Section 5.6.

Blinded medical review of participants that receive the selected concomitant medication listed in Table 4 will be performed before database lock by considering the type of medication, indication, timing, frequency, and the potential impact on efficacy to make the final decision about the list.

Table 4 - Selected prohibited/permitted/rescue concomitant medications

Class of Medications	Selection Criteria	Composite variable strategy[1]
[redacted]		

Class of Medications	Selection Criteria	Composite variable strategy[1]
[redacted]		

strategy. When no, a treatment policy strategy will be applied.

- Population-level summary: Difference in the percentage of participants achieving PASI75 response at Week 12 between each active arm and placebo. The Cochran-Mantel-Haenszel (CMH) test for odds ratio will be used for the primary endpoint analysis, adjusting for baseline disease severity defined by baseline PASI (<= 20, >20). The two-sided p-value based on CMH test for odds ratio and 95% confidence intervals (CI) based on Newcombe method (1) for Mantel-Haenszel treatment difference will be presented (SAS code example in Section 5.4) . Multiplicity adjustment will be provided (See Section 3.5).
- After applying the rules for the ICEs, the remaining missing data will be handled as follows:
  - Participants will be considered as non-responders.

3.2.3 Sensitivity analyses

Not applicable.

3.2.4 Supplementary analyses

The following supplementary analysis will be conducted to assess the robustness of the primary estimand.

- As observed analysis (including all data after taking selected concomitant medications)

  The Cochran-Mantel-Haenszel analysis will be performed, but the data after taking the selected prohibited/permitted/rescue concomitant medications will be used in this supplementary analysis to evaluate the robustness of the primary analysis results with respect to the intercurrent event handling strategy. It implies that, in as observed analysis, treatment policy strategy will be used for all intercurrent events. Missing data will be imputed to non-responders when the response to PASI75 is missing.

3.2.5 Exploratory analyses

Dose-response relationship

For NTIP population, the dose-response relationship of QD doses will be evaluated by a 2-step MCP-Mod procedure (2, 3) on the primary endpoint among three QD doses (200 mg QD, 100 mg QD and 50 mg QD) vs. placebo. The first step of this procedure tests for an efficacy signal (compared to the null hypothesis of a flat, no dose-response curve) in a procedure. To account for the uncertainty of the dose-response shape, [redacted] (see Figure 2 on logit scale and Figure 3 on original scale). The second step is the estimation of the dose-response curve, provided that an efficacy signal is established in the first step.

A logistic regression model with covariates for PASI75 response rate, treatment and baseline severity will be used to assess the response rate of PASI75 in each of 3 QD dose groups and placebo group at the end of 12 weeks treatment. A logit transformation of the PASI75 response rate will be entered into the MCP-Mod procedure (see R code in Appendix 5.5). The null hypothesis of a flat dose-response curve (ie, no dose–response relationship) at the end of 12 weeks treatment for the primary endpoint will be jointly evaluated for each of the 6 candidate dose response models with a contrast test at 2-sided alpha = 0.05. If step 1 yields significant results, the best fitting model (smallest AIC) from the 6 predefined candidate models will be chosen using the generalized AIC. The suggested optimal dose will then be estimated from the final selected model.


Dose

3.3 SECONDARY ENDPOINT(S) ANALYSIS

The secondary endpoints detailed in this section are:

- PASI percent change from baseline to Week 12.
- Proportion of participants with sPGA score 0 (complete clearance) or 1 (minimal disease) at Week 12.

Other secondary endpoints analyses are defined in Section 3.6.2 (AE, SAE), Section 3.6.3.1 (laboratory abnormalities) and Section 3.7.1.1 (PK).

3.3.1.1 Definition of endpoint(s)

➢ **PASI percent change from baseline to Week 12**

Please refer to Section 3.2.1 for the definition of PASI. This secondary endpoint is the continuous endpoint to summarize the percent change of PASI at Week 12 comparing to the PASI at baseline.

- **Proportion of participants with sPGA score 0 (complete clearance) or 1 (minimal disease) at Week 12**

This secondary endpoint is the binary endpoint to summarize the proportion of participants with sPGA score 0 (complete clearance) or 1 (minimal disease) at Week 12, where sPGA score is defined as below.

static Psoriasis Global Assessment (sPGA)

The sPGA is a 5-point score ranging from 0 to 4, based on the physician's assessment of the average thickness, erythema, and scaling of all psoriatic lesions. The assessment is considered "static", which refers to the participant's disease state at the time of the assessments, without comparison to any of the participant's previous disease states, whether at Baseline or at a previous visit. A lower score indicates less body coverage, with 0 being clear and 1 being almost clear.

Erythema

- 0 Normal (post-inflammatory hyper/hypopigmentation may be present).
- 1 Faint, diffuse pink or slight red coloration.
- 2 Mild (light red coloration).
- 3 Definite red coloration (Dull to bright red).
- 4 Bright to Deep red coloration of lesions.

Induration (plaque elevation)

- 0 None.
- 1 Just detectable (slight elevation above normal skin).
- 2 Mild thickening (slight but definite elevation, typically edges are indistinct or sloped).
- 3 Clearly distinguishable to moderate thickening (marked definite elevation with rough or sloped edges).
- 4 Severe thickening with hard edges (marked elevation typically with hard or sharp edges).

Desquamation

- 0 No scaling.
- 1 Minimal focal scaling (surface dryness with some desquamation).
- 2 Predominately fine scaling (fine scale partially or mostly covering lesions).
- 3 Moderate scaling (coarser scale covering most or all of the lesions).

Overall Scoring resulting of the average of the Erythema, Induration and Desquamation score:

- Clear 0 = 0 for all three symptoms. Post-inflammatory hyper/hypopigmentation may be present.

- Almost clear 1 = mean >0, <1.5. Normal to pink coloration; just detectable (possible slight elevation above normal skin). No to minimal focal scaling.
- Mild 2 = mean >= 1.5, <2.5. Pink to light red coloration; mild thickening (slight but definite elevation, typically edges are indistinct or sloped). Predominantly fine scaling.
- Moderate 3 = mean >=2.5, <3.5. Dull to bright red coloration; clearly distinguishable to moderate thickening; moderate scaling.
- Severe 4 = mean >=3.5. Bright to deep dark red coloration; severe thickening with hard edges; severe coarse scaling covering almost all or all lesions.

The sPGA overall score will be set to missing if any item is missing.

3.3.1.2 Main analytical approach

➢ **PASI percent change from baseline to Week 12**

This endpoint will be analyzed according to the following attributes:

- Endpoint: PASI percent change from baseline to Week 12
- Intervention condition: SAR441566 200 mg BID, 100 mg BID, 200 mg QD, 100 mg QD and 50 mg QD will be compared to placebo
- Analysis population: NTIP population
- Intercurrent events:
  - IMP discontinuation: it will be handled with the treatment policy strategy. This endpoint will be assessed based on all assessments irrespective of the IMP discontinuation.
  - Starting the selected concomitant medication (see Table 4): It will be handled with the composite variable strategy. For this endpoint, data after the selected concomitant medication use will be assigned using the worst post-baseline value on or before the time of the medication usage (ie, WOCF). For participants whose postbaseline values are all missing, the participant's baseline value will be used.
- Population-level summary: PASI score will be analyzed using an ANCOVA on the percent change from baseline in PASI at Week 12, including treatment as categorical effect and baseline value as continuous covariate. The least-squares means estimates of the percent changes from baseline at Week 12 in each treatment group and their corresponding two-sided 95% CI will be reported, as well as the differences between each SAR441566 groups and placebo in least square mean change from baseline (and 95% CIs) and p-values comparing the treatment groups. No multiplicity adjustment will be made.
- After applying the rules for the ICEs, the remaining missing data will be handled as follows:
  - "Worst observation carried forward" (WOCF) approach will be used to impute missing data

➢ **Proportion of participants with sPGA score 0 or 1 at Week 12**

This endpoint will be analyzed according to the following attributes:

- Endpoint: Proportion of participants with sPGA score 0 or 1 at Week 12.
- Intervention condition: SAR441566 200 mg BID, 100 mg BID, 200 mg QD, 100 mg QD and 50 mg QD will be compared to placebo
- Analysis population: NTIP population
- Intercurrent events:
  - IMP discontinuation: it will be handled with the treatment policy strategy. This endpoint will be assessed based on all assessments irrespective of the IMP discontinuation.
  - Starting the selected concomitant medication (see Table 4): It will be handled with the composite variable strategy. For this endpoint, participants who receive selected prohibited medications will be considered as non-responders for time points after the medication usage. For other participants, all available data including those collected during the off-treatment period will be used to determine the responder/non-responder status.
- Population-level summary: Difference in the percentage of participants with sPGA score 0 or 1 at Week 12 between each active arm and placebo. The CMH test will be used for this endpoint analysis, adjusting for baseline disease severity defined by baseline PASI (<=20, >20). The two-sided p-value based on CMH test for odds ratio and 95% confidence intervals (CI) based on Newcombe method (1) for Mantel-Haenszel treatment difference will be presented (SAS code example in Section 5.4). No multiplicity adjustment will be made.
- After applying the rules for the ICEs, the remaining missing data will be handled as follows:
  - Participants will be considered as non-responders

3.4 TERTIARY/EXPLORATORY ENDPOINT(S) ANALYSIS

The tertiary endpoints detailed in this section are:

- PASI percent change from baseline to Week 4 and 8
- The proportion of participants with a 50% or greater PASI reduction from baseline (PASI50) at Week 4, 8 and 12
- The proportion of participants with a 90% or greater PASI reduction from baseline (PASI90) at Week 4, 8 and 12
- The proportion of participants with a 100% PASI reduction from baseline (PASI100) at Week 4, 8 and 12
- The proportion of participants with PASI75 at Week 4 and 8

- [redacted]
- Time until the first achievement of PASI75
- Time until the first achievement of PASI90

[redacted]

- Change in Dermatology Life Quality Index (DLQI) from baseline to Week 12.

[redacted]

Other tertiary endpoints analyses are defined in Section 3.6.2 (AE, SAE), Section 3.6.3.1 (laboratory abnormalities), Section 3.7.1.1 (PK), Section 3.7.1.2 (quality of life), Section 3.7.1.3 (biomarkers).

In addition, the primary and secondary endpoints will be analyzed in ETIP population and ITT population for exploratory purpose.

3.4.1 Definition of endpoint(s)

For PASI and sPGA related endpoints, please refer to Section 3.2 and Section 3.3 for the definition of scores.

➢ **Changes in affected BSA (%) from baseline to Week 4, 8 and 12.**

This is a continuous endpoint based on BSA defined as below.

Body Surface Area (BSA)

BSA will be calculated from the integrated BSA within the PASI assessment.

Percent BSA will be evaluated as the percent involvement of psoriasis on each patient's BSA on a continuous scale from 0% (no involvement) to 100% (full involvement), where 1% corresponds to the size of the patient's hand (including the palm, fingers, and thumb).

- **Change in Dermatology Life Quality Index (DLQI) from baseline to Week 12.**

This is a continuous endpoint based on DLQI defined as below.

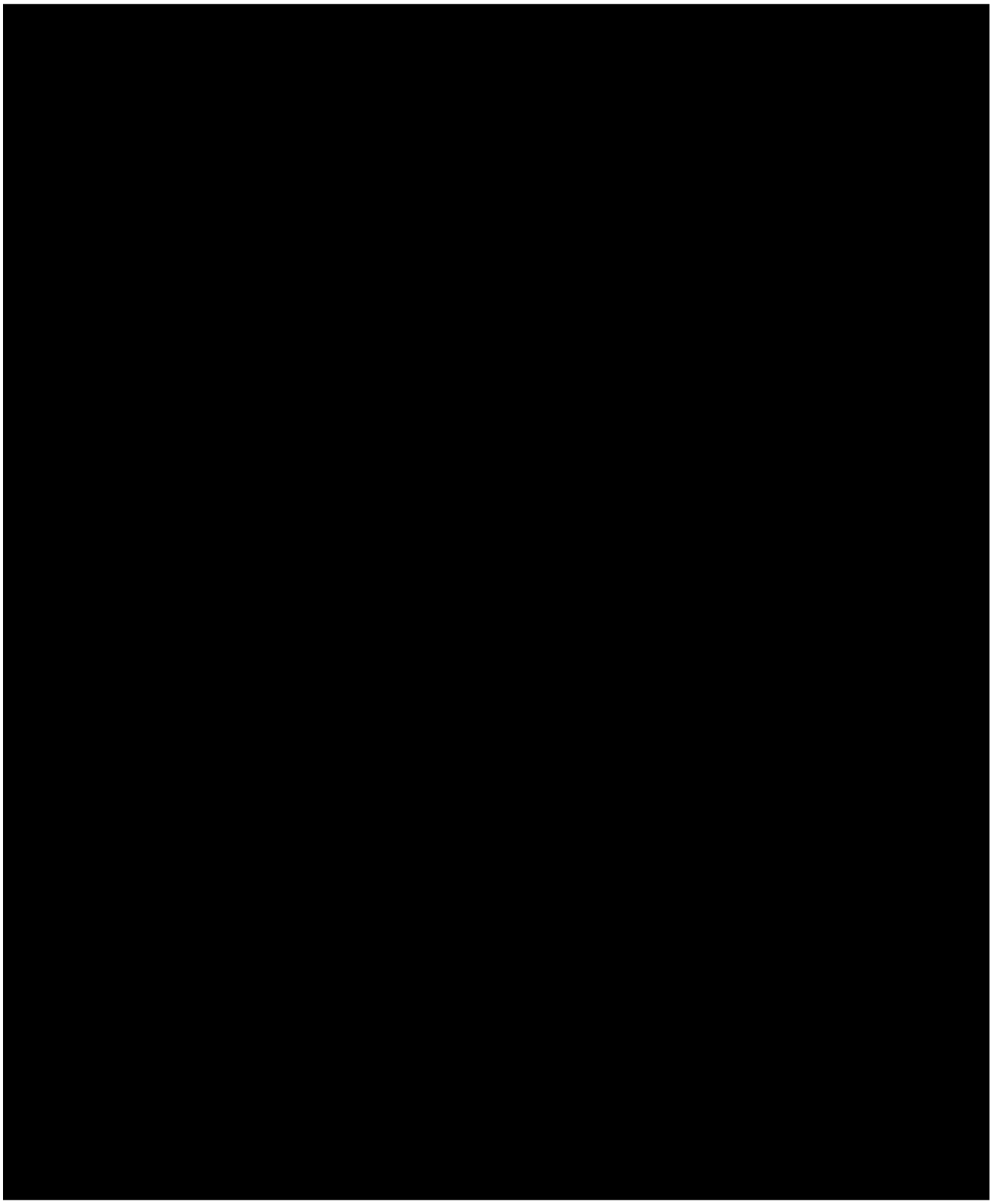
Dermatology Life Quality Index (DLQI)

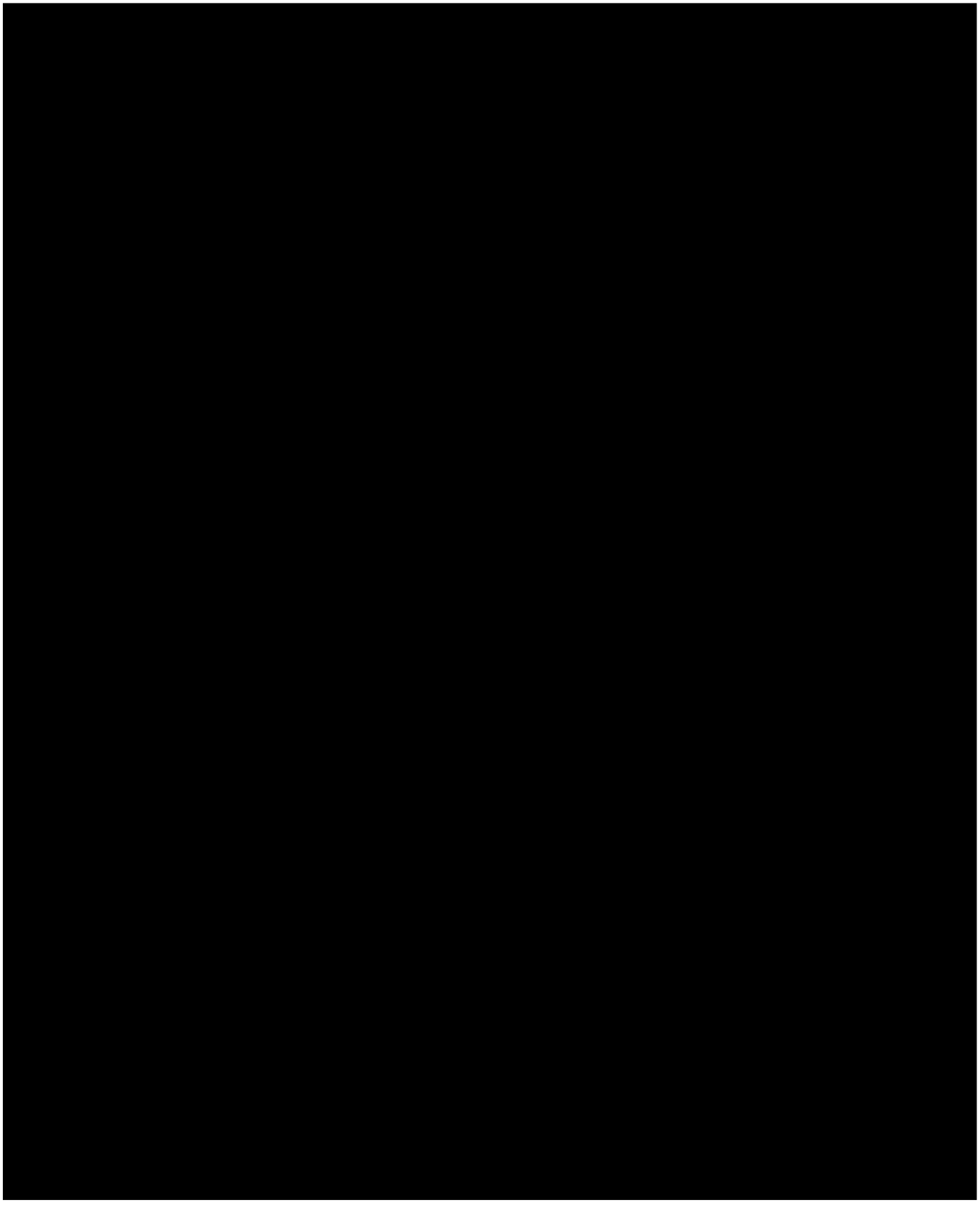
The DLQI is one of the most widely used measures in dermatology populations to evaluate participants' Health-Related Quality of Life. It is a patient-reported outcome instrument consisting of 10 items exploring six dimensions: 'Symptoms and feelings" (2 items), "Daily activities" (2 items), "Leisure" (2 items), "Work and school" (1 item), "Personal relationships" (2 items), "Treatment" (1 item). Each item is rated on a dichotomous: Yes/No and 3- and 4-point Likert/Likert-type scale for capturing skin symptom-related experiences over the previous weeks.

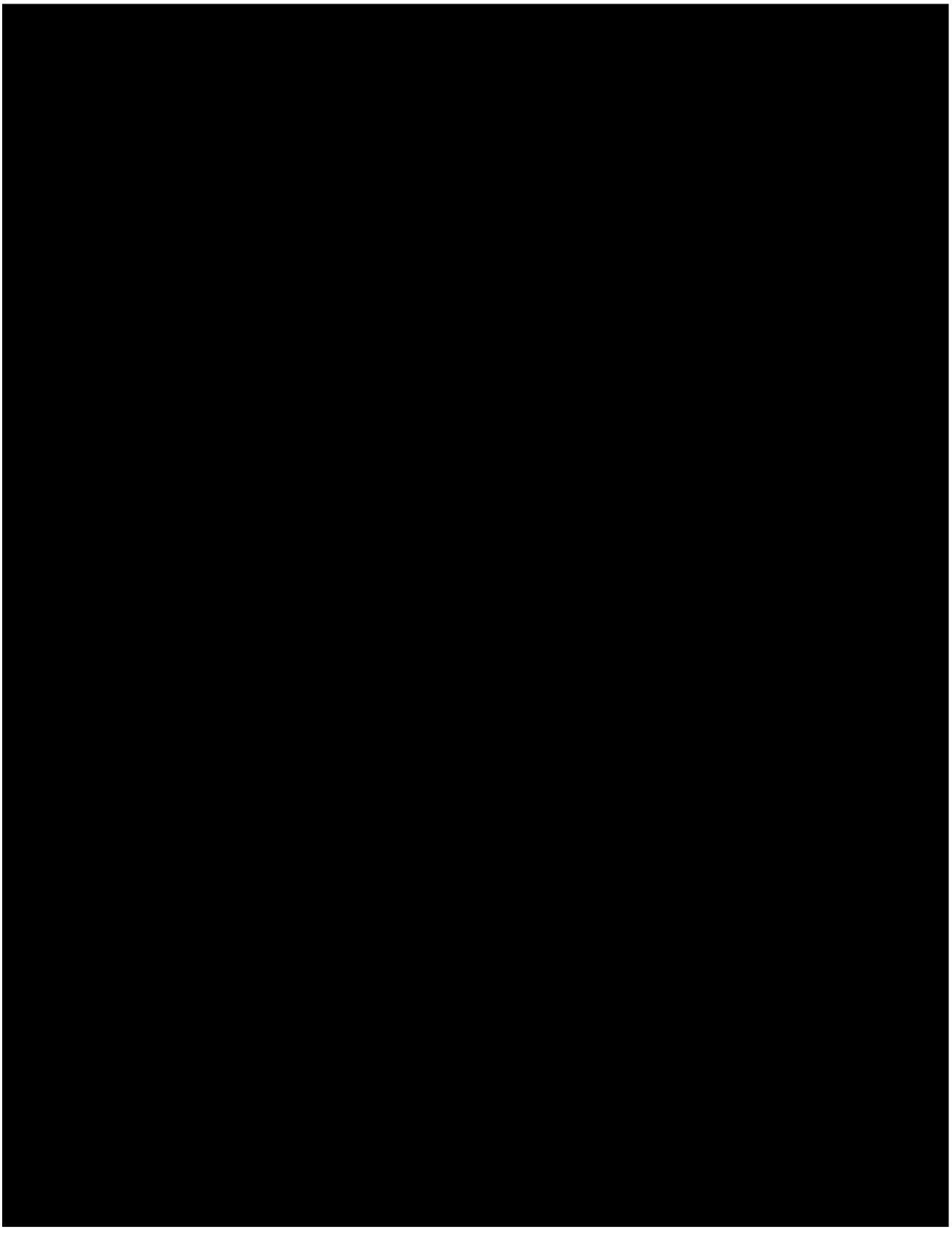
Scores are computed overall and for the six domains. The total DLQI score ranges from 0 to 30, the higher the score, the greater the impairment of quality of life.

If one of the 10 items are left unanswered, it is scored 0 and the scores are summed and expressed as usual out of a maximum of 30. If two or more of the ten items are left unanswered, DLQI total score will be left missing. When using sub-scales, if the answer to one item in a sub-scale is missing, the score is set to missing for that sub-scale.

The instrument has good evidence of content validity and psychometric properties supporting its reliability, construct validity and responsiveness (4).







[redacted]

3.4.2 Main analytical approach

For this section, statistical outputs will be displayed by randomized intervention group based on NTIP and ETIP populations respectively. P-value will not be presented due to the exploratory nature of the endpoints.

In addition, the primary, secondary and the following selected exploratory endpoints will be analyzed based on the ITT population for exploratory purpose and the randomization stratum of NTIP vs. ETIP will be adjusted in the analyses accordingly:

- The proportion of participants with PASI50, PASI90, PASI100 at Week 4, 8 and 12
- The proportion of participants with PASI75 at Week 4, and 8.
- Proportion of participants with sPGA score of clear or almost clear (0 or 1) at Week 4 and 8.
- PASI percent change from baseline to week 4 and 8
- [redacted]

The following continuous exploratory endpoints will follow the similar analytical approaches describe for the secondary endpoint “PASI percent change from baseline to Week 12” (see Section 3.3.1.2) and will include assessment of raw values and change from baseline:

- PASI percent change from baseline to week 4 and 8
- Changes in affected Body Surface Area (BSA) (%) from baseline to Week 4, 8 and 12
- Change in DLQI from baseline to Week 12

- [redacted]

The following binary exploratory endpoints will follow the similar primary analytical approaches described for the primary endpoint "proportion of participants with PASI75 at Week 12" (see Section 3.2.2):

- The proportion of participants with PASI50, PASI90, PASI100 at Week 4, 8 and 12
- The proportion of participants with PASI75 at Week 4, and 8.

The following binary exploratory endpoints will follow the similar analytical approaches described for the secondary endpoint "Proportion of participants with sPGA score 0 or 1 at Week 12" (see Section 3.3.1.2):

- Proportion of participants with sPGA score of clear or almost clear (0 or 1) at Week 4 and 8

The following time to event endpoints will be estimated and presented using the Kaplan-Meier product-limit method:

- Time until the first achievement of PASI50, PASI75, PASI90, PASI100, sPGA of 0 or 1

Kaplan-Meier plots of time to event will also be presented. In these Kaplan-Meier plots, the line will start at 0 (since there are no event at Baseline) and will increase over time, representing time to event. The median time to event, including the two-sided 95% confidence interval, will be calculated. The estimates of the hazard ratio and 95% CI will be provided using a Cox Proportional Hazard Model stratified by the baseline PASI (<=20, >20). The censoring events include receiving selected concomitant medication or by the last assessment of targeted efficacy endpoint. The time at risk/time to event will be defined as follows:

1. If the subject has at least one event before receiving selected concomitant medication or by the last assessment of targeted efficacy endpoint, then time to event is defined as the first event date – the first dose date + 1.
2. If the subject does not have an event or receives selected concomitant medication before any event(s), the time at risk is defined as the minimum of (the last assessment date of targeted efficacy endpoint – the first dose date + 1, the date of receiving selected concomitant medication – the first dose date + 1).

[redacted]

3.5 MULTIPLICITY ISSUES

To control the overall Type I error of 0.05 under circumstance of multiple comparisons for the primary endpoint in the NTIP, the comparison between each dose of SAR441566 three doses (200 mg BID, 100 mg BID, 200 mg QD) and placebo will be conducted in a pairwise manner following a step-down procedure. The hierarchy will be 200 mg BID vs placebo, 100 mg BID vs placebo and 200 mg QD vs. Placebo. The testing will continue to the next level only if the previous comparison is statistically significant. The p-value (if presented) for all the other endpoints will be considered nominal since it is not under the multiplicity control.

3.6 SAFETY ANALYSES

All safety analyses will be performed on the safety population as defined in Section 2, 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.

3.6.1 Extent of exposure

The extent of IMP exposure will be assessed by the duration of IMP exposure and compliance and summarized within the safety population.

Duration of IMP exposure

Duration of IMP exposure is defined as last IMP administration date – first IMP administration date + 1 days, regardless of unplanned intermittent discontinuations. If the date of the last dose of IMP is missing, the duration of IMP will be left as missing.

Duration of IMP exposure will be summarized quantitatively and categorically: 1 to 2, 3 to 4, 5 to 6, 7 to 8, 9 to 10, 11 to 12 and >12 weeks.

Additionally, the cumulative duration of treatment exposure (expressed in participant-years) will be provided.

Treatment compliance

A given administration will be considered noncompliant if the participant did not receive the number of tablets as required by the protocol.

Percentage of treatment compliance for a participant will be defined as the number of tablets that the participant has taken divided by the total number of tablets 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 quantitatively and categorically: <80%, ≥80%.

3.6.2 Adverse events

General common rules for adverse events

All adverse events (AEs) will be coded to a lower-level term (LLT), preferred term (PT), high-level term (HLT), high-level group term (HLGT), and associated primary system organ class (SOC) using the Medical Dictionary for Regulatory Activities (MedDRA) Version 27.1.

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.
- Treatment-emergent adverse events (TEAE)s: AEs that developed, worsened or became serious during the treatment-emergent period
- Post-treatment AEs: AEs that developed, worsened or became serious during the post-treatment period

Similarly, the deaths will be analyzed in the pre-treatment, treatment-emergent and post-treatment periods.

The primary AE analyses will be on TEAEs. Pre-treatment and post-treatment AEs will be described separately.

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. Missing severity will be left as missing.

Multiple occurrences of the same event in the same participant will be counted only once in the tables within a treatment phase.

The AE tables will be sorted as indicated in Table 5.

Table 5 - 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 SAR441566 200 mg BID intervention group.
b The table of all TEAEs presented by primary SOC and PT will define the presentation order for all other tables (eg, treatment-emergent SAE) presented by SOC and PT, unless otherwise specified.

Analysis of all adverse events

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

- Any TEAE
- Any treatment-emergent SAE
- TEAE leading to death
- Any TEAE leading to permanent IMP discontinuation

The AE summaries of Table 6 will be generated with number (%) of participants experiencing at least one event.

Table 6 - Analyses of adverse events

Type of AE	MedDRA levels
All TEAE	Primary SOC and PT
Common TEAE (≥4% in at least one treatment group)	Primary SOC and PT
TEAE related to IMP as per Investigator's judgment	Primary SOC and PT
TEAE by maximal intensity	Primary SOC and PT
Treatment emergent SAE	Primary SOC and PT
Treatment emergent SAE related to IMP as per Investigator's judgment	Primary SOC and PT
TEAE leading to permanent IMP discontinuation	Primary SOC and PT
TEAE leading to death[b]	Primary SOC and PT
Pretreatment AE	Overview[a]

Type of AE	MedDRA levels
Post-treatment AE	Overview[a]
Post-treatment SAE	Primary SOC and PT

a Will include the following AE categories: any AEs, any serious AEs, any AEs leading to death, any AEs leading to permanent IMP discontinuation
b Death as an outcome of the AE as reported by the Investigator in the AE page

Analysis of deaths

In addition to the analyses of deaths included in Table 6 the number (%) of participants in the following categories will be provided:

- Deaths during the treatment-emergent and post-treatment periods by main reason for death

Analysis of adverse events of special interest (AESIs)

AESIs will be selected for analyses as indicated in Table 7. 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 5.

Table 7 - Selections for AESIs

AESIs	Selection[a]
Pregnancy	AETERMC = 'Pregnancy' or 'Partner pregnancy' and AESI = 'Y'
Symptomatic overdose (serious or nonserious) with IMP	Symptomatic Overdose is answered Yes, with Overdose of IMP answered Yes on AE eCRF (AESI='Y' and AEOVSYMP='Y' and AEOVIMP='Y')
Symptomatic overdose (serious or nonserious) with NIMP	Symptomatic Overdose is answered Yes, with Overdose of NIMP answered Yes on AE eCRF (AESI='Y' and AEOVSYMP='Y' and AEOVOTCM='Y')
Drug abuse with IMP[b]	AESI='Y' and CMQsn00101 Drug abuse and dependence Narrow
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

a The list of terms may be adjusted according to MedDRA version changes.
b This is not listed as an AESI in the protocol dated 25APR2024 or after.

3.6.3 Additional safety assessments

3.6.3.1 Laboratory variables, vital signs and electrocardiograms (ECGs)

The following laboratory variables, vital signs and electrocardiogram (ECG) variables will be analyzed. They will be converted into standard international units.

- Hematology:
  - Red blood cells and platelets and coagulation: hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, red blood cell count, %Reticulocytes, platelet count
  - White blood cells: white blood cell count, neutrophils, lymphocytes, monocytes, basophils, eosinophils
- Clinical chemistry:
  - Metabolism: glucose, [redacted] total protein, albumin, creatine phosphokinase
  - Electrolytes: sodium, potassium, chloride, calcium, calcium corrected, bicarbonate

    Calcium Corrected (mmol/L) = Total calcium (mmol/L) + 0.8 * 0.25 * [4 – Serum albumin (g/L) * 0.1]
  - Renal function: creatinine, creatinine clearance, blood urea nitrogen.

    Creatinine clearance will be derived with the equation of Cockcroft and Gault using weight assessed at the same visit as creatinine.
  - Liver function: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, total and direct bilirubin
  - Pregnancy test: Serum β-human chorionic gonadotropin (choriogonadotropin Beta as needed for women of childbearing potential)
- Vital signs: sitting heart rate, sitting systolic and diastolic blood pressure, temperature.
- ECG variables: heart rate, PR, QRS, QT, and corrected QTcF. The average of the triplicate ECG assessments will be used.

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 will be replaced by ULOQ value.

Quantitative analyses

When relevant, for laboratory variables, vital signs and ECG variables above, descriptive statistics for results and changes from baseline will be provided for each planned visit, the last value and the worst value (minimum and/or maximum value depending on the parameter) during the on-treatment period. These analyses will be performed using central measurements only for laboratory variables and ECG variables.

For selected laboratory variables including hemoglobin, hematocrit, erythrocyte, platelets, leukocytes, neutrophils, lymphocytes, monocytes, glucose, cholesterol, triglycerides, sitting systolic blood pressure, sitting diastolic blood pressure, and sitting heart rate mean changes from baseline with the corresponding standard error will be plotted over time.

Analyses according to PCSA

Potentially clinically significant abnormality (PCSA) analyses will be performed based on the PCSA list currently in effect at Sanofi at the time of the database lock. For parameters for which no PCSA criteria are defined, similar analyses will be done using the normal range, if applicable.

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

For laboratory variables, vital signs and ECG variables above, the incidence of participants with at least one PCSA during the treatment-emergent 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

In case of missing local assay methods, they will be considered similar as those used in central lab for the analysis of PCSA as soon as the laboratory parameters correspond to the PCSA reference table.

Even if the local and central specimen are different, they can be considered similar for the analysis of PCSA as soon as the laboratory parameters correspond to the PCSA reference table.

Additional analyses for drug-induced liver injury

The following additional analyses will be performed for drug-induced liver injury:

- Time to onset of the initial alanine aminotransferase (ALT) or aspartate aminotransferase (AST) elevation (>3 x ULN) and total bilirubin elevation (>2 x ULN) during the treatment-emergent period may be analyzed using Kaplan-Meier method.
- A graph of the distribution of peak values of ALT versus peak values of total bilirubin during the treatment-emergent period will be provided.
- For each liver function test (eg, ALT), participants having experienced a PCSA (eg, ALT >5 ULN) will be summarized using the following categories: Returned to baseline PCSA status (or returned to value ≤ ULN in case of missing baseline) before last IMP dose, returned to baseline PCSA status after last IMP dose, Never returned to baseline PCSA status, No assessment after elevation. This summary will be performed by categories of elevation (ALT >3, >5, >10, >20 ULN).

3.7 OTHER ANALYSES

3.7.1 Other variables and/or parameters

3.7.1.1 PK analyses

All PK analyses will be conducted on the PK population. The data after receiving the wrong dose will be excluded from PK analyses. The exception is that, if one participant receives the same wrong dose during the entire study treatment period, then this participant will be included in the PK analyses and the analyses will be done according to the dose received.

Individual plasma concentrations of SAR441566 will be listed by nominal visit and intervention group. Plasma concentrations of SAR441566 will be summarized using arithmetic and geometric means, standard deviation (SD), standard error of the mean (SEM), coefficient of variation (CV%), minimum, median and maximum by intervention groups. All concentration values below the lower limit of quantitation (LLOQ) will be treated as zero in all summary statistics. Graphical presentation of PK concentration over time may be provided if appropriate.

The PK parameters will be estimated by a population PK approach and will be presented in a separate report.

3.7.1.2 Quality of life analyses

Analysis for Quality of Life endpoints are included in Section 3.4.

3.7.1.3 Biomarker analyses

The biomarker analyses will be performed using PDy population defined in Section 2.

The following biomarkers will be evaluated if applicable:

- Peripheral blood soluble biomarkers (including but not limited to hsCRP, IL-17A, IL-17F, IL-22, IL-19) from baseline to Week 4 and 12
- [redacted]

The following analyses will be performed if applicable:

- Descriptive statistics by treatment arm at baseline, intermediate timepoints and end of treatment
- Plots of fold changes from baseline in soluble protein biomarkers per treatment arm and visit
- Appropriate statistical methods based on the sample size such as linear mixed models, ANOVA (parametric), Kruskal-Wallis test, Wilcoxon signed rank test (non-parametric)
- Correlation of (a) biomarker results at baseline and (b) changes of biomarker results from baseline to post treatment visits with participant's clinical parameters

If measurement values below LLoQ occur, then the number of these values will be reported, computations and plots will be conducted setting values below LLoQ to LLoQ/2 and corresponding points in plots will be marked by dedicated symbols.

Additional analysis for the biomarkers listed above and other exploratory biomarkers (eg, gene expression and proteomics data and DNA genotype data) may be performed and will be summarized in a separate document.

3.7.2 Subgroup analyses

Subgroup analyses of the primary efficacy endpoint will be performed to assess the homogeneity of the treatment effect across the following subgroups (categories with fewer than 30 participants may be combined with other categories):

- Region (Western Countries, Latin America, Rest of world)
- Hispanic ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Age group (≥18 to <40, ≥40 to <60, ≥60 to ≤75, >75 years)
- Gender (Male, Female)
- Baseline body mass index (BMI) level (<30, ≥30 kg/m²)
- Baseline PASI score (≤15, >15)
- Baseline PASI score (≤20, >20)

Treatment-by-subgroup interaction term and the subgroup factor term will be added in the primary model. In the case that the subgroup factor is identical or similar to a randomization strata factor, the strata factor will not be kept in the model.

The treatment effects (SAR441566 versus placebo) for the primary endpoint will be provided, as well as the corresponding 95% CI, for each subgroup, using the same method as applied to the primary analysis. Forest plots may be provided.

3.8 INTERIM ANALYSES

No interim analysis will be performed.

3.9 CHANGES TO PROTOCOL-PLANNED ANALYSES

1. The exploratory/tertiary endpoint “PASI change from baseline to Week 4 and 8” in Table 1 from the protocol dated 25-Apr-2024 has been updated to “PASI percent change from baseline to Week 4 and 8” in this SAP, to be aligned with the secondary endpoint.
2. Due to the fast enrollment, the final analysis will be performed 5 months ahead of original timeline at the time the interim analysis was planned. Hence, the interim analysis planned in the protocol dated 25-Apr-2024 is considered unnecessary by the project team and Therapeutic Area Immunology&Inflammation leadership and is cancelled.

4 SAMPLE SIZE DETERMINATION

A total sample size of approximately 207 participants will be randomized to the intervention groups in two different strata, ie, NTIP vs. ETIP.

In the stratum of NTIP, approximately 144 participants will be randomized in a randomization ratio 1:1:1:1:1:1 to SAR441566 200 mg BID, SAR441566 100 mg BID, SAR441566 200 mg QD, SAR441566 100 mg QD, SAR441566 50 mg QD and placebo, ie, 24 participants in each of six groups. The NTIP is the primary population for efficacy analysis.

In the stratum of ETIP, approximately 63 participants will be randomized in a randomization ratio 2:2:2:1 to SAR441566 200 mg BID, SAR441566 200 mg QD, SAR441566 100 mg QD and placebo, ie, 18 participants in each of SAR441566 200 mg BID, 200 mg QD and 100 mg QD groups and 9 participants in the placebo group. The ETIP is for exploratory purpose only.

In the NTIP, assuming a 10% dropout rate, the sample size of 24 participants per group will provide about [redacted]% power to demonstrate superiority of SAR441566 200 mg BID or 100 mg BID or 200 mg QD versus placebo with a 2-sided significance level of 0.05, based on Chi-square test with the following assumptions on the primary endpoint:

- PASI75 Placebo rate of[redacted]%.
- PASI75 SAR441566 rate of [redacted]%.

To estimate the dose-response curve on QD regimen in the NTIP, the sample size of 24 participants per group will provide an minimum power of [redacted]% to detect the presence of a dose response, based on the assumption of a maximum effect in terms of PASI75 of treatment difference of [redacted]% in SAR441566 comparing with placebo rate of [redacted]%, using [redacted].

Calculations for Chi-square test were done using [redacted]

5 SUPPORTING DOCUMENTATION

5.1 APPENDIX 1 LIST OF ABBREVIATIONS

AE: adverse event
AESIs: adverse events of special interest
ALT: alanine aminotransferase
ANCOVA: analysis of covariance
AST: asparate aminotransferase
BID: bis in die - twice a day
BMI: body mass index
BSA: body surface area
CI: confidence interval
CMH: Cochran-Mantel-Haenszel
DLQI: dermatology life quality index
DNA: deoxyribonucleic acid
ECG: electrocardiogram
ETIP: Experienced targeted immunotherapy population
HLGT: high-level group term
HLT: high level term
hsCRP: high-sensitivity C-reactive protein
ICE: Intercurrent event(s)
ICF: informed consent form
IL: interleukin
IMP: investigational medicinal product
ITT: intent-to-treat
IWRS: interactive web response system
LLOQ: lower limit of quantitation/detection limit
LLT: lower-level term
MCP-Mod: Multiple Comparisons Procedure - Modelling
MedDRA: medical dictionary for regulatory activities
MTX: methotrexate
[redacted]
NTIP: Naive targeted immunotherapy Population
[redacted]
PCSA: potentially clinically significant abnormality
PK: pharmacokinetic
PPASI: palmoplantar psoriasis area and severity index
PT: preferred term
QD: quaque die - once a day
RNA: ribonucleic acid
SAE: serious adverse event
SAP: statistical analysis plan
SD: standard deviation

SOC:	system organ class
sPGA:	static Psoriasis Global Assessment
TE:	treatment-emergent
TEAE:	treatment-emergent adverse event
TNFR:	tumor necrosis factor receptor
ULN:	upper limit of normal
ULOQ:	upper limit of quantification
WHO-DD:	World Health Organization-drug dictionary
WOCF:	worst observation carried forward

5.2 APPENDIX 2 PARTICIPANT DISPOSITIONS

The number (%) of participants included in each of the analysis populations listed in Table 3 will be summarized.

Screen failures are defined as participants who consent to participate in the study 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:

- Exposed and not randomized participants
- Randomized participants
- Randomized but not exposed participants
- Randomized and exposed participants
- Participants who completed the 12-week study treatment period as per protocol
- Participants who did not complete the 12-week study treatment period as per protocol, main reason for permanent intervention discontinuation and main reason for treatment withdrawal by subject
- 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.

Reasons for permanent study intervention and study discontinuation “adverse event” and “other reasons” will be split as related versus not related to COVID-19, if applicable.

In addition, the number (%) of participants screened, screened-failed, randomized, with permanent IMP discontinuation and with early study discontinuation will be provided by country and by country/site.

Protocol deviations

Critical and major protocol deviations (automatic or manual) will be summarized in the randomized population.

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 NTIP/ETIP population and overall.

Demographic and baseline characteristics

- Age in years as quantitative variable and in categories (From 18 - 39 years, From 40 - 59 years, From 60 - 75 years, 76 years and over)
- Sex (Male, Female)
- Race (White, Black or African American, Asian, Native Hawaiian or other Pacific Islander, American indian or Alaska native, Not reported, Unknow)
    - Asian subcategories (Chinese, Japanese, Asian Indian, Korean, Other Asian Origin)
        - Other Asian Origin subcategories (Asian Origin Not reported, Asian Origin Unknow)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not Reported, Unknown)
- Region (Western country, Latin America, Rest of World)
    - Western country includes Bulgaria, Canada, Czech Republic, Georgia, Germany, Hungary, Poland, Portugal, Spain, Turkey, United Kingdom and USA
    - Latin America includes Argentina and Chile
    - Rest of world includes China, Japan and Mauritius
- Body weight as quantitative variable (kg) and in categories (<70, ≥70 to <90, ≥90 kg)
- Body mass index as quantitative variable (kg/m2) and in categories (<18.5, ≥18.5 to <25, 25 to <30, ≥30 kg/m2)
- Smoking habit (Never, Former, Current)
- Alcohol Habit: Alcohol drinking frequency (Never, Occasional, At least monthly, At least weekly and At least daily) and number of standard alcohol drinks on a typical day when drinking (1 or 2, >2)
- HIV and Hepatitis screen: HIV-1 and HIV-2 antibodies, hepatitis B surface antigen, hepatitis B core antibody, hepatitis-C antibodies

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

Medical (or surgical) history includes all the relevant medical (or surgical) history during the lifetime of the participant. Medical and surgical history will be coded to a LLT, PT, HLT, HLGT, and associated primary SOC using the MedDRA version in effect at Sanofi at the time of database lock.

Disease characteristics at baseline

- Age at diagnosis of psoriasis (years) as quantitative variables defined as:
  (date of diagnosis* – date of birth+1)/365.25.
- Age at diagnosis of psoriasis (years) in categories (Before 18 years, From 18 – 39 years, From 40 – 59 years, From 60 – 75 years, 76 years and over
- Time since diagnosis of psoriasis (years), defined as:
  (date of ICF – date of diagnosis*+1)/365.25.
- PASI score
- sPGA score
- BSA score
- Prior systemic treatment use (Yes or No)
  - If yes, description of the three following categories:
    - TNFi biologics
    - Other biologics [IL-12, IL-17, IL-23 biologics]
    - Small molecules [phosphodiesterase 4, janus kinase, tyrosine kinase 2 inhibitors])

*In case the day of diagnosis would be missing, it will be imputed as to 01. In case the month and day of diagnosis would be missing, it will be imputed as 01JANUARY if the year of diagnosis equals the year of informed consent; it will be imputed as 01JULY if the year of diagnosis does not equal the year of informed consent.

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 received prior to first IMP intake. Prior medications can be discontinued before first administration or can be ongoing during treatment period.
- Concomitant medications are any medications received by the participant concomitantly to the IMP from the first administration of IMP to the last IMP intake + 1 day.
- Post-treatment medications are those the participant received in the period running from the end of the concomitant medications period up to the end of the study.
- 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 and post-treatment medications will be summarized for the randomized and exposed population, by anatomic and therapeutic level. Participants will be counted once in each ATC category (anatomic or therapeutic) linked to the medication.

5.4 APPENDIX 4 DATA HANDLING CONVENTIONS

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 and safety.

A measurement (scheduled or unscheduled) will be used if it is available and measurement date is within the analysis window, except for vital signs, laboratory test and ECG for which only scheduled measurement will be used.

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.

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

Table 8 - Time-window definition for safety endpoints analyses

			Time-window (days)
Scheduled visit	**Analysis visit**	**Targeted study day**	**Vital signs, laboratory tests, 12-lead ECG and Targeted Physical examination**
Week 2 (Visit 3)	Week 2	15	2-21
Week 4 (Visit 4)	Week 4	29	22-42
Week 8 (Visit 5)	Week 8	57	43-70
Week 12 (Visit 6, EOT)	Week 12	85	71-91
Week 14/16 (Visit 7, EOS)	Week 14/16	99	>91

Study days are calculated considering Day 1 as the day of first administration of intervention (or the day of randomization for participant not exposed).

Table 9 - Time-window definition for efficacy endpoints analyses

			Time-window (days)	
Scheduled visit	**Analysis visit**	**Targeted study day**	**Disease Assessment (including PASI, sPGA, BSA and PPASI)**	**Disease Assesment (including NAPSI)**
Week 4 (Visit 5)	Week 4	29	2-42	
Week 8 (Visit 6)	Week 8	57	43-70	
Week 12 (Visit 7, EOT)	Week 12	85	>70	>1

Study days are calculated considering Day 1 as the day of first administration of intervention (or the day of randomization for participant not exposed).

Table 10 - Time-window definition for patient reported outcomes measures analyses

			Time-window (days)	
Scheduled visit	**Analysis visit**	**Targeted study day**	**DLQI, PGIS, PGIC, PQATv2**	**PSSD, Joint-Pain NRS, Joint Stiffness NRS, FACIT-Fatigue**
Week 2 (Visit 4)	Week 2	15		2-21
Week 4 (Visit 5)	Week 4	29		22-42
Week 8 (Visit 6)	Week 8	57		43-70
Week 12 (Visit 7, EOT)	Week 12	85	>1	>70

Study days are calculated considering Day 1 as the day of first administration of intervention (or the day of randomization for participant not exposed).

Table 11 - Time-window definition for PK endpoints analyses

			Time-window (days)
Scheduled visit	**Analysis visit**	**Targeted study day**	**PK Assessments**
Week 0 (Visit 2)	Week 0	1	2.5-3.5 hour after Day 1 dose
Week 2 Pre-dose (Visit 3)	Week 2	15	1 hour before Day 7-21 dose
Week 2 Post-dose (Visit 3)	Week 2	15	2.5-3.5 hour after Day 7-21 dose
Week 4 Pre-dose (Visit 4)	Week 4	29	1 hour before Day 22-42 dose
Week 4 Post-dose (Visit 4)	Week 4	29	2.5-3.5 hour after Day 22-42 dose
Week 8 Pre-dose (Visit 5)	Week 8	57	1 hour before Day 43-70 dose
Week 8 Post-dose (Visit 5)	Week 8	57	2.5-3.5 hour after Day 43-70 dose
Week 12 Pre-dose (Visit 6)	Week 12	85	1 hour before Day >70 dose
Week 12 Post-dose (Visit 6)	Week 12	85	2.5-3.5 hour after Day >70 dose

Study days are calculated considering Day 1 as the day of first administration of intervention (or the day of randomization for participant not exposed).

Unscheduled visits

Unscheduled visit measurements of laboratory data, vital signs, ECG and ADA will be used 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.

5.5 APPENDIX 5 SAMPLE SAS/R CODE

CMH analysis

The following SAS sample code would be used for the analysis:

```
proc freq data= <input dataset>;
tables severity*treatment*response / cmh commonriskdiff(test=mh
CL=Newcombe) alpha=0.05;
ods output cmh commonPdiff CommonPdiffTests; /* CMH test for weighted
OR*/
run;
```

with severity as the PASI score at baseline (<=20 vs. >20).

MCP-mod analysis

The following R sample code would be used for the analysis:

```
require(DoseFinding)
########## Response ###########
logit <- function(p){log(p / (1-p)) }
inv_logit <- function(y){1 / (1 + exp(-y) ) }
select.pbo.resp <- logit(0.13)
select.max.resp <- logit(0.54)-logit(0.13)
select.doses <- c(0, 50, 100, 200)

######### Candidate Curves ######
emax1 <- guesst(d = c(0,50, 100,200), p = c(0.13, 0.35, 0.4, 0.54),
model = "emax")
quad1 <- guesst(d = 150, p = 1, "quadratic")
quad2 <- guesst(d = 175, p = 1, "quadratic")
quad3 <- guesst(d = 100, p = 1, "quadratic")
my.model.list  <- list(
  emax = c(20, emax1),
  logistic = c(50,15),
  linear = NULL ,
  exponential = max(select.doses) * 0.200,
  quadratic = quad1,
  placEff = select.pbo.resp,
  doses = select.doses ,
  maxEff = select.max.resp
```

```
)
models.basic <- do.call( Mods , my.model.list)
plotMods(models.basic)

plotMods(models.basic, trafo = inv_logit)


#Simulate the data for illustration purpose
set.seed(1, kind = "Mersenne-Twister", sample.kind = "Rejection",
normal.kind = "Inversion")
group_size <- 24
dose_vector <- rep(select.doses, each = group_size)
N <- length(dose_vector)
## generate covariates
x1 <- rnorm(N, 0, 1)
x2 <- factor(sample(c("A", "B"), N, replace = TRUE, prob = c(0.6,
0.4)))
## assume approximately logit(13%) placebo and logit(54%) asymptotic
response with ED50=50
prob <- inv_logit(emax(dose_vector, -1.9, 2.06, 50) + 0.3 * x1 + 0.3 *
(x2 == "B"))
dat <- data.frame(y = rbinom(N, 1, prob),dose = dose_vector, x1 = x1,
x2 = x2)


## fit logistic regression (without intercept), no covariates
logfit <- glm(y~factor(dose)-1, family = binomial, data=dat)
muHat <- coef(logfit)
S <- vcov(logfit)

MCTtest(select.doses, muHat, S=S, models = models.basic, type =
"general")
MCPMod(select.doses, muHat, S=S, models=models.basic, type = "general",
Delta = 1.8)

##fit logistic regression (without intercept), with covariates
fit_cov <- glm(y~factor(dose) -1 + x1 + x2, data = dat, family =
binomial)

covariate_adjusted_estimates <- function(mu_hat, S_hat, formula_rhs,
doses, other_covariates, n_sim) {
  ## predict every patient under *every* dose
  oc_rep <- as.data.frame(lapply(other_covariates, function(col)
rep(col, times = length(doses))))
  d_rep <- rep(doses, each = nrow(other_covariates))
  pdat <- cbind(oc_rep, dose = d_rep)
  X <- model.matrix(f
rmula_rhs, pdat)
  ## average on probability scale then backtransform to logit scale
  mu_star <- logit(tapply(inv_logit(X %*% mu_hat), pdat$dose, mean))
  ## estimate covariance matrix of mu_star
```

```
  pred <- replicate(n_sim, logit(tapply(inv_logit(X %*%
drop(mvtnorm::rmvnorm(1, mu_hat, S_hat))),pdat$dose, mean)))
  return(list(mu_star = as.numeric(mu_star), S_star = cov(t(pred))))
}

ca <- covariate_adjusted_estimates(coef(fit_cov), vcov(fit_cov),
~factor(dose)+0+x1+x2,select.doses, dat[, c("x1", "x2")], 1000)

MCTtest(select.doses, ca$mu_star, S = ca$S_star, type = "general",
models = models.basic)
MCPMod(select.doses, ca$mu_star, S = ca$S_star, models=models.basic,
type = "general", Delta = 1.8)

#### The clinical relevance threshold Delta=1.8 given by logit(0.475)-
logit(0.13) for the target effect of 47.5% vs. 13%.
```

ANCOVA analysis

The following SAS sample code would be used for the analysis:

```
proc mixed data=<input dataset>;
class treatment (ref='Placebo');
model percentChange = base treatment / outp=predicts residual;
estimate 'SAR441566 50 mg QD' treatment 1 0 0 0 0 -1 / e  alpha=0.05;
estimate 'SAR441566 100 mg QD' treatment 0 1 0 0 0 -1 / e  alpha=0.05;
estimate 'SAR441566 200 mg QD' treatment 0 0 1 0 0 -1 / e  alpha=0.05;
estimate 'SAR441566 100 mg BID' treatment 0 0 0 1 0 -1 / e  alpha=0.05;
estimate 'SAR441566 200 mg BID' treatment 0 0 0 0 1 -1 / e  alpha=0.05;
lsmeans treatment / diff=control('Placebo') cl e alpha=0.05;
ods output diffs lsmeans;
run;
```

Time-to-event analysis

The following SAS sample code would be used for the Kaplan-Meier analysis:

```
proc lifetest data=<input dataset> method=km alphaqt=0.05;
id usubjid;
time 'time period' * EVENT(1);
strata treatment;
run;
```

with 'time period' as the number of months between first IMP and date of event or censoring.

The following SAS sample code would be used for the Cox Proportional Hazard Model analysis:

```
proc phreg data=<input dataset>;
class treatment (ref='placebo') / param=ref;
model 'time period' * EVENT(1) = treatment / risklimits alpha=0.05;
strata severity;
```

```
run;
```

with ‘time period’ as the number of months between first IMP and date of event or censoring and ‘severity’ as the PASI score at baseline (<=20 vs. >20).

5.6 APPENDIX 6 IMPUTATION RULES FOR START DATES OF MEDICATION IN ICE

The date format is: YYYY-MM-DD

1. If the year is missing
   - No imputation can be done. Medication will be assumed to start prior to the randomization date. Set the date to one day before the randomization date.
2. If the month is missing and year is not missing
   - If year is equal to year of randomization date, then set the date of one day prior the randomization date
   - If year is not equal to year of randomization date, then Impute day and month with 01-January
3. If the day is missing and year and month are not missing:
   - Impute the day with 01
   - Exception: If the given year and month (YYYY-MM) correspond to the randomization date's year and month, impute one day before the randomization date.
   - Example:
     - If the IE start date is 2024-03, the imputed date is 2024-03-01.
     - However, if the randomization date is 2024-03-08, the imputed date will be 2024-03-07.

6 REFERENCES

1. Yan X, Su XG. Stratified Wilson and Newcombe Confidence Intervals for Multiple Binomial Proportions. Stat Biopharm Res. 2010;2:329-35.

2. Bretz F, Pinheiro JC, Branson M. Combining multiple comparisons and modeling techniques in dose-response studies. Biometrics. 2005;61(3):738-48.

3. Pinheiro J, Bornkamp B, Glimm E, Bretz F. Model-based dose finding under model uncertainty using general parametric models. Stat Med. 2014;33(10):1646-61.

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