STATISTICAL ANALYSIS PLAN

Protocol title:	**A multinational, multicenter, double-blind, placebo-controlled Phase 2 study to evaluate efficacy and safety of SAR444656 in adult participants with moderate to severe atopic dermatitis**
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VERSION HISTORY

This Statistical Analysis Plan (SAP) for Study ACT17754 is based on the protocol amendment dated 24-July-2024. This section summarizes major changes to the statistical analysis features in the SAP. The first participant was randomized on 30-Nov-2023. This SAP is approved before the first interim analyses is conducted.

Major changes in statistical analysis plan

SAP Version	Approval Date	Changes	Rationale
1	20-Mar-2025	Not Applicable	Original version

1 INTRODUCTION

1.1 STUDY DESIGN

This is a multinational, multicenter, double-blind, placebo-controlled, parallel-group, Phase 2, 4-arm study to evaluate the efficacy and safety of SAR444656 in adult participants with moderate to severe AD who are inadequately controlled with topical therapies or for whom such topical therapies are inadvisable and who are candidates for systemic therapy.

Participants will be randomized to receive SAR444656 with food at the higher dose [redacted]mg [redacted], or SAR444656 medium dose [redacted] mg [redacted], or SAR444656 [redacted] dose [redacted] mg[redacted], or matching placebo.

Participants who meet inclusion/exclusion criteria will be stratified for randomization by severity of AD (moderate [baseline EASI score <22] versus severe [baseline EASI score ≥22]).

The total duration of study is approximately 24 weeks, including 1 to 4 weeks for screening, 16 weeks for double-blind study treatment and 4 weeks for follow-up.

There will be visit every week for the initial 4 weeks of treatment, followed by visit every other week until the end of the study. Between the planned visits, if deemed necessary, unscheduled remote or clinic visits could be performed.

An Independent Data Monitoring Committee (IDMC) will perform safety monitoring on an ongoing basis for this study.

The IDMC may make recommendation regarding study continuation as well as the potential need for modification of the high dose level, based on safety data of active studies of SAR444656. The first interim IDMC may be performed no later than when about 25 participants were randomized and treated with IMP for at least 4 weeks (~10 patients treated on [redacted] mg/[redacted]). If the IDMC's recommendation is to [redacted]the dose in the [redacted] mg/[redacted] treatment group, participants will switch from [redacted] dose ([redacted] mg) to [redacted] dose (ie, [redacted] mg).

This study includes a total of 200 participants overall, with 53, 49, 45 and 53 participants randomized to SAR444656 [redacted] mg/[redacted], SAR444656 [redacted] mg/[redacted], SAR444656 [redacted] mg/[redacted] or matching placebo, respectively. The randomization ratio varies during the study: The initial 95 participants will be randomized to SAR444656 [redacted] mg/[redacted], SAR444656 [redacted] mg/[redacted] or matching placebo at a 2:1:2 ratio. The remaining 105 participants will be randomized to SAR444656 [redacted] mg/[redacted], SAR444656 [redacted] mg/[redacted], SAR444656 [redacted] mg/[redacted] or matching placebo at a 1:2:3:1 ratio, targeting an overall allocation of 1:1:1:1.

If medically necessary, rescue therapy for AD is allowed at the discretion of the Investigator. If possible, Investigators should attempt to limit the first step of rescue therapy to topical medications, eg, low to medium potency TCS, TCI and topical PDE4 inhibitor. Only for participants who do not respond adequately after at least 7 days of this first step rescue therapy, Investigators may escalate to high potency TCS or systemic medications. If a participant receives

rescue treatment with systemic corticosteroids or nonsteroidal systemic immunosuppressive drugs, study intervention will be immediately interrupted. After the treatment with these medications is completed, study intervention may be resumed if deemed appropriate by the Investigator and the medical monitor, but not sooner than 5 half-lives after the last dose of the rescue medication.

Study primary analysis will be conducted after study completion.

1.2 OBJECTIVES AND ENDPOINTS

Table 1 - Objectives and endpoints

Objectives	Endpoints
Primary	
• To assess the efficacy of SAR444656 on AD lesions compared with placebo in adult participants with moderate to severe AD.	• Percent change from baseline in EASI at Week 16.
Secondary	
• To assess the efficacy of SAR444656 on additional clinical assessments of AD compared with placebo in adult participants with moderate to severe AD.	• Proportion of participants with vIGA-AD of 0 or 1 and a reduction from baseline of ≥2 points at Week 16. • Proportion of participants achieving EASI-75 (reduction of EASI score by ≥75% from baseline) at Week 16. • Absolute change from baseline in EASI at Week 16. • Proportion of participants achieving EASI-50 (reduction of EASI score by ≥50% from baseline) at Week 16. • Proportion of participants achieving EASI-90 (reduction of EASI score by ≥90% from baseline) at Week 16. • Change from baseline in percent BSA affected by AD at Week 16.
• To assess the efficacy of SAR444656 on patients reported outcomes (PRO) compared with placebo in adult participants with moderate to severe AD.	• Proportion of participants with reduction of weekly average of daily PP-NRS ≥4 points from baseline at Week 16. • Percent change from baseline in weekly average of daily PP-NRS at Week 16. • Absolute change from baseline in weekly average of daily PP-NRS at Week 16.
• To assess the safety of SAR444656 in adult participants with moderate to severe AD. • To assess the pharmacokinetic profile of SAR444656 in adult participants with moderate to severe AD.	• Incidence of TEAEs, SAEs, and AESIs, IMP discontinuation due to TEAEs. • Plasma SAR444656 concentration at Week 0, Week 1, Week 2, Week 4 and Week 16.
Exploratory	
[redacted]	[redacted]

Objectives	Endpoints
[redacted]	

1.2.1 Estimands

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

For all these estimands, the comparison of interest will be the comparison of SAR444656 versus control.

Table 2 - Summary of primary estimand for main endpoints

Endpoint Category	Estimands			
	Endpoint	Population	Intercurrent event(s) handling strategy	Population-level summary (Analysis and missing data handling)
Primary objective: To assess the efficacy of SAR444656 on AD lesions compared with placebo in adult participants with moderate to severe AD.				
Primary endpoint	Percent change from baseline in EASI at Week 16	Efficacy	The IEs will be handled with the following strategies; only measurements assessed up to the IE will be considered, data collected after start of IE will be excluded from the analysis: • Intake of rescue/prohibited medications will be handled with the composite variable strategy. • Misallocation of treatment will be handled with the treatment policy strategy. • Discontinuation of study intervention will be handled with treatment policy strategy.	Bayesian Linear Mixed Model (BLMM) will include effects for participant specific baseline EASI score, visit, treatment group, and visit-by-treatment group interaction. Repeated measurements for each visit will be taken within participant. Historical data will be used to enrich the prior distribution of the placebo arm. Participants with missing data (after IE handling) will be imputed with participant's WOCF. For participants with no post-baseline value, the baseline value will be used.

Endpoint Category	Estimands			
	Endpoint	**Population**	**Intercurrent event(s) handling strategy**	**Population-level summary (Analysis and missing data handling)**
Secondary objective: To assess the efficacy of SAR444656 on additional clinician assessments of AD compared with placebo in participants with moderate to severe AD.				
Secondary endpoint	Proportion of participants with vIGA-AD of 0 or 1 and a reduction from baseline of ≥2 points at Week 16.	Efficacy	The IEs will be handled with the following strategies; only measurements assessed up to the IE will be considered, data collected after start of IE will be excluded from the analysis: • Intake of rescue/prohibited medications will be handled with the composite variable strategy. • Misallocation of treatment will be handled with the treatment policy strategy • Discontinuation of study intervention will be handled with treatment policy strategy.	Logistic Bayesian Generalized Linear Mixed Model (BGLMM) adjusted for randomization stratum (moderate: EASI<22; severe: EASI≥22) and will include effect for treatment group. Participants with missing data (after IE handling) will be imputed as non-responder.
Secondary endpoint	Proportion of participants achieving EASI-75 (reduction of EASI score by ≥75% from baseline) at Week 16.	Efficacy	The IEs will be handled with the following strategies; only measurements assessed up to the IE will be considered, data collected after start of IE will be excluded from the analysis: • Intake of rescue/prohibited medications will be handled with the composite variable strategy. • Misallocation of treatment will be handled with the treatment policy strategy • Discontinuation of study intervention will be handled with treatment policy strategy.	Logistic BGLMM adjusted for randomization stratum (moderate: EASI<22; severe: EASI≥22) and will include effect for treatment group. Participants with missing data (after IE handling) will be imputed as non-responder.

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 IRT regardless of whether the intervention was received or not.
Efficacy population	All randomized participants who have taken at least one dose of study intervention. Participants will be analyzed according to the intervention allocated by randomization.
Safety	All randomized participants who have taken at least one dose of study intervention, regardless of the amount of treatment administered. Participants will be analyzed according to the intervention they actually received.
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 actually received.
Pharmacodynamics (PD)	All participants from the safety population with at least one baseline and one post-baseline PD parameter assessed.

Abbreviations: ICF = informed consent form; IRT = interactive response technology; PK = pharmacokinetics; PD = pharmacodynamics

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 defined by the first dose received.

3 STATISTICAL ANALYSES

3.1 GENERAL CONSIDERATIONS

The baseline value of all parameters 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.

The baseline value for efficacy questionnaires is defined as the value collected at Day 1.

Unless otherwise specified, analyses will be performed by intervention group (and overall, for baseline and demographics characteristics) SAR444656 [redacted] mg or SAR444656 [redacted] mg (if applicable), SAR444656 [redacted] mg, SAR444656 [redacted] mg and matching placebo.

Observation period

The observation period will be divided into 4 segments:

- The **pre-treatment period** is defined as the period from the signed informed consent date up to first IMP administration.
- The **treatment-emergent (TE) period** is defined as the period from the first IMP administration up to EOS (EOS included). 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 + 15 days.
  - The **residual treatment period** is defined as the period from the end of the on-treatment period +1 day to the end of the TE period.
- The **post-treatment period** is defined as the period starting after the TE period.

The on-study period is defined as the day from first IMP administration until the end of the study defined as the last scheduled visit for those who completed the study and the end-of-study date collected on electronic case report form (e-CRF) page “Completion of End of Study” for those who did not complete the study. If death is the end-of-study reason, date of death will be used.

Missing data handling

For continuous endpoints “worst observation carried forward” (WOCF) will be applied. The value to be carried forward is the worst value observed from first IMP up to the occurrence of the missing value. For binary endpoints a “no response” will be imputed.

Descriptive summary statistics

Continuous data will be summarized using the number (n) of non-missing observations available, mean, Standard Deviation (SD) or Standard Error Mean (SEM), median, [Q1, Q3], minimum, and maximum, unless specified otherwise.

For categorical and ordinal efficacy endpoints, data will be summarized using counts and percentages, unless specified otherwise. Percentages will be calculated based on the total number of subjects in the respective treatment group with available data after handling of IEs and missing data.

3.2 PRIMARY ENDPOINT(S) ANALYSIS

3.2.1 Definition of endpoint(s)

The primary endpoint is the percent change of EASI from baseline at Week 16.

The EASI is an Investigator-assessed validated tool used to measure the extent (area) and severity of AD. The Investigator will assess the severity of 4 disease characteristics (erythema [E], induration/papulation [I], excoriation (X) and lichenification [L]) present in four different body areas using a 4-point scale; 0 (absent) to 3 (severe). In addition, the extent of involvement of AD in 4 body regions; head/neck, trunk, upper extremities, and lower extremities will be assessed. The possible highest score for extent of involvement in each region is 100%. For each region, the percentage of BSA will be converted to an area score; 0 = No eruption (in that region), 1 = 1%-9%, 2 = 10%-29%, 3 = 30%-49%, 4 = 50%-69%, 5 = 70%-89% and 6 = 90%-100% for each major region of the body (head, upper extremities, trunk and lower extremities), EASI score = (E + I + X + L) × Area Score. The total EASI score is the weighted total of the region EASI using the weights 10% (head), 20% (upper extremities), 30% (trunk) and 40% (lower extremities).

Total score ranges from 0 to 72 with a higher score indicating increased extent and severity of AD.

The EASI score will be collected at screening, Day 1 (Baseline), Week 2, Week 4, Week 8, Week 12 and Week 16 (EOT).

3.2.2 Main analytical approach

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

- Endpoint: Percent change from baseline in EASI at Week 16.
- Treatment condition: SAR444656 will be compared to placebo.
- Analysis population: Efficacy population.
- The following “Intercurrent events” (IE) strategy will be followed:
  - Intake of selected rescue/prohibited medications impacting efficacy will be handled with the composite variable strategy. Data collected after rescue/prohibited medications impacting the efficacy will be imputed by WOCF. The rescue/prohibited medications will be reviewed by the medical team to confirm the medication was used for AD treatment failure and not an unrelated condition and, if it has an impact on efficacy.

- Misallocation of treatment will be handled with the treatment policy strategy.
- Discontinuation of study intervention will be handled with treatment policy strategy (data collected after treatment discontinuation will be included).

- Missing data handling:
  - Missing data (after IE handling) will be imputed with participant's worst observation carried forward (WOCF). For participants with no post-baseline value, the baseline value will be used.

Population-level summary: A Bayesian Linear Mixed Model (BLMM) will be used to estimate the difference between interventions, based on all participants who received matching placebo or SAR444656. The model will be adjusted for randomization stratum (EASI<22; EASI≥22) and will include effects for participant specific baseline EASI score, visit, treatment group, and visit-by-treatment group interaction. Participants with missing EASI score at baseline will not be included in the analysis. The unstructured covariance will be used. In case of convergence issues, other covariance structures will be applied. Historical data will be used to enrich the prior distribution of the placebo arm by an equivalent of 5 participants (Week 16 only). Repeated measurements for each visit will be taken within participant. The conditional prior distribution for the reduction in placebo has been chosen as a normal distribution with mean 35, standard deviation 40 (1). A non-informative prior will be used for the active arm such as a flat normal distribution centered on 0 with a large variance. [redacted].

3.2.3 [redacted]

[redacted]

[redacted]

3.2.4 [redacted]

[redacted]

[redacted]

[redacted]

3.3 SECONDARY ENDPOINT(S) ANALYSIS

The secondary endpoints detailed in this section are only efficacy endpoint.

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 Key secondary endpoint(s)

The secondary endpoints detailed in this section are:

- Proportion of participants with vIGA-AD of 0 or 1 and reduction from baseline of ≥2 points at Week 16 (labeled as vIGA(0,1)-AD).
- Proportion of participants achieving EASI-75 at Week 16.

3.3.1.1 Definition of endpoint(s)

Validated investigator global assessment - atopic dermatitis (vIGA-AD)

The vIGA-AD is an Investigator-lead assessment scale used to determine severity of AD and clinical response to treatment. The vIGA-AD is based on a 5-point scale, ranging from 0 (clear) to 4 (severe).

EASI-75

EASI-75 is defined as a reduction of EASI score by ≥75% from baseline. Please refer to Section 3.2.1 for the definition of EASI score.

The EASI and vIGA-AD score will be collected at screening, Day 1 (Baseline), Week 2, Week 4, Week 8, Week 12 and Week 16 (EOT).

3.3.1.2 Main analytical approach

The following analyses will be based on the Efficacy population.

Analysis of the Proportion of participants with vIGA-AD of 0 or 1 and reduction from baseline of ≥2 points:

A logistic Bayesian Generalized Linear Mixed Model (BGLMM) will be applied, on response data for Week 16. The model will be adjusted for randomization stratum (moderate: EASI<22; severe: EASI≥22) and will include effect for treatment group. A non-informative prior will be used for the placebo and active arms. [redacted].

The data collected after start of the IEs will be set to non-responder as indicated in Table 2.

Missing data will be imputed as non-responder.

Analysis Proportion of participants with at least a 75% reduction from baseline in EASI-75:

Descriptive statistics (ie, number, response frequency and rate with [redacted] Confidence Interval) will be provided for each visit by treatment group.

A logistic Bayesian Generalized Linear Mixed Model (BGLMM) will be applied on response data for Week 16. The model will be adjusted for randomization stratum (moderate: EASI<22; severe: EASI≥22) will include effect for treatment group. [redacted].

The data collected after start of the IEs will be set to non-responder as indicated in Table 2.

Missing data (after IE handling) will be imputed as non-responder.

3.3.1.3 [redacted]

[redacted]

[redacted]

3.3.2 Supportive secondary endpoint(s)

The following supportive secondary efficacy endpoints will be analyzed:

The binary supportive secondary efficacy endpoints are:

- Proportion of participants achieving EASI-50 (reduction of EASI score by ≥50% from baseline) at Week 16.
- Proportion of participants achieving EASI-90 (reduction of EASI score by ≥90% from baseline) at Week 16.
- Proportion of participants with reduction of weekly average of daily PP-NRS ≥4 points from baseline at Week 16.

The continuous supportive secondary efficacy endpoints are:

- Absolute change from baseline in EASI at Week 16.
- Change from baseline in percent BSA affected by AD at Week 16.
- Percent change from baseline in weekly average of daily PP-NRS at Week 16.
- Absolute change from baseline in weekly average of daily PP-NRS at Week 16.

3.3.2.1 Definition of endpoint(s)

BSA

The BSA affected by AD will be assessed by the Investigator for each section of the body

(each body region is weighted using the 'rule of nines': head and neck [9%], anterior trunk [18%], back [18%], upper limbs [18%], lower limbs [36%], and genitals [1%]) and will be reported as a percentage of all major body sections combined.

EASI

EASI-50 is defined as a reduction of EASI score by ≥50% from baseline. EASI-90 is defined as a reduction of EASI score by ≥90% from baseline. Please refer to Section 3.2.1 for the definition of EASI score.

Peak pruritus (PP-NRS)

The PP-NRS is a validated single item 0-10 numeric rating scale assessing peak pruritus (itch) associated with AD during the past 24 hours. The participant is asked about the severity of his/her pruritus with 0 = no itch and 10 = worst itch imaginable. The PP-NRS will be completed daily as a daily diary, ideally at the same time each day (evening). The content of the PP-NRS was validated using in-depth qualitative interviews with participants and the psychometric properties have been assessed using data from Phase IIb and Phase III dupilumab clinical trials. The threshold for interpreting clinically meaningful within-patient change is ≥2–4-point change in the PP-NRS (20). The PP-NRS will be completed using an internet-enabled device. Participants will be asked to complete the PP-NRS for 7 consecutive days leading up to the baseline visit with a minimum requirement of 4 completions.

The baseline for weekly average PP-NRS score is defined as the average of all available daily non-missing scores obtained during the 7 days prior to randomization. A minimum of 4 daily scores out of the 7 days is required to calculate the post-baseline weekly averages.

3.3.2.2 Main analytical approach

Binary supportive secondary endpoints

For the binary secondary endpoints, descriptive statistics after management of IEs and missing data handling (number of participants and percentage with the events) will be provided by visit, treatment group and stratum (moderate: EASI<22; severe: EASI≥22). [redacted]

Analysis of proportion of participants achieving EASI-50 and proportion of participants achieving EASI-90

Descriptive statistics (ie, number, response frequency and rate with [redacted] Confidence Interval) will be provided for each visit by treatment group.

A logistic Bayesian Generalized Linear Mixed Model (BGLMM) will be applied, including data obtained in a treatment group (placebo or SAR444656) on a dose deemed as safe during safety review, based on response data for Week 16. The model will be adjusted for randomization stratum (moderate: EASI<22; severe: EASI≥22) will include effect for treatment group. [redacted]

The data collected after start of the IEs will be set to non-responder as indicated in Table 2.

Missing data will be imputed as non-responder.

Continuous supportive secondary endpoints

The continuous endpoints will be summarized by descriptive statistics after management of IEs and missing data handling on absolute score with change from baseline by treatment group, scheduled visits and also by randomization stratum (moderate: EASI<22; severe: EASI≥22). The estimated mean treatment difference with [redacted] credibility interval will be provided.

IEs and missing data will be handled as for the primary endpoint.

3.4 EXPLORATORY ENDPOINT(S) ANALYSIS

[redacted]

3.4.1 Definition of endpoint(s)

[redacted]

[redacted]

3.4.2 Main analytical approach

[redacted]

3.5 MULTIPLICITY ISSUES

No adjustment for multiplicity will be applied.

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.

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. Drug administrations are planned [redacted] from randomization to Week 16 (EOT).

Duration of IMP exposure

Duration of IMP exposure is defined as last IMP administration date – first IMP administration date + 1 day, regardless of unplanned intermittent discontinuations.

Duration of IMP exposure will be summarized quantitatively and categorically:

- 0 and ≤2 weeks
- >2 and ≤4 weeks
- >4 and ≤6 weeks
- >6 and ≤8 weeks
- >8 and ≤10 weeks
- >10 and ≤12 weeks
- >12 and ≤14 weeks
- >14 and ≤16 weeks
- >16 weeks

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

Treatment compliance

A given administration will be considered noncompliant if the participant did not receive the planned number of tablets of treatment on the given day as required by the protocol. This will be assessed based on the exposure information entered in the eCRF.

Percentage of treatment compliance for a participant will be defined as the number of days that the participant was compliant divided by the total number of 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 quantitatively and categorically (<80%, ≥80%).

Of note, according to the protocol, cases of overdose are reported in the e-CRF as Adverse Events and will be described as part of the AE analyses.

3.6.2 Adverse events

General common rules for adverse events

The analyses of the adverse events (AEs) will be performed by the following groups: placebo, SAR444656 [redacted]mg, SAR444656 [redacted]mg, SAR444656 [redacted] mg.

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 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.
- 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.

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 4.

Table 4 - 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 SAR444656 intervention group of highest dose.
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 severe TEAE.
- Any treatment-emergent SAE.
- TEAE leading to death, if any.
- Any TEAE leading to permanent study intervention discontinuation.

- Any TEAE leading to study intervention interruption.
- Any TEAE leading to permanent study discontinuation.
- Any treatment emergent AESI.
- Any treatment-related TEAE

The AE summaries of Table 5 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 4).

Table 5 - Analyses of adverse events

Type of AE	MedDRA levels
All TEAE	Overview[a]
	Primary SOC and PT
	PT
Common TEAE (≥5% in any 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 study intervention discontinuation	Primary SOC and PT
TEAE leading to study intervention interruption	Primary SOC and PT
TEAE leading to death[b]	Primary SOC and PT
Pre-treatment AE	Overview[a]
	Primary SOC and PT
Pre-treatment SAE	Primary SOC and PT
Post-treatment AE	Overview[a]
	Primary SOC and PT
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 full intervention 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 5 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.
- Deaths in non-randomized participants or randomized but not treated participants.

Analysis of adverse events of special interest (AESIs)

Adverse events of special interest (AESIs) will be selected for analyses as indicated in Table 6. Number (%) of participants experiencing at least one event will be provided for each event of interest, by primary SOC and PT if applicable. Tables will be sorted as indicated in Table 4.

Table 6 - Selections for AESIs and other AEs of interest

AESIs and other AEs of interest	Selection
Pregnancy of a female participant entered in a study as well as pregnancy occurring in a female partner of a male participant entered in a study with IMP	e-CRF specific tick box on the AE page linked to pregnancy on the Pregnancy page
Symptomatic overdose (serious or non-serious) with IMP	e-CRF specific tick box on the Overdose page
Increase in ALT >3×ULN	e-CRF specific tick box on the AE page
Serious infection	e-CRF specific tick box on the AE page
QT/QTcF > 500 msec	e-CRF specific tick box on the AE page
Confirmed QTcF prolongation >60 msec from baseline	e-CRF specific tick box on the AE page
Torsade de pointes	e-CRF specific tick box on the AE page
Sudden cardiac death	e-CRF specific tick box on the AE page
Ventricular tachycardia	e-CRF specific tick box on the AE page
Ventricular fibrillation and flutter	e-CRF specific tick box on the AE page
Unexplained or presumptive cardiac syncope	e-CRF specific tick box on the AE page
Seizures	e-CRF specific tick box on the AE page

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) parameters will be analyzed. They will be converted into standard international units and will be used in all listings and tables.

- Hematology:
  - Red blood cells (RBC), platelets and coagulation: red blood cell count, platelet count, hemoglobin, hematocrit
  - White blood cells: white blood cell count, neutrophils, lymphocytes, monocytes, eosinophils, basophils

- Clinical chemistry:
  - Metabolism: glucose (fasting or non-fasting), albumin, total protein, creatine phosphokinase (CPK), high sensitivity C-reactive protein (hs-CRP), lactase dehydrogenase (LDH)
  - Electrolytes: sodium, potassium, chloride, calcium, phosphate, bicarbonate, magnesium
  - Renal function: creatinine (serum creatinine), creatinine clearance, blood urea nitrogen (BUN), uric acid.
  - Liver function: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, gamma glutamyl transferase (Gamma GT), total and direct bilirubin
  - Pregnancy test: [Serum or highly sensitive urine] β-human chorionic gonadotropin (as needed for women of childbearing potential)
- Urinalysis:
  - Urinalysis for quantitative analysis: pH, specific gravity, protein, glucose, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick, microscopic examination (if blood or protein is abnormal)
- Vital signs:
  - pulse rate (beats per minute) and systolic and diastolic blood pressure according to position (sitting, supine), weight (kg), temperature (°C)
- ECG variables:
  - Triplicate ECG including heart rate (HR), RR, PR, QRS, QT, and QT intervals (QTcB and QTcF), J-T peak intervals, JT peak and morphological analysis of ECG waveform.

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

For triplicate ECG, the mean of the 3 planned values collected will be calculated, and the average will be used for analyses. If there is no triplicate available, the mean will be calculated with the values available.

When relevant, for laboratory variables, vital signs and ECG variables above, descriptive statistics for results and changes from baseline as appropriate 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 TE period. These analyses will be performed using central measurements only (when available) for laboratory variables and ECG variables.

For QT, QTcB and QTcF ECG parameters, mean of raw data, percent change and mean changes from baseline with the corresponding standard error will be tabulated and plotted over time by treatment group.

If applicable, descriptive statistics will be provided on rhythm and conduction performed on 24-hour Holter data (mean, minimum, maximum). Time profile plots on 24-hour Holter will also be provided.

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 laboratory 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 scheduled, nonscheduled or repeated).

For laboratory variables, vital signs 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

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

- Normal/missing
- Abnormal

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 will 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).

Analysis of participants with QTcF >480 msec and/or change from baseline QTcF >60 msec

If any, a frequency table of number (%) participants with QTcF >480 msec, QTcF >500 msec will be provided. A frequency table of number (%) with change from baseline in QTcF >30 msec and QTcF >60 msec will be provided.

An additional listing of participants with change from baseline QTcF >30 msec will also be provided.

3.7 OTHER ANALYSES

3.7.1 Other variables and/or parameters

3.7.1.1 PK analyses

SAR44656 PK parameters will be defined as follows:

- C_{trough}: SAR444656 concentration in PK sample taken just prior to IMP administration (pre dose) on Week 0 (V2), Week 1 (V3), Week 2 (V4), Week 4 (V6), and Week 16 (V12), as defined in protocol SOA.
- C2h: SAR444656 concentration in PK sample taken 2h ± 30 minutes after IMP administration on Week 0 (V2) and Week 2 (V4), as defined in protocol SOA
- C4h: SAR444656 concentration in PK sample taken 4h ± 30 minutes after IMP administration on Week 0 (V2) and Week 2 (V4), as defined in protocol SOA
- C7h: SAR444656 concentration in PK sample taken 7h ± 1 hour after IMP administration on Week 0 (V2), Week 1 (V3), Week 2 (V4), Week 4 (V6), and Week 16 (V12), as defined in protocol SOA.

These PK parameters will be summarized on the PK population for each planned visit and by dose level if applicable, using the following descriptive statistics: number of observations, arithmetic and geometric means, median, standard deviation, coefficient of variation, minimum and maximum. Time profile plots (mean +/- SD) will be provided for Week 0 (V2) and Week 2 (V4), where multiple PK samples are collected during a visit. In addition, plots for the mean of C_{trough} +/- SD for all available planned days will be provided.

PK samples collected outside of the sampling time window (see Section 5.4, Table 9) or PK samples collected as unscheduled samples will be classified as “undefined concentrations”. No descriptive statistics will be performed on these concentrations.

All concentration values below the LLOQ will be treated as zero in individual listing and respective descriptive statistics except for the geometric mean and associated coefficient of variation for which they will be considered as missing. Arithmetic means below LLOQ will be reported as LLOQ in the tables and not plotted in the figures. 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 be for ease of presentation and will not be meant to imply accuracy to more than 3 significant figures.

3.7.1.2 [redacted]

[redacted]

3.7.1.2.1 [redacted]

[redacted]

3.7.1.2.2 [redacted]

3.7.1.2.2.1 [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

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 5 participants may be combined with other categories):

- Race (Caucasian, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Other).
- Ethnicity (Hispanic or Latino, not Hispanic or Latino).
- Age group (18 to <40, 40 to <60, ≥60 years)
- Gender (Male, Female)
- BMI (<25, 25-<30, ≥30)
- Severity of AD (EASI<22; EASI≥22)

3.8 INTERIM ANALYSES

No formal interim analyses for efficacy evaluation are planned during the study. However, in order to support project strategic planning and design of future studies, informal interim analysis(es) may be conducted.

3.9 CHANGES TO PROTOCOL-PLANNED ANALYSES

This section summarizes major statistical changes in the protocol amendment(s).

Major statistical changes in protocol amendment(s)

Amendment Number	Approval Date	Changes	Rationale
1	24-Jul-2024	Added, additional arm participants to achieve a targeted overall ratio of 1:1:1:1 ([redacted] of SAR444656 or Placebo). In total approximately 200 participants will be included in the study.	To further characterize the dose/exposure response relationship of SAR444656 and guide future development. The allocation ratio was adjusted to accommodate for the additional patients included with the added dose group.

The following changes to the protocol-planned analysis will be applied:

Analysis population

- ITT population has been removed to avoid confusion with Efficacy population.
- PD population has been clarified to include the participants from safety population with at least one baseline and post-baseline PD parameter assessed.

Estimands

- Misallocation of treatment will be handled with the treatment policy strategy (previously: while on randomized treatment strategy).
- Discontinuation of study intervention will be handled with treatment policy strategy (previously: this IE was not specified).

Daily diary

- For PP-NRS, all available daily non-missing observations during the 7 days prior to randomization will be used for the calculation of the averages. Only the post-baseline weekly average will be calculated with a minimum of 4 daily scores out of the 7 days.

4 SAMPLE SIZE DETERMINATION

This study includes a total of 200 participants overall, with 53, 49, 45 and 53 participants randomized to SAR444656 [redacted] mg/[redacted], SAR444656 [redacted] mg/[redacted], SAR444656 [redacted] mg/[redacted] or matching placebo, respectively. The randomization ratio varies during the study: The initial 95 participants will be randomized to SAR444656 [redacted] mg/[redacted], SAR444656 [redacted] mg/[redacted] or matching placebo at a 2:1:2 ratio. The remaining 105 participants will be randomized to SAR444656 [redacted] mg/[redacted], SAR444656[redacted] mg/[redacted], SAR444656 [redacted] mg/[redacted] or matching placebo at a 1:2:3:1 ratio, targeting an overall allocation of 1:1:1:1.

Data from historical studies which have similar target population may be used as prior information supplementing the placebo arm, using a Bayesian approach.

The primary endpoint is the percent change of EASI from baseline at Week 16. The conditional prior distribution for the reduction in placebo has been chosen as a normal distribution with mean 35, standard deviation 40 (1), and assuming that historical information takes a weight of 5 additional patients treated with placebo, while a non-informative prior is used for the active arm.

With 53 and 53 participants randomized to SAR444656 [redacted] mg and placebo, and applying the above Bayesian framework, the half-width for the 2-sided [redacted] CI of the mean % change in EASI score from baseline to Week 16 of SAR444656 group as compared to the placebo group will be [redacted]. Similarly, with 45 and 53 participants randomized to SAR444656 [redacted] mg and placebo, respectively, the corresponding CI will have a half-width of [redacted].

5 SUPPORTING DOCUMENTATION

5.1 APPENDIX 1 LIST OF ABBREVIATIONS

AD: Atopic Dermatitis
AE: adverse event
AESIs: adverse events of special interest
ALT: alanine aminotransferase
AST: aspartate aminotransferase
BGLMM: bayesian generalized linear mixed model
BLMM: bayesian linear mixed model
BMI: body mass index
BSA: body surface area
BUN: blood urea nitrogen
CPK: creatine phosphokinase
[redacted]
EASI: Eczema Area and Severity Index
ECG: electrocardiogram
e-CRF: electronic case report form
EOS: end of study
EOT: end of treatment
[redacted]
HLGT: high level group term
HLT: high level term
hs-CRP: high sensitivity C-reactive protein
IDMC: Independent Data Monitoring Comittee
IE: intercurrent event
IMP: investigational medicinal product
IRAK4: interleukine 1 receptor associated kinase 4
LDH: lactase dehydrogenase
LLOQ: lower limit of quantification
LLT: lower-level term
MedDRA: medical dictionary for regulatory activities
MESF: molecules of equivalent soluble fluorochrome
PBMC: peripheral blood mononuclear cells
PCSA: potentially clinically significant abnormality
PD: pharmacodynamics
PDE4: topical phophodiesterase 4
PK: pharmacokinetic
[redacted]
PP-NRS: peak pruritus numeric rating scale
[redacted]
PRO: patient reported outcome
PT: preferred term

[redacted]

RBC:	red blood cells
SAE:	serious advese event
SAP:	statistical analysis plan
SD:	standard deviation
SEM:	standard error mean
SOC:	system organ class
TCI:	topical calcineurin inhibitor
TCS:	topical corticosteroids
TE:	treatment-emergent
TEAE:	treatment-emergent adverse event
ULN:	upper limit of normal
ULOQ:	upper limit of quantification
UPS:	ubiquitin proteasome system
vIGA:	validated investigational global assessment
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:

- Nonrandomized and treated participants, if applicable.
- Randomized participants.
- Randomized and not treated participants, if applicable.
- Randomized and treated participants.
- Participants who completed the study treatment period as per protocol.
- 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.

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

In addition, the number (%) of participants screened, screened-failed, randomized, with permanent intervention discontinuation and with early study discontinuation will be provided by country and 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 or 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 <40, ≥40 to ≤60, ≥60)
- Gender (Male, Female)
- Race (Caucasian, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Other, Not reported, Unknown)
- Ethnicity (Hispanic or Latino, not Hispanic or Latino)
- Country (Germany, Greece, Poland, Spain [HS only], United States)
- Body weight in kg as quantitative variable
- Body Mass Index (BMI) as quantitative variable and in categories (<25, ≥25-<30, ≥30 kg)
- Alcohol habits (Current, Previous, Never)
- Tobacco habits (Current, Previous, Never)

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

Disease characteristics at baseline

The following baseline disease characteristics will be summarized:

- Age of AD disease onset (years)
- Time since first diagnosis of AD disease (years)
- Prior disease therapy use (Yes/No)
- Prior disease therapies

- Disease characteristics at baseline
- The following baseline disease characteristics will be summarized for both studies:

Medical history

All medical history and surgical history will be coded to 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 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).

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 participants used prior to first IMP intake. Prior medications can be discontinued before first administration of IMP or can be ongoing during study intervention period.
- Concomitant medications are any medications received by the participant concomitantly to the IMP during the on-treatment period.
- Post-treatment medications are those the participant took 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 only, it will be considered as all of prior, concomitant, and post-treatment medication.

The prior, concomitant and post medications will be summarized for the safety population, by anatomic and therapeutic level. Participants will be counted once in each ATC category (anatomic or therapeutic) linked to the medication.

Medications used for rescue therapy will be also summarized as well as concomitant prohibited medications.

5.4 APPENDIX 4 DATA HANDLING CONVENTIONS

Analysis windows for time points

For daily e-Diary data (PP-NRS), the 7 consecutive days average (7 days preceding the target study day for the week of measurement, see Table 7) will be used. A minimum of 4 completions in their daily diary for time points that are post Day 1 (Week 0) is required to calculate the score.

Table 7 - Analysis windows definition for eDiary efficacy endpoints

Time	Targeted study day	Day range for calculating weekly score
Screening	-28 to -7	<-7
Week 0	1	-7- <1
Week 1	8	1-7
Week 2	15	8-14
Week 3	22	15-21
Week 4	29	22-28
Week 5	36	29-35
Week 6	43	36-42
Week 7	50	43-49
Week 8	57	50-56
Week 9	64	57-63
Week 10	71	64-70
Week 11	78	71-77
Week 12	85	78-84
Week 13	92	85-91
Week 14	99	92-98
Week 15	106	99-105
Week 16	113	106-112
Week 17	120	113-119
Week 18	127	120-126
Week 19	134	127-133
Week 20	141	134-140

Study days are calculated considering Day 1 as the day of first blinded IMP administration.

For efficacy and biomarker endpoints, the analysis windows in Table 8 will decide how the scheduled and/or unscheduled visits will be used in the by-visit analyses.

For the other assessments (safety, PK, laboratory, vital signs, ECG), the analysis windows in Table 9 will decide how the schedule and/or unscheduled visits will be used in the by-visit analyses. For ECG measurements and PK data collected at several timepoints for a same visit, Table 10 and Table 11 specify the analysis windows to use.

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

After applying these time windows, if multiple assessments are associated to the same time point, the closest from the targeted study day/timepoint 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 - Analysis windows definition of efficacy endpoints

Scheduled visit post baseline	Targeted study day	Analysis time windows	
		EASI, vIGA-AD, BSA [redacted]	[redacted]
Visit 1 (up to W0) -30 to 1		-30 to 1	
Baseline - Week 0 (Visit 2)	≤1	1	1
Week 1 (Visit 3)	8		
Week 2 (Visit 4)	15	8 to 21	(2-28)
Week 3 (Visit 5)	22		
Week 4 (Visit 6)	29	22 to 42	
Week 6 (Visit 7)	43		
Week 8 (Visit 8)	57	43 to 70	29 to 84
Week 10 (Visit 9)	71		
Week 12 (Visit 10)	85	71 to 98	
Week 14 (Visit 11)	99		
Week 16 (Visit 12)	113	99 to EOT	85 to EOT
Week 18 (Visit 13)	127		
Week 20 (Visit 14)	141		

Study days are calculated considering Day 1 as the day of first administration of intervention (or the day of enrollment for participant not exposed).
Visits with time windows provided within parentheses are not planned to be included in the analyses.

Table 9 - Analysis windows definition of safety/ ECG/Lab/Vital signs endpoints

Scheduled visit post baseline	Targeted study day	Analysis time windows
Visit 1 (up to W0) -30 to 1		-30 to 1
Baseline - Week 0 (Visit 2)	≤1	1
Week 1 (Visit 3)	8	2 to 11
Week 2 (Visit 4)	15	12 to 18
Week 3 (Visit 5)	22	19 to 25
Week 4 (Visit 6)	29	26 to 35
Week 6 (Visit 7)	43	36 to 49
Week 8 (Visit 8)	57	50 to 63

Scheduled visit post baseline	Targeted study day	Analysis time windows
Week 10 (Visit 9)	71	64 to 77
Week 12 (Visit 10)	85	78 to 91
Week 14 (Visit 11)	99	92 to 105
Week 16 (Visit 12)	113	106 to 119
Week 18 (Visit 13)	127	120 to 133
Week 20 (Visit 14)	141	134 to 147

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

Table 10 - Analysis windows for ECG measurements

Timepoint	Targeted study day	Analysis window in study days
Week 0 (Visit 2) / Pre dose	Week 0 (Visit 2) / Pre dose	Before Week 0 (Visit 2) dose
Week 0 (Visit 2) / 1st post dose	Week 0 (Visit 2) / 2h post dose	1h30 to 2h30 after Week 0 (Visit 2) dose
Week 0 (Visit 2) / 2nd post dose	Week 0 (Visit 2) / 4h post dose	3h30 to 4h30 after Week 0 (Visit 2) dose
Week 0 (Visit 2) / 3rd post dose	Week 0 (Visit 2) / 7h post dose	6h to 8h after Week 0 (Visit 2) dose
Week 1 (Visit 3) / pre dose	Week 1 (Visit 3) / Pre dose	Before Week 1 (Visit 3) dose
Week 1 (Visit 3) / 1st post dose	Week 1 (Visit 3) / 7h post dose	6h to 8h after Week 1 (Visit 3) dose
Week 2 (Visit 4) / Pre dose	Week 2 (Visit 4) / Pre dose	Before Week 2 (Visit 4) dose
Week 2 (Visit 4) / 1st post dose	Week 2 (Visit 4) / 2h post dose	1h30 to 2h30 after Week 2 (Visit 4) dose
Week 2 (Visit 4) / 2nd post dose	Week 2 (Visit 4) / 4h post dose	3h30 to 4h30 after Week 2 (Visit 4) dose
Week 2 (Visit 4) / 3rd post dose	Week 2 (Visit 4) / 7h post dose	6h to 8h after Week 2 (Visit 4) dose
Week 3 (Visit 5) / Pre dose	Week 3 (Visit 5) / Pre dose	Before Week 3 (Visit 5) dose
Week 4 (Visit 6) / Pre dose	Week 4 (Visit 6) / Pre dose	Before Week 4 (Visit 6) dose
Week 4 (Visit 6) / 1st post dose	Week 4 (Visit 6) / 7h post dose	6h to 8h after Week 4 (Visit 6) dose
Week 6 (Visit 7) / Pre dose	Week 6 (Visit 7) / Pre dose	Before Week 6 (Visit 7) dose
Week 8 (Visit 8) / Pre dose	Week 8 (Visit 8) / Pre dose	Before Week 8 (Visit 8) dose
Week 10 (Visit 9) / Pre dose	Week 10 (Visit 9) / Pre dose	Before Week 10 (Visit 9) dose
Week 12 (Visit 10)) / Pre dose	Week 12 (Visit 10) / Pre dose	Before Week 12 (Visit 10) dose
Week 14 (Visit 11) / Pre dose	Week 14 (Visit 11) / Pre dose	Before Week 14 (Visit 11) dose
Week 16 (Visit 12) / Pre dose	Week 16 (Visit 12) / Pre dose	Before Week 16 (Visit 12) dose
Week 16 (Visit 12) / 1st post dose	Week 16 (Visit 12) / 7h post dose	6h to 8h after Week 16 (Visit 12) dose
Week 18 (Visit 13)	Week 18 (Visit 13)	Week 18 (Visit 13)
Week 20 (Visit 14)	Week 20 (Visit 14)	Week 20 (Visit 14)

Table 11 - Analysis windows for PK

Timepoint	Targeted study day	Analysis window in study days
Week 0 (Visit 2) / Pre dose	Week 0 (Visit 2) / Pre dose	Before Week 0 (Visit 2) dose
Week 0 (Visit 2) / 1st post dose	Week 0 (Visit 2) / 2h post dose	1h30 to 2h30 after Week 0 (Visit 2) dose
Week 0 (Visit 2) / 2nd post dose	Week 0 (Visit 2) / 4h post dose	3h30 to 4h30 after Week 0 (Visit 2) dose
Week 0 (Visit 2) / 3rd post dose	Week 0 (Visit 2) / 7h post dose	6h to 8h after Week 0 (Visit 2) dose
Week 1 (Visit 3) / pre dose	Week 1 (Visit 3) / Pre dose	Before Week 1 (Visit 3) dose
Week 1 (Visit 3) / 1st post dose	Week 1 (Visit 3) / 7h post dose	6h to 8h after Week 1 (Visit 3) dose
Week 2 (Visit 4) / Pre dose	Week 2 (Visit 4) / Pre dose	Before Week 2 (Visit 4) dose
Week 2 (Visit 4) / 1st post dose	Week 2 (Visit 4) / 2h post dose	1h30 to 2h30 after Week 2 (Visit 4) dose
Week 2 (Visit 4) / 2nd post dose	Week 2 (Visit 4) / 4h post dose	3h30 to 4h30 after Week 2 (Visit 4) dose
Week 2 (Visit 4) / 3rd post dose	Week 2 (Visit 4) / 7h post dose	6h to 8h after Week 2 (Visit 4) dose
Week 4 (Visit 6) / Pre dose	Week 4 (Visit 6) / Pre dose	Before Week 4 (Visit 6) dose
Week 4 (Visit 6) / 1st post dose	Week 4 (Visit 6) / 7h post dose	6h to 8h after Week 4 (Visit 6) dose
Week 16 (Visit 12) / Pre dose	Week 16 (Visit 12) / Pre dose	Before Week 16 (Visit 12) dose
Week 16 (Visit 12) / 1st post dose	Week 16 (Visit 12) / 7h post dose	6h to 8h after Week 16 (Visit 12) dose

Unscheduled visits

Unscheduled visit measurements of efficacy, laboratory data, vital signs, ECG and biomarkers 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.

6 REFERENCES

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