STATISTICAL ANALYSIS PLAN

Protocol title:	**A randomized, double blinded, Placebo-controlled, proof-of-concept study assessing the efficacy and safety of an anti-TNF-OX40L NANOBODY® molecule, SAR442970, in participants with moderate to severe hidradenitis suppurativa**
Protocol number:	**ACT16852**
Compound number (INN/Trademark):	**SAR442970** **Not applicable**
Study phase:	**Phase 2**
Short Title:	**A study to test the efficacy and safety of SAR442970 in adults with hidradenitis suppurativa** **HS OBTAIN**
Statistician:	[redacted]
Statistical project leader:	[redacted]
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VERSION HISTORY

This Statistical Analysis Plan (SAP) for study ACT16852 is based on the protocol dated 16-Feb-2024. This section summarizes major changes to the statistical analysis features in the SAP analyses.

The first participant was randomized on 11-Jul-2023.

Table 1 - Major changes in statistical analysis plan

SAP Version	Approval Date	Changes	Rationale
1	30-Jul-2024	Not Applicable	Original version

1 INTRODUCTION

There are no major changes to the analyses described in the protocol.

1.1 STUDY DESIGN

This is a multinational, randomized, placebo-controlled, double-blind, Phase 2a proof-of-concept study. The purpose of this study is to evaluate the efficacy, safety, PK, biological effects of SAR442970 compare with placebo in adult participants with moderate to severe hidradenitis suppurativa (HS).

The study is composed of 3 parts: a double-blind, placebo-controlled period (Period A), followed by an open-label period (Period B), and then a safety Follow-up Period (Period C). After a screening period of 2 to 4 weeks, participants will receive SAR442970 150 mg or matching placebo Q2W at the Week 0 visit up to the Week 14 visit as part of Period A. Beginning at the Week 16 visit, all participants will receive SAR442970 150 mg Q2W up to the visit prior to the individual participant's end of treatment (EOT) visit as part of Period B. Period C will commence with the End of Treatment (EOT) visit and conclude with the End of Study (EOS) visit. For participants in the US, response will be assessed at the Week 20 visit (see definition of response in Section 2.2.1). Responders at Week 20 will continue in Period B to complete the 12-week open-label period. Non-responders at Week 20 will move directly to the safety follow-up period (Period C) with the Week 20 visit serving as their EOT visit.

Approximately 84 participants will be randomized in a 2:1 ratio to SAR442970 150 mg Q2W or matching placebo. Randomization will be stratified by HS treatment history (biologic and small molecule immunosuppressive-naïve or TNF-experienced) and Hurley stage (II or III). The recruitment target is approximatively 66 biologic and small molecule immunosuppressive-naïve and approximatively 18 TNF-experienced. Within the biologic and small molecule immunosuppressive-naïve subgroup, the number of participants with Hurley Stage III is not to exceed more than 50%. Within the biologic and small molecule TNF-experienced subgroup, the number of participants with Hurley Stage III is not to exceed more than 50%.

The primary analysis population is the biologic and small molecule immunosuppressive-naïve subgroup. Efficacy objectives and endpoints will be evaluated in an exploratory manner in the TNF-experienced subgroup.

1.2 OBJECTIVES AND ENDPOINTS

Table 2 - Objectives and endpoints

Objectives	Endpoints
Primary	
• To evaluate the efficacy of SAR442970 during the double-blind, placebo-controlled period in the biologic and small molecule immunosuppressive-naïve subgroup of participants with HS	• The clinical response as measured by the percentage of biologic and small molecule immunosuppressive-naïve participants achieving Hidradenitis Suppurativa Clinical Response

Objectives	Endpoints
	(HiSCR50) (defined as ≥ 50% reduction from Baseline in the total abscess and inflammatory nodule [AN] count, with no increase from Baseline in abscess or draining tunnel count) at Week 16
Secondary	
• To evaluate the efficacy and safety of SAR442970 in the biologic and small molecule immunosuppressive-naïve subgroup of participants with HS	• Time to onset of achieving HiSCR50 • Percentage of participants achieving HiSCR75 (defined as ≥ 75% reduction from Baseline in the total AN count, with no increase from Baseline in abscess or draining tunnel count) at Week 16 • Percentage of participants achieving HiSCR90 (defined as ≥ 90% reduction from Baseline in the total AN count, with no increase from Baseline in abscess or draining tunnel count) at Week 16 • Percentage of participants who experience improvement by at least one International Hidradenitis Suppurativa Severity Score System (IHS4) stage at Week 16 (See also Section 2.3.2 for definition of IHS4) • Change in absolute score from Baseline in IHS4 at Week 16 • Percentage of participants who experience a flare, defined as at least a 25% increase in AN count (with a minimum increase of 2) relative to Baseline at Week 16 (See also Section 2.3.4.1 for definition of flare) • Percentage of participants achieving IHS4-55 at Week 16 (defined as achievement of a 55% reduction in IHS4 score from Baseline) • Incidence of treatment-emergent adverse events (TEAEs), adverse events of special interest (AESIs), and serious adverse events (SAEs) including local reactions • Incidence of potentially clinically significant abnormalities in laboratory tests, vital signs, and electrocardiograms
• To evaluate the effect of SAR442970 on pain in the biologic and small molecule immunosuppressive-naïve subgroup of participants with HS	• Percentage of participants achieving at least 30% reduction and at least 1 unit reduction from Baseline in weekly average of daily [redacted]
• To evaluate the pharmacokinetics (PK) of SAR442970 and anti-drug antibodies (ADA) to SAR442970 in the biologic and small molecule immunosuppressive-naïve subgroup of participants with HS	• Serum SAR442970 concentrations throughout the study • Incidence of anti-SAR442970 antibody positive response throughout the study

Objectives	Endpoints
Exploratory	
[redacted]	
• To evaluate the effect of SAR442970 on quality of life in participants with HS	• [redacted] DLQI [redacted] DLQI ≥4
[redacted]	

Objectives	Endpoints
[redacted]	

1.2.1 Estimands

Primary estimand defined for main endpoints are summarized Table 3 below. More details are provided in Section 2. Additional secondary objectives/endpoints are not included in this table but would be handled with a similar strategy as the endpoint type (i.e., continuous, proportion, or time-to-event). For all these estimands, the comparison of interest will be the comparison of SAR442970 vs. placebo.

Table 3 - Summary of estimands for the primary and selected secondary endpoints

Endpoint Category	Estimands			
	Endpoint(s)	**Population**	**Intercurrent event(s) handling strategy**	**Population-level summary and missing data handling**
Primary objective: To evaluate the efficacy of SAR442970 during the double-blind, placebo-controlled period in the primary analysis population of the biologic and small molecule immunosuppressive-naïve subgroup participants with moderate to severe HS.				
Primary endpoint-Proportion	Percentage of participants achieving HiSCR50 at Week 16	Biologic and small molecule immunosuppressive-naïve population of Period A	The following intercurrent events (IEs) will be handled with the composite variable strategy; participants will be considered as non-responders after such IE. • Starting or increase in dose of oral antibiotic therapy for HS prior to Week 16. • Starting selected prohibited medications[a]. • Discontinuation of study intervention due to lack of efficacy. The following IEs will be handled with the treatment policy strategy (without IEs that need to be handled with composite variable strategy). Data collected after starting such IE will be included. • Starting other prohibited medications. • Discontinuation of study intervention due to reasons other than lack of efficacy.	The statistical analysis will be conducted using a Bayesian logistic regression model that includes the treatment group and stratified by baseline Hurley Stage. An informative prior on the placebo response rate will be used, based on the available historical studies. The difference of response rates between SAR442970 and placebo along with the 80% and the 90% credible intervals will be derived. Missing data will be imputed as non-responder.
Secondary objective: To evaluate the efficacy and safety of SAR442970 in the biologic and small molecule immunosuppressive-naïve subgroup of participants with HS.				
Secondary endpoint- Time-to-event	Time to onset of achieving HiSCR50	Biologic and small molecule immunosuppressive-naïve population of Period A	The following IEs will be handled with the composite variable strategy; analysis will be censored at Week 16: • Starting or increase in dose of oral antibiotic therapy for HS prior to Week 16 • Starting selected prohibited medications prior to Week 16[a].	This time-to-event endpoint will be analyzed using a Cox proportional hazards model that includes treatment group and stratified by baseline Hurley Stage.

Endpoint Category	Estimands			
	Endpoint(s)	**Population**	**Intercurrent event(s) handling strategy**	**Population-level summary and missing data handling**
			• Discontinuation of study intervention due to lack of efficacy. The following IEs will be handled with the treatment policy strategy (without IEs that need to be handled with composite variable strategy). Data collected after starting such IE will be included. • Starting other prohibited medications. • Discontinuation of study intervention due to reasons other than lack of efficacy.	The hazard ratio along with the 80% and 90% confidence intervals will be reported. Analyses will be censored at the time of last HS clinical parameter assessment.
Secondary endpoint-Proportion	Percentage of participants who experience improvement by at least one in IHS4 stage at Week 16	Biologic and small molecule immunosuppressive-naïve population of Period A	The following IEs will be handled with the composite variable strategy; participants will be considered as non-responders after such IE. • Starting or increase in dose of oral antibiotic therapy for HS during the treatment period. • Starting selected prohibited medications[a]. • Discontinuation of study intervention due to lack of efficacy. The following IEs will be handled with the treatment policy strategy (without IEs that need to be handled with composite variable strategy). Data collected after starting such IE will be included. • Starting other prohibited medications. • Discontinuation of study intervention due to reasons other than lack of efficacy.	Cochran -Mantel -Haenszel (CMH) method including treatment group and stratified by baseline Hurley Stage will be used. The difference of the response rates between SAR442970 and placebo and the 80% and 90% confidence intervals will be derived. Participants with missing data will be imputed as non-responders.

Endpoint Category	Estimands			
	Endpoint(s)	**Population**	**Intercurrent event(s) handling strategy**	**Population-level summary and missing data handling**
Secondary endpoint- Continuous	Change in absolute score from baseline in IHS4 at Week 16	Biologic and small molecule immunosuppressive-naïve population of Period A	The following IEs will be handled with the composite variable strategy; data after the IE will be excluded from the analysis, and the participant's worst post-baseline value (WOCF) on or before the time of the IE will be assigned to the Week 16 value. For participants with no post-baseline value, the baseline value will be used. • Starting or increase in dose of oral antibiotic therapy for HS during the treatment period. • Starting selected prohibited medications[a]. • Discontinuation of study intervention due to lack of efficacy. The following IEs will be handled with the treatment policy strategy (without IEs that need to be handled with composite variable strategy). Data collected after starting such IE will be included. • Starting other prohibited medications. • Discontinuation of study intervention due to reasons other than lack of efficacy.	Analysis of covariance (ANCOVA) including the baseline value, treatment group and stratified by baseline Hurley Stage. The difference of the SAR442970 group against placebo in mean response and the corresponding the 80% and 90% confidence intervals will be provided. Participants with missing data will be imputed with participants' WOCF. For participants with no post-baseline value, the baseline value will be used.
Secondary objective: To evaluate the effect of SAR442970 on pain in the biologic and small molecule immunosuppressive-naïve subgroup of participants with HS				
Secondary endpoint- Skin pain	Percentage of participants achieving at least 30% reduction and at least 1 unit reduction from Baseline in weekly average of daily HS Skin Pain NRS at Week 16 among participants with Baseline NRS = 3 (HS-Skin Pain NRS is based on worst skin pain in a 24-hour recall period [daily assessment is averaged over 7-day period])	Biologic and small molecule immunosuppressive-naïve population of Period A	The following IEs will be handled with the composite variable strategy; participants will be considered as non-responders after such IE. • Using analgesic therapy within 5 days of Week 16 will be considered as non-responders • Discontinuation of study intervention due to lack of efficacy. The following IE will be handled with the treatment policy strategy (without IEs that need to be handled with	CMH method including treatment group and stratified by baseline Hurley Stage. The difference of the response rates between SAR442970 and placebo and the 80% and 90% confidence intervals will be derived. Participants with missing data will be imputed as non-responder.

Endpoint Category	Estimands			
	Endpoint(s)	**Population**	**Intercurrent event(s) handling strategy**	**Population-level summary and missing data handling**
			composite variable strategy). Data collected after starting such IE will be included. • Discontinuation of study intervention due to reasons other than lack of efficacy.	

a The list of medications will be selected by blinded medical review prior to database lock. Participants that receive the selected treatment will also be reviewed in a blinded fashion to make sure the medication was used due for HS treatment failure and not an unrelated condition.

1.3 ANALYSIS POPULATIONS

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 participants receiving more than one study intervention during the study, the intervention group for as-treated analyses will be SAR442970 150 mg q2w if the participant received at least one administration of SAR442970.

The following populations for analyses are defined. The primary population of the efficacy endpoints will be the biologic and small molecule immunosuppressive-naïve population.

Table 4 - Populations for analyses

Period	Population	Description
Period A and Period B	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.
Period A		
	Modified ITT (mITT) of Period A	All randomized participants who have taken at least 1 dose of study intervention of Period A. Participants will be analyzed according to the intervention allocated by randomization. Randomized participants for whom it is unclear whether they took the study medication will be included.
	Biologic and small molecule immunosuppressive-naïve of Period A	All randomized participants in the biologic and small molecule immunosuppressive-naïve subgroup who have taken at least 1 dose of study intervention of Period A. Participants will be analyzed according to the intervention allocated by randomization. Randomized participants for whom it is unclear whether they took the study medication will be included.
	TNF-experienced of Period A	All randomized participants in the TNF-experienced subgroup who have taken at least 1 dose of study intervention of Period A. Participants will be analyzed according to the intervention allocated by randomization. Randomized participants for whom it is unclear whether they took the study medication will be included.
	Safety of Period A	All randomized participants who have taken at least one dose of study intervention of Period A, regardless of the amount of intervention administered.

		Participants will be analyzed according to the intervention they actually received. For participants who receive at least one dose of SAR442970, the actual intervention allocation for as-treated analysis will be the SAR442970 group.
	Pharmacokinetics (PK) of Period A	All participants from the safety population of Period A with at least one post-Baseline PK result. Participants having received only placebo will not be part of the PK population. Participants will be analyzed according to the intervention they actually received. For participants who receive at least one dose of SAR442970, the actual intervention allocation for as-treated analysis will be the SAR442970 group.
	Biomarker PD of Period A	All participants from the safety population of Period A with biomarker results available at baseline and at least one post-baseline visit. Participants will be analyzed according to the intervention the actually received. Randomized participants for whom it is unclear whether they took the study medication will be included.
	Biomarker predictive of Period A	All participants from the safety population of Period A with a baseline biomarker result. Participants will be analyzed according to the intervention they actually received. Randomized participants for whom it is unclear whether they took the study medication will be included.
Period B		
	mITT of Period B	All randomized participants who continue in Period B and have taken at least 1 dose of study intervention in this period. Randomized participants for whom it is unclear whether they took the study medication will be included.
	Biologic and small molecule immunosuppressive-naïve of Period B	All randomized participants in the biologic and small molecule immunosuppressive-naïve subgroup who continue in Period B and who have taken at least 1 dose of study intervention of Period B. Randomized participants for whom it is unclear whether they took the study medication will be included.
	TNF-experienced of Period B	All randomized participants in the TNF-experienced subgroup who continue in Period B and who have taken at least 1 dose of study intervention of Period B. Randomized participants for whom it is unclear whether they took the study medication will be included.
	Safety of Period B	All randomized participants who continue in Period B and who have taken at least one dose of study intervention of Period B, regardless of the amount of intervention administered. Participants will be analyzed according to the intervention they actually received.
	Pharmacokinetics (PK) of Period B	All participants from the safety population of Period B with at least one post-Baseline PK result. Participants will be analyzed according to the intervention they actually received.
	Biomarker PD of Period B	All participants from the safety population of Period B with biomarker results available at baseline and at least one post-baseline visit.

		Participants will be analyzed according to the intervention they actually received. Randomized participants for whom it is unclear whether they took the study medication will be included.
	Biomarker predictive of Period B	All participants from the safety population of Period B with a baseline biomarker result. Participants will be analyzed according to the intervention they actually received. Randomized participants for whom it is unclear whether they took the study medication will be included.
Period A and Period B	Antidrug antibody (ADA)	All participants from the safety population treated with SAR442970 with at least one post-Baseline ADA result (positive, negative, or inconclusive). Participants will be analyzed according to the intervention they actually received.

Abbreviations: ADA=anti-drug antibody; ICF=informed consent form; IRT= interactive response technology; PK=pharmacokinetic(s); PD=Pharmacodynamic(s); TNF=tumor necrosis factor.

2 STATISTICAL ANALYSES

2.1 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 baseline value is defined as the last available value before the first dose of double-blind IMP. For participants randomized but not treated, the baseline value is defined as the last available value before randomization.

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

The intervention groups will be presented as follows:

- Period A: SAR442970 150mg q2w and Placebo.
- Period B and Period C: SAR442970 150 mg q2w/SAR442970 150 mg q2w, Placebo/SAR442970 150 mg q2w and overall unless otherwise specified.

Observation period

The observation period will be divided into the following segments:

The pre-treatment period is defined as the period up to first blinded IMP administration.

Period A:

- The **treatment-emergent (TE) period of Period A** is defined as the period from the first blinded IMP administration to the last blinded IMP administration + 75 days or the first open-label IMP administration, whichever occurs earlier. The TE period of Period A includes the following 2 sub-periods:
  - The **on-treatment period of Period A** is defined as the period from the first blinded IMP administration to the last blinded administration of the IMP + 14 days, or the first open-label IMP administration, whichever occurs earlier.
  - The **residual treatment period of Period A** is defined as the period after the end of the on-treatment period of Period A to the end of the TE period of Period A.

Period B:

- The **treatment-emergent (TE) period of Period B** is defined as the period from the first open-label IMP administration to the last open-label IMP administration + 75 days. The TE period of Period B includes the following 2 sub-periods:
  - The **on-treatment period of Period B** is defined as the period from the first open-label IMP administration to the last open-label administration of the IMP + 14 days.

- The **residual treatment period of Period B** is defined as the period after the end of the on-treatment period of Period B to the end of the TE period of Period B.

The post-treatment period is defined as the period after the end of the TE period of Period B, or after the end of TE period of Period A if the participant does not enter the Period B.

Any lesion that is treated with steroid injection, deroofing, or other local intervention, the lesion is considered present throughout the double-blind period and open-label period. Types of lesions include abscess, non-inflammatory nodule, inflammatory nodule, nondraining tunnel, draining tunnel, hypertrophic scar.

2.2 PRIMARY ENDPOINT(S) ANALYSIS

2.2.1 Definition of endpoint(s)

The primary endpoint is the percentage of biologic and small molecule immunosuppressive-naïve participants achieving HiSCR50 at Week 16. It is defined as ≥ 50% reduction from Baseline in the total abscess and inflammatory nodule (AN) count, with no increase from Baseline in abscess or draining tunnel count.

2.2.2 Main analytical approach

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

- Endpoint: Percentage of participants achieving HiSCR50 at Week 16.
- Treatment condition: SAR442970 will be compared to Placebo.
- Analysis population: Biologic and small molecule immunosuppressive-naïve population of Period A.
- Intercurrent events (IE):

  The following intercurrent events will be handled with the composite variable strategy; participants will be considered as non-responders after such IE:

  - Starting or increase in dose of oral antibiotic therapy for HS prior to Week 16
  - Starting selected prohibited medications. Participants that receive the selected treatment listed in Table 5 will be reviewed in a blinded fashion to make sure the medication was used due for HS treatment failure and not an unrelated condition.
  - Discontinuation of study intervention due to lack of efficacy

  The following IEs will be handled with the treatment policy strategy (without IEs that need to be handled with composite variable strategy). Data collected after starting such IE will be included:

  - Starting other prohibited medications

- Discontinuation of study intervention due to reasons other than lack of efficacy

- Population-level summary: A Bayesian logistic regression model including intervention group and stratified by baseline Hurley Stage will be used with an informative prior on the placebo response rate based on the historical studies available. Participant with missing data will be imputed as non-responders. Descriptive statistics will be presented by treatment group.

Table 5 - Selected prohibited and/or rescue medications and procedures impact on efficacy

Endpoints	Intervention (Intercurrent Event)	Intervention in the main statistical analysis (Yes/No)[a] / Selection criteria
Percentage of participants acheiving HiSCR50 at Week 16 and other endpoints derived from HS clinical parameters (eg, HiSCR75, HiSCR90, IHS4, flares, DLQI, HiSQOL)	**Immunosuppressive or immunomodulatory therapy**	
	Examples: natalizumab, rituximab, adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, anakinra, canakinumab, bermekimab, ustekinumab, guselkumab, secukinumab, JAK inhibitors (e.g., abrocitinib, baricitinib, filgotinib, pacritinib, upadacitinib), or TYK inhibitors (e.g., brepocitinib deucravacitinib,ropsacitinib), or apremilast, corticosteroids, methotrexate, cyclosporine, retinoids, acitretin/etretinate, non-contraceptive hormonal therapy, zinc gluconate, intramuscular gamma globulin, colchicine, fumaric acid esters, or metformin (except for continuous treatment of pre-existing diabetes), or other systemic therapies that can also be used to treat HS.	No
	Antibiotic therapy	
	Antibiotic therapy (topical and/or systemic [oral or IV]) for HS-related infection other than doxycycline or minocycline	Yes (CDGsn00892)
	Doxycycline or minocycline: Increase from stable dose established 28 days prior to baseline; or increase dose regimen greater than 100 mg PO BID for doxycycline or minocycline	Yes (CDGsn00892)
	Corticosteroid therapy	
	Intralesional corticosteroids	No
	Corticosteroids for HS with systemic potential (e.g., injectable or high dose intralesional corticosteroids)	Yes (CDGsn00010)
Pain endpoints (HS skin pain NRS, PP NRS)	**Analgesic therapy within 5 days preceding Week 16 visit**	
	Opioid analgesics and Non-opioid analgesics (e.g., antiepileptics (e.g., gabapentin), tricyclics (e.g., nortriptyline), or selective serotonin norepinephrine reuptake inhibitors (e.g., duloxetine, venlafaxine) other than ibuprofen or acetaminophen	Yes (CDGsn00195; CDGsn00229 ;CDGsn01761; CDGsn00009; CDGsn01793)
	Corticosteroid therapy	
	Intralesional corticosteroids for HS	Yes (CDGsn00010)
	Incision and drainage procedure for HS	Yes (CMQ40194)

a When yes, if confirmed through blinded medical review the estimand for the intercurrent event handling strategy will be as follows: hypothetical for continuous endpoints, and composite for responder and time-to-event endpoints. When no, a treatment policy strategy will be applied.

Bayesian modeling

The following Bayesian logistic regression for the mean binary response will be used:

$$\text{Ln}\left(\frac{E(y)}{1-E(y)}\right) = logit\big(E(y)\big) = \beta_{PBO}X_{PBO} + \beta_{TRT}X_{TRT} + \beta_{HS2}X_{HS2} + \beta_{HS3}X_{HS3}$$

Where X_{PBO}, X_{TRT} are dummy variables taking the value 1 or 0 according to whether or not each of participant is in the placebo or SAR442970 treatment group respectively, X_{HS2}, X_{HS3} are dummy variables taking the value 1 or 0 according to whether or not each of participant is in the Hurley stage II or III groups respectively.

For parameter estimation, the following constraint will be used:

$$\beta_{HS2} = -\beta_{HS3}$$

Giving the model:

$$\text{Ln}\left(\frac{E(y)}{1-E(y)}\right) = logit\big(E(y)\big) = \beta_{PBO}X_{PBO} + \beta_{TRT}X_{TRT} + \beta_{HS2}(X_{HS2} - X_{HS3})$$

so that the influence of Baseline Hurley Stage on the model estimated treatment group mean responses are more evident.

The expectations of the prior distributions for the biologic and small molecule immunosuppressive-naïve population in the placebo group response rates will be set to match the observed treatment group response rates in the available historical studies. An informative prior distribution for the HiSCR50 rate has been chosen as a beta distribution with parameter (2.1; 4.9) which have expectations equal to 30% for the placebo group to match the observed treatment group response rates of the historical studies. A vague uninformative prior (a prior with a large variance) will be used for the biologic and small molecule immunosuppressive-naïve population in the treatment group because there are few to no prior data published on SAR442970 in HS).

IF p_{TRT}, p_{PBO} denote the probability of response in the treatment group and placebo group respectively, to map the probability scale priors for the group response rates and the logit scale treatment group we will use the following equations :

$$p_{PBO} = logit^{-1}(\beta_{PBO})$$

$$p_{TRT} = logit^{-1}(\beta_{TRT})$$

Accordingly, the priors to be used are :

$$p_{PBO} \sim \beta\ (2.1; 4.9)$$

$$\beta_{TRT} \sim N\ (0; 10000)$$

$$\beta_{HS2} \sim N\ (0; 10000)$$

The model equation will be updated to parameterize β_{PBO} as the model intercept with the active treatment being additive effects (on the logit scale). We note that model (2) can be re-parameterized as follows:

$$\beta_{PBO} = \gamma_{PBO}$$

$$\beta_{TRT} = \gamma_{TRT} + \gamma_{PBO}$$

$$\beta_{HS2} = \gamma_{HS2}$$

Giving the model:

$$\text{Ln}\left(\frac{E(y)}{1-E(y)}\right) = logit\big(E(y)\big) = \gamma_{PBO} + \gamma_{TRT}X_{TRT} + \gamma_{HS2}(X_{HS2} - X_{HS3})$$

Presentation of results from the primary analysis

The priors and observed data will be combined and used to derive posterior distributions for the response rates in each treatment arm. The posterior distributions will be summarized using means, medians, SDs and the 80% and 90% credible intervals.

The posterior probability that the difference in response rates between placebo and SAR442970 groups is greater than zero (i.e., SAR442970 demonstrates a greater response compared with placebo) will also be presented.

2.2.3 Frequentist analysis

Frequentist analysis (non-Bayesian) of the primary endpoint will be implemented to provide complementary perspective, offering validation and robustness checks to the Bayesian results. Furthermore, by incorporating informative priors in Bayesian analysis, the subsequent use of frequentist analysis allows for the examination of how these prior assumptions influence the final results, enhancing transparency and understanding.

Treatment difference in achieving HiSCR50 (SAR442970 versus placebo), and the treatment response rates in each intervention group will be provided using the CMH method stratified by baseline Hurley stage. Handling of IEs will follow that of the primary approach. Missing data will be imputed as non-responders. The reported results will include 80% and 90% confidence intervals of the treatment difference.

2.2.4 [redacted]

[redacted]

[redacted]

2.3 SECONDARY EFFICACY ENDPOINT(S) ANALYSIS

The endpoints detailed in this section are the secondary efficacy endpoints. Other secondary endpoints analyses are defined in Section 2.7.2 (AE, SAE), Section 2.7.3.1 (laboratory abnormalities) and Section 2.8 (Others analyses).

2.3.1 Time to onset of achieving HiSCR50

The time to onset of achieving HiSCR50 by Week 16 will be defined as [date of first time achieving HiSCR50 - date of randomization] in days.

The estimand for time to event endpoint defined in Table 3 will be used. The following IEs will be handled with the composite variable strategy; participants will be censored at Week 16:

- Starting or increase in dose of oral antibiotic therapy prior to Week 16
- Starting selected prohibited medications prior to Week 16. Participants that receive the selected treatment Table 5 will be reviewed in a blinded fashion to make sure the medication was used due for HS treatment failure and not an unrelated condition
- Discontinuation of study intervention due to lack of efficacy

The following IEs will be handled with the treatment policy strategy (without IEs that need to be handled with composite variable strategy). Data collected after starting such IE will be included.

- Starting other prohibited medications
- Discontinuation of study intervention due to reasons other than lack of efficacy

Participants discontinuing the study follow-up before Week 16 will be censored at the time of their last HS clinical parameters assessment.

Comparison of treatment response (SAR442970 vs Placebo) will be summarized using the Cox proportional hazards model, including intervention groups, and stratified by baseline Hurley Stage. The hazards ratios and the 80% and 90% confidence intervals. Kaplan-Meier curves along with associated summary statistics will be provided by intervention group.

2.3.2 Absolute change from Baseline in IHS4 at Week 16

The IHS4 is a validated tool to assess HS severity. The determination of IHS4 requires counting inflammatory nodules, abscesses and draining tunnels and multiplying each by a specific coefficient making it straightforward to apply in both research and clinical practice and easy to use in conjunction with the HiSCR50. A continuous IHS4 score can be derived based on this weighted score. A categorial IHS4 score can also be derived from the weighted score: a total score of 3 or less signifies mild, 4 to 10 signifies moderate, and 11 or higher signifies severe disease.

Two IHS4 scores are to be derived from the primary continuous IHS4. The first one is defined as the improvement by at least one IHS4 stage at Week 16 and the second which is also known as IHS4-55 is defined as a 55% reduction in IHS4 score from Baseline.

The change from baseline in the IHS4 score at Week 16 will be analyzed using the ANCOVA model including the baseline value, intervention group and baseline Hurley Stage.

The estimand for continuous endpoints defined in Table 3 will be used. The IE handling is as follow:

- Data of participants starting or increasing the dose of oral antibiotic therapy for HS during the treatment period or started selected prohibited medication listed in Table 5 or discontinued study intervention because of lack of efficacy will be excluded after such IE, and participant's worst postbaseline value on or before the time of the IE will be used to assign the endpoint value (WOCF). Participants with no post-baseline value, the baseline value will be used. Participants that receive the selected treatment listed in Table 5 will be reviewed in a blinded fashion to make sure the medication was used due for HS treatment failure and not an unrelated condition.
- For participants who started other prohibited medication or discontinue the treatment prematurely due to other reasons than efficacy, all data collected after the event will be used in the analysis.

Missing data at Week 16 will be imputed with participant worst postbaseline value. For participants with no post-baseline value, the baseline value will be used.

The least square (LS) means of the absolute change from baseline to Week 16 in IHS4 per study invention group will be reported. The difference of SAR442970 against placebo in LS means and the corresponding 80% and 90% confidence intervals will be reported. Descriptive statistics will also be provided.

2.3.3 HS Skin Pain NRS at Week 16

The HS-Skin Pain NRS is a unidimensional numeric rating scale (NRS) that allows for rapid measure of skin pain that can be administered multiple times with minimal administrative burden. The HS-Skin Pain NRS is scored on a 0 to 10 scale with 0 indicating "no skin pain" and 10 indicating "worst skin pain possible". The HS-Skin Pain NRS has a 24-hour recall period and will be completed as a daily diary, ideally at the same time each day (evening) throughout the Treatment Period.

The percentage of participants achieving at least 30% reduction and at least 1 unit reduction from Baseline in weekly average of daily HS Skin Pain NRS at Week 16 among participants with Baseline NRS ≥ 3 (HS-Skin Pain NRS is based on worst skin pain in a 24-hour recall period [daily assessment is averaged over 7-day period]) will be analyzed. Participants must have a minimum of 4 diary entries within the 7-day period prior to Week 16 to calculate the week's average. Those who don't meet this requirement will have missing data for that week.

The estimand for skin pain endpoint will be used and participants with missing data will be imputed as non-responders. The following IEs will be handled with the composite variable strategy; participants will be considered as non-responders after such IE.

- Using analgesic therapy within 5 days of Week 16 will be considered as non-responders.
- Starting selected prohibited medications. Participants that receive the selected treatment listed in Table 5 will be reviewed in a blinded fashion to make sure the medication was used due for HS treatment failure and not an unrelated condition.
- Discontinuation of study intervention due to lack of efficacy.

The following IE will be handled with the treatment policy strategy (without IEs that need to be handled with composite variable strategy). Data collected after starting such IE will be included.

- Discontinuation of study intervention due to reasons other than lack of efficacy.

Participants with missing data will be imputed as non-responders.

An estimate of the treatment difference (SAR442970 versus placebo) will be obtained using CMH method, stratified by baseline Hurley stage. The estimated treatment difference will be reported along with the 80% and 90% confidence intervals.

2.3.4 Secondary efficacy endpoints - Proportions

2.3.4.1 Definition of endpoint(s)

Secondary efficacy endpoints defined as proportions:

- Percentage of participants achieving HiSCR75 (defined as ≥75% reduction from Baseline in the total AN count, with no increase from Baseline in abscess or draining tunnel count) at Week 16
- Percentage of participants achieving HiSCR90 (defined as ≥90% reduction from Baseline in the total AN count, with no increase from Baseline in abscess or draining tunnel count) at Week 16
- Percentage of participants who experience improvement by at least one IHS4 stage at Week 16
- Percentage of participants achieving IHS4-55 at Week 16 (defined as achievement of a 55% reduction in IHS4 score from Baseline)
- Percentage of participants who experience a flare, defined as at least a 25% increase in AN count (with a minimum increase of 2) relative to Baseline at Week 16 (See also protocol 8.2.1.4 for definition of flare)

HiSCR75 and HiSCR90

Exploratory outcome measures that evaluated deeper clinical response included an HiSCR modification to assess the proportion of participants achieving at least 75% (HiSCR75) and 90% (HiSCR90) reduction from baseline AN count, with no increase from Baseline in abscess or draining tunnel count) at Week 16, as defined in Table 2, will be analyzed.

Dichotomous IHS4

IHS4 is defined in Section 2.3.2 above. Two dichotomous IHS4 scores are to be derived from the primary continuous IHS4. The first one is defined as the improvement by at least one IHS4 stage at Week 16 and the second which is also known as IHS4-55 is defined as a 55% reduction in IHS4 score from Baseline.

Disease flare

Disease flare is defined when at least a 25% increase in AN count with a minimum increase of 2 AN relative to baseline is observed. A participant's disease flare status is a dichotomous status which will be determined at each visit using these criteria and will be listed with the other lesion count assessment data in the data listings.

2.3.4.2 Main analytical approach

The estimand for proportions defined in Table 3 above will be used. For the following endpoints: HiSCR75, HiSCR90 and Dichotomous IHS4; Participants with missing data at Week 16 will be imputed as non-responders. For disease flare, participants with missing data at Week 16 will be imputed as flare if a flare had occurred already before Week 16. Otherwise, no flare will be imputed. The treatment difference in response rates in SAR442970 against placebo and the corresponding 80% and 90% confidence intervals will be reported.

2.4 [redacted]

[redacted]

2.4.1 [redacted]

[redacted]

[redacted]

The Peak Pruritus Numerical Rating Scale

The Peak Pruritus Numerical Rating Scale (PP-NRS) is a validated single item 0-10 numeric rating scale assessing peak pruritus (itch) during the past 24 hours. The participant is asked about the severity of their pruritus with 0 = no itch and 10 = worst itch imaginable. The PP-NRS will be completed daily as a daily diary. The Week 16 average PP-NRS is calculated based on the available 7 daily assessment. Participants must have a minimum of 4 diary entries within the 7-day period prior to Week 16 to calculate the week's average. Those who don't meet this requirement will have missing data for that week.

2.4.2 [redacted]

[redacted]

2.4.3 Main analytical approach

Biologic and small molecule immunosuppressive-naïve population

Exploratory efficacy endpoints at Week 16 in the biologic and small molecule immunosuppressive-naïve population will be analyzed with the same estimand and analysis approach as the secondary efficacy endpoints defined in Table 3 for the same data type (binary, continuous or skin pain), except for the following endpoint:

- Percentage of participants without analgesic use in the past 2 weeks at Weeks 16

For the percentage of participants without analgesic use in the past 2 weeks at Week 16, descriptive statistics will be provided based on data as collected i.e., without IE handling and without missing data imputation.

TNF-experienced population

Descriptive statistics will be provided for the exploratory efficacy endpoints at Week 16 in the TNF-experienced population, using the estimand defined in Table 3 for binary endpoints.

2.5 EXPLORATORY EFFICACY ENDPOINT(S) ANALYSIS OF PERIOD B

The analysis of exploratory efficacy endpoints of Period B (See Table 2 above) will be only descriptive. The general consideration defined in Section 2.1 will be applied and no statistical testing will be implemented.

2.6 MULTIPLICITY ISSUES

No multiplicity adjustment will be applied in this proof-of-concept study.

2.7 SAFETY ANALYSES

All safety analyses will be performed for Period A and Period B separately, on the safety populations as defined in Section 1.3, unless otherwise specified, using the following common rules:

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

2.7.1 Extent of exposure

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

Duration of IMP exposure during Period A

Duration of IMP exposure during Period A is defined as minimum of (the first open-label IMP administration date - the first blinded IMP administration, the last blinded IMP administration date- the first blinded IMP administration date + 14 days), regardless of unplanned intermittent discontinuations.

Duration of IMP exposure during Period A will be summarized descriptively as a quantitative variable (number, mean, SD, median, minimum, and maximum). In addition, duration of treatment exposure during Period A will be summarized categorically by numbers and percentages for each of the following categories and cumulatively according to these categories:

- > 0 and ≤ 2 weeks
- > 2 and ≤ 4 weeks
- > 4 and ≤ 8 weeks
- > 8 and ≤ 12 weeks
- > 12 and ≤ 16 weeks
- > 16 weeks

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

Duration of IMP exposure during Period B

Duration of IMP exposure during Period B is defined as the last open-label IMP administration date- the first open-label IMP administration date + 14 days, regardless of unplanned intermittent discontinuations. If the date of the last open-label dose is missing, the duration of IMP exposure will be missing.

Duration of IMP exposure during Period B will be summarized descriptively as a quantitative variable (number, mean, SD, median, minimum, and maximum). In addition, duration of treatment exposure during Period B will be summarized categorically by numbers and percentages for each of the following categories and cumulatively according to these categories:

- > 0 and ≤ 2 weeks
- > 2 and ≤ 4 weeks
- > 4 and ≤ 8 weeks
- > 8 and ≤ 12 weeks
- > 12 weeks

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

Treatment compliance during Period A

A given administration will be considered noncompliant if the participant did not receive the number of administrations as required by the protocol. No imputation will be made for participants with missing or incomplete data.

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

Treatment compliance will be summarized quantitatively and categorically: <80%, ≥80%.

Treatment compliance during Period B

A given administration will be considered noncompliant if the participant did not receive the number of administrations as required by the protocol. No imputation will be made for participants with missing or incomplete data.

Percentage of treatment compliance for a participant during Period B will be defined as the number of administrations that the participant was compliant divided by the total number of administrations that the participant was planned to take from the first open-label administration of IMP up to the actual last open-label administration of IMP during Period B.

Treatment compliance will be summarized quantitatively and categorically: <80%, ≥80%.

2.7.2 Adverse events

General common rules for adverse events

All adverse events (AEs) will be coded to a preferred term (PT) 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 (TEAEs): 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 period 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 6. .

Table 6 - Sorting of AE tables

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

a Sorting will be based on the SAR442970 intervention group

Analysis of all adverse events

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

- Any TEAE
- Any treatment-emergent SAE

- Any severe TEAE
- TEAE leading to death
- Any TEAE leading to permanent intervention discontinuation
- Any treatment-emergent AESI
- Any TEAE related to IMP as per the Investigator's judgment

The AE summaries of Table 7 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 6).

Table 7 - Analyses of adverse events

Type of AE	MedDRA levels
All TEAE	Primary SOC and PT
TEAE related to IMP as per Investigator's judgement	Primary SOC and PT
TEAE by maximal intensity	Primary SOC and PT
Treatment-emergent SAE	Primary SOC and PT
TEAE leading to permanent intervention discontinuation	Primary SOC and PT
TEAE leading to death[a]	Primary SOC and PT
Pre-treatment AEs	Overview
Post-treatment AEs	Overview

a 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 7 the number (%) of participants in the following categories will be provided:

- Deaths during the treatment-emergent period and post-treatment periods
- Deaths in non-exposed 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 8. 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 6.

Table 8 - Selection of AESIs

AESI	Criteria
Pregnancy	"Pregnancy" or "Partner Pregnancy" ticked on the Pregnancy eCRF page
Symptomatic overdose with IMP	Symptomatic Overdose ticked Yes, with Overdose of Study Treatment ticked Yes on the Overdose eCRF
Significant ALT elevation (ALT>3×ULN)	"ALT increase" and AESI ticked "Yes" on AE eCRF
Any severe or opportunistic viral, bacterial, fungal, or helminthic infection	AESI ticked "Yes" and (CMQsn00235 [Opportunistic infections Narrow] or CMQ10544 [HLGT Helminthic disorders] or CMQ10176 [GLB_INFECTIONS])
Malignancy	AESI ticked "Yes" and CMQsn00090 [Malignancies Narrow]
Systemic or localized allergic reactions that require immediate treatment	AESI ticked "Yes" and CMQsn00214 [Hypersensitivity Narrow]
Reactivation of hepatitis B	AESI ticked "Yes" and CMQ00071 [GLB_HEPATITIS_B]
Demyelinating disorders or progressive multifocal leukoencephalopathy	AESI ticked "Yes" and CMQsn00154 [Demyelination Narrow]
Congestive heart failure	AESI ticked "Yes" and CMQ10064 [Cardiac failure congestive-single PT]
Myocardial infarction	AESI ticked "Yes" and CMQsn00047 [Myocardial infarction Narrow]
Lupus-like reaction or systemic lupus erythematosus	AESI ticked "Yes" and CMQsn00045 [Systemic lupus erythematosus Narrow]

ALT: alanine aminotransferase; ULN: upper limit of normal

2.7.3 Additional safety assessments

2.7.3.1 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, red blood cell count, platelet count, mean corpuscular volume, mean corpuscular hemoglobin concentration, mean corpuscular hemoglobin and reticulocytes
  - White blood cells: white blood cell count, neutrophils, lymphocytes, monocytes, basophils, eosinophils
- Clinical chemistry:
  - Metabolism: fasting glucose, fasting total cholesterol, fasting triglycerides, fasting high-density lipoprotein, fasting low-density lipoprotein, fasting very low-density lipoprotein, total protein, albumin, creatine phosphokinase
  - Electrolytes: sodium, potassium

  - 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)/ Serum glutamic-pyruvic transaminase, aspartate aminotransferase (AST)/ Serum glutamic-oxaloacetic transaminase, alkaline phosphatase, total and direct bilirubin
- Vital signs: heart rate (beats per minute), systolic and diastolic blood pressure (mmHg) in sitting or semi-supine position, weight (kg), respiratory rate, temperature
- ECG variables: heart rate, PR, QRS, QT, and corrected QTcF (according to Fridericia).

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 laboratory variables, vital signs, and ECG variables above, descriptive statistics for results and changes from baseline will be provided for each analysis window during the on-treatment period. These analyses will be performed using central measurements only (when available) for laboratory variables.

For all parameters, 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. For parameters defined as efficacy endpoints, PCSA summaries will not be provided.

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

2.8 OTHER ANALYSES

2.8.1 PK analyses

SAR442970 concentrations at selected time points will be reported using the following descriptive statistics: mean, geometric mean, median, standard deviation, coefficient of variation, minimum and maximum. All concentration values LLOQ/2 will be treated as zero in all summary statistics excepted for the geometric mean and associated coefficient of variation for which they will be considered as missing. A listing of PK concentration will be provided, using "<LLOQ/2" for values below LLOQ/2.

PK parameters such as C_{max}, t_{max}, $t_{1/2z}$, and $AUC_{0\text{-}tau}$ will be estimated using a population PK approach. These parameters will be presented in a separate standalone report provided under the responsibility of Sanofi TMED PKDM Department.

2.8.2 Immunogenicity analyses

Antidrug antibodies were assessed at baseline (before first IMP administration), Week 2, Week 4, Week 16, Week 28/EOT or premature and at EOS (Week 36 or 8 weeks after premature EOT).

A 3-tiered approach will be employed to generate titer data. Serum samples will be screened for antibodies binding to SAR442970 and the titer of confirmed positive samples will be reported as a quantitative variable.

Incidence will be provided for the following ADA response categories:

- Participants with **pre-existing ADAs** correspond to participants with ADAs present in samples drawn before first administration of intervention. Participants with missing ADA sample at baseline will be considered as without pre-existing ADA.
- Participants with **treatment-emergent ADA** correspond to participants with at least one treatment-induced/boosted ADA.
    - Participants with **treatment-induced ADAs** correspond to participants with ADAs that developed at any time after first IMP administration and without pre-existing ADA (including participants without pre-treatment samples).
    - Participants with **treatment-boosted ADAs** correspond to participants with pre-existing ADAs that are boosted at any time after first IMP administration to a significant higher titer than the baseline. A 3-fold serial dilution schema is used during titration, so at least a 9-fold increase will be considered as significant.
- Participants with **unclassified ADA** correspond to participants with pre-existing ADAs that cannot be classified as treatment-boosted ADA because of missing titer(s) (i.e., a positive ADA sample at any time after first IMP administration in a participant with pre-existing ADA but with missing titer at this sample or at baseline).
- Participants **without treatment-emergent ADA** correspond to participants without treatment-induced/boosted ADA and without any inconclusive sample nor unclassified ADA at any time after first IMP administration.

- Participants **with inconclusive ADA** are defined as participants which cannot irrefutably be classified as with or without treatment-emergent ADA.

Summary of ADA at baseline, listing of participants with treatment-emergent ADA and summary table of incidence will be provided for each SAR442970 related ADA variables on the ADA population. A summary of ADA at baseline and at each visit during the treatment-emergent period (including follow-up) might be provided depending on ADA incidence.

Additional analysis may be performed to further characterize the immunogenicity of SAR442970.

2.8.3 Biomarker analyses

This section outlines the planned analyses for biomarkers related to Hidradenitis Suppurativa (HS). The analyses aim to characterize the effect of SAR442970 on pre-defined biomarkers in participants with HS and to evaluate the pharmacodynamic effect of SAR442970.

Unless otherwise specified, all data will be summarized in the safety populations of Period A and Period B. The continuous data will be summarized using the number of non-missing values (including the ones <LLOQ and >ULOQ), number of values under the limit of quantitation (LLOQ) if applicable, arithmetic mean, geometric mean, standard deviation, median, Q1, Q3, minimum and maximum. Categorical and ordinal data will be summarized using the count and percentage of non-missing, as appropriate.

The analysis will focus on markers associated with HS and SAR442970 activity, to be included in the Clinical Study Report (CSR). This analysis will include:

- Serum PD: sTNF and s OX40L measured at baseline, at week 4, at week 10, at Week 16, at Week 28 (EOT) and at week 36 (EOS).
- Serum: Lipocalin-2, CRP, hsCRP, SAA, ASCA, ACPA and YKL40 measured at baseline, at week 4, at week 12, at Week 16 and at Week 28 (EOT).
- Blood: Absolute neutrophil count, ESR measured at baseline, at week 4, at week 12, at Week 16 and at Week 28 (EOT).
- Plasma: IL-6 (Olink48) and CXCL13 measured at baseline, at week 4, at week 12, at Week 16 and at Week 28 (EOT).

Exploratory analyses, which will be detailed separately from the CSR, including but not limited t

[redacted]

- [redacted]

2.8.3.1 Biomarkers-specific analyses

2.8.3.1.1 Blood biomarkers

Analysis of blood biomarkers will be performed for markers associated with HS and/or SAR442970 activity, including:

- sTNF (soluble Tumor Necrosis Factor)
- sOX40L (soluble OX40 Ligand)
- Lipocalin-2
- CRP (C-Reactive Protein)
- hsCRP (High-Sensitivity C-Reactive Protein)
- SAA (Serum Amyloid A)
- ASCA (Anti-Saccharomyces cerevisiae antibodies)
- ACPA (Anti-Citrullinated Protein Antibodies)
- Absolute neutrophil count
- ESR (Erythrocyte Sedimentation Rate)
- IL-6 (Interleukin-6)
- CXCL13 (C-X-C Motif Chemokine Ligand 13)
- YKL40

For all the blood biomarkers,

- descriptive statistics at baseline and under treatment (table),
- boxplots and/or time profile plots (means ± SEM)

will be reported by the study intervention group at each visit in both Periods A and B. Both the raw analysis values, change and percent change from baseline will be reported. Data will be log-transformed as appropriate.

Additionally, for period B, fold change, percent change, and absolute change from Week 16 to Week 28 will be calculated for all biomarkers mentioned above. These analyses will compare participants from period A and B. Also, for sTNF and sOX40L, fold change, percent change, and absolute change from Week 16 to Week 36 will also be presented for both groups of participants.

2.8.3.1.2 Skin biopsy analyses

Optional punch biopsy of lesional and non-lesional skin will be performed for analysis by Immunohistochemistry (IHC). IHC is laboratory techniques used to detect specific proteins in tissue samples. This technique involves the use of antibodies that bind to target proteins, allowing

their visualization under a microscope. IHC is used to detect OX40 and OX40L proteins levels in participants under SAR442970 intervention.

Descriptive statistics for the change from baseline through Week 16 will be performed in histological features of lesional skin by Immunohistochemistry (IHC) for participants who consent to participate in this optional assessment. If we have fewer than 10 patients, a listing will be done instead.

Categorical data to be reported:

- H&E inflammation score (0-5)

Numerical data to be reported include but not limited to:

- H&E neutrophil infiltration %
- OX40 and OX40L – Adnexa (dermis) cellular density (cells/mm^2)
- OX40 and OX40L – Epidermis % of positive inflammatory cells
- OX40 and OX40L – Adnexa in epidermis % of positive cells
- OX40 and OX40L – Dermis + Adnexa cellular density (cells/ mm^2)

For categorical data:

- the number and frequency of each category will be tabulated by study intervention group and time point,
- a shift table of the number and percent of patients in each category at baseline vs. post-baseline

will be reported.

For numerical (percent and density) data:

- descriptive statistics at baseline and under treatment (table) of raw values, Change from baseline and Percent Change from baseline,
- boxplots

will be reported by study intervention group and visit.

2.8.3.1.3 Olink T48

Olink T48 cytokines data panel will be provided as pg/ml values. Cytokines of interest will be analyzed as described for blood biomarkers.

2.8.3.1.4 [redacted]

[redacted]

2.8.3.2 Pharmacodynamic assessment

The following analyses will be performed on the biological-naïve participant of the biomarker PD population of Period A.

A mixed-effect model with repeated measures (MMRM) will be used to assess overall treatment effect on biomarker fold change from baseline (IL-6, sTNF, sOX4OL, CXCL13, YKL40, Absolute neutrophil count, CRP, hs-CRP, SAA, ASCA, ACPA, ESR and Lipocalin-2). A log2 transformation will be applied. All post-baseline data until Week 16/EOT will be considered. The model will include the fixed categorical effects of study intervention group (SAR442970 vs placebo), visit and intervention-by-visit interaction, as well as the continuous fixed covariate of baseline biomarker value and will consider a participant-level random effect.

log2(1+ Fold Change) ~ baseline value + time + treatment + time*treatment + (1 | subjectID)

The Restricted Maximum Likelihood (REML) method will be used to estimate the variance of the parameters of the MMRM.

The point estimate of the biomarker change at a given time point, with the corresponding 90% confidence intervals will be reported as percent change from baseline.

$$Percent\ change\ from\ baseline\ =\ 100(FC-1)$$

Where the baseline value will be the median biomarker value at baseline across all patients, and time and treatment will be fixed for each treatment group.

The estimated percent change from baseline for all visits and treatment groups will be reported in a table.

Additionally a boxplot of the percent change from baseline of biomarker level at Week 16 vs. HiSCR50 response at Week 16 by study intervention group will be provided in the biomarker PD population of Period A.

2.8.3.3 Correlation between biomarkers and primary efficacy endpoint

This analysis aims to evaluate the predictive performance of biomarkers for the primary efficacy endpoint: HiSCR50 at Week 16.

For numerical biomarkers of interest, a boxplot of the biomarker level at baseline by HiSC50 response at Week 16 in the predictive population of Period A

The baseline biomarker data might be included in a binary logistic regression model with responders/non responders as endpoint (response defined by the HiSCR50 criteria), defined across different treatment intervention groups. For this analysis, the resulting odds ratio and the corresponding 90% confidence interval will be reported.

Outputs not included into the CSR might also include a heatmap visualization of all biomarkers except transcriptomic data reported on a separate heatmap. For a multivariate predictive analysis, all baseline biomarkers will be included into a multivariate logistic model with elastic net penalization. A 10-fold cross-validation will be conducted; ROC curve; AUC and selected predictive biomarker set will be reported.

2.8.4 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). Descriptive statistics will be provided.

- Age (<30, >=30 years)
- Gender (Male, Female)
- Baseline Hurley Stage (Hurley Stage II, Hurley Stage III)
- BMI (<25, 25 to 30, ≥30 Kg/m^2)
- Smoking status (Current smoker, Former smoker, Never smoker)
- Disease duration (<10, ≥10 years)

2.9 INTERIM ANALYSES

No interim analysis is planned.

2.10 CHANGES TO PROTOCOL-PLANNED ANALYSES

This section summarizes major statistical changes to protocol-planned analysis.

Table 9 - Major statistical changes to protocol-planned analyses

Section # and Name	Description of Change	Rationale
Section 1.2 Objectives and endpoints	Exploratory endpoint changed from "Percentage of participants who experience 5-point reduction in DLQI at Weeks 16 and 28 among participants with Baseline DLQI ≥4" to "Percentage of participants who experience 4-point reduction in DLQI at Weeks 16 and 28 among participants with Baseline DLQI ≥4"	ACT16852 Protocol section 8.2.2.3 on the DLQI claims that "A 4-point change in the DLQI score (DLQI response) has been reported to be meaningful for the participant.

3 SAMPLE SIZE DETERMINATION

Data from historical studies which have similar target population and study design will be used as prior information supplementing the placebo arm, using a Bayesian approach. A prior distribution of the percentage of participants that achieved HiSCR50 at Week 16 of the placebo arm was determined based on the data observed in the historical studies (1).

For the biologic and small molecule immunosuppressive-naïve population, an informative prior distribution for the placebo group HiSCR50 rate has been chosen as a beta distribution with parameter ([redacted]). This prior distribution contributes an approximate effective sample size of [redacted] participants for the placebo treatment group. Sample size calculations were performed to ensure reasonable accuracy for the estimation of the response rate. [redacted]

Table 10 - Accuracy of the 80% credible interval in the Biologic and small molecule immunosuppressive-naïve population

SAR442970 incidence rate (n)	Placebo rate (n)	Lower limit	Upper limit	Half-width
[redacted]				

A sample size of [redacted] participants randomized in a 2:1 ratio to SAR442970 versus placebo will provide a half-width for the 80% credible interval of less than [redacted] which is deemed sufficient.

Table 11 - Accuracy of the 80% credible interval in the TNF-experienced population

SAR442970 incidence rate (n)	Placebo rate (n)	Lower limit	Upper limit	Half-width
[redacted]				

For TNF-experienced population, an informative prior distribution for the placebo group HiSCR50 rate has been chosen as a beta distribution with parameter ([redacted]). This prior distribution contributes an approximate effective sample size of 2 participants for the placebo treatment group. Sample size calculations were performed to ensure reasonable accuracy for the estimation of the response rate. [redacted]

A sample size of 18 participants randomized in a [redacted] ratio to SAR442970 versus placebo will provide a half-width for the 80% credible interval of less than [redacted] which is deemed sufficient.

4 SUPPORTING DOCUMENTATION

4.1 APPENDIX 1 LIST OF ABBREVIATIONS

ACPA: Anti-Citrullinated Protein Antibodies

ADA: Anti-drug antibody, Anti-drug antibodies

AE: adverse event

AESIs: Adverse event of special interest

ALT: Alanine aminotransferase

ANCOVA: analysis of covariance

ASCA: Anti-Saccharomyces Cerevisiae Antibodies

AST: Aspartate aminotransferase

CMH: Cochran-Mantel-Haenszel

CRP: C-Reactive protein

CXCL13: C-X-C Motif Chemokine Ligand 13

DLQI: Dermatology Life Quality index

ECG: electrocardiogram

EOS: End of study, End of study

EOT: End of treatment

ESR: Erythrocyte Sedimentation Rate

HiSCR: Hidradenitis Suppurativa Clinical Response

HiSQOL: Hidradenitis Suppurativa Quality Of Life

HS: Hidradenitis suppurativa

hsCRP: High-Sensitivity C-Reactive Protein

IEs: Intercurrent events

IHS4: International Hidradenitis Suppurativa Severity Score

IL-6:	Interleukin-6
IMP:	investigational medicinal product
ITT:	Intent-to-treat
LLOQ:	Lower limit of quantification
MedDRA:	Medical Dictionary for Regulatory Activities
MedDRA:	medical dictionary for regulatory activities
MMRM:	Mixed effect model with repeated measures
NRS:	Numeric rating scale
OX40L:	Soluble OX40 Ligand
PCSA:	Potentially clinically significant abnormality
PCSA:	potentially clinically significant abnormality
PK:	Pharmacokinetics
PT:	preferred term
REML:	Restricted Maximum Likelihood
SAA:	Serum Amyloid A
SAEs:	Serious adverse events
SD:	standard deviation
SOC:	system organ class
TE:	treatment-emergent, treatment-emergent
TEAE:	treatment-emergent adverse event
TEAEs:	Treatment-emergent adverse events
[redacted]	
WHO-DD:	World Health Organization-drug dictionary
WOCF:	Worst observation carried forward

4.2 APPENDIX 2 PARTICIPANT DISPOSITIONS

The number (%) of participants included in each of the analysis populations listed in Table 4 will be provided.

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.

Period A:

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

- Randomized participants
- Randomized but not exposed participants
- Randomized and exposed participants
- Participants who completed Treatment Period A as per protocol
- Participants who did not complete the Treatment Period A as per protocol and main reason for permanent intervention discontinuation

Period B:

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

- Enrolled participants
- Enrolled but not exposed participants
- Enrolled and exposed participants
- Participants who completed Treatment Period B as per protocol
- Participants who did not complete Treatment Period B as per protocol and main reason for permanent intervention discontinuation
- Vital status at last study contact

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

In addition, the number (%) of participants screened, screened-failed, randomized, with permanent intervention discontinuation in Period A, with permanent study intervention discontinuation in Period B, and with early study discontinuation will be provided by country and site.

Protocol deviations

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

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

Demographics and baseline characteristics, medical and surgical history

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

Demographics and baseline characteristics:

Provided for safety population, and other analyses populations if deemed necessary,

- Age in years as quantitative variable and in categories (<18, ≥18 - <40, ≥40 - <60, ≥60 - ≤70)
- Gender (Male, Female)
- Race (White, Black or African American, Asian, Native Hawaiian or Other Pacific Islander, American Indian or Alaska Native, Multiple, Unknown, Not Reported)
- Ethnicity (Hispanic or Latino, not Hispanic or Latino, Unknown, Not Reported)
- Region (**Western Countries:** Australia, Belgium, Canada, Denmark, France, Germany, Greece, Italy, Netherlands, Spain, Sweden, USA; **Eastern Europe:** Poland, Czech Republic; **Latin America:** Chile)
- Body weight as quantitative variable (kg) and in categories (< 90; ≥ 90 kg)
- Body mass index (BMI) as quantitative variable (kg/m2) and in categories (<25; ≥ 25- <30; ≥ 30- < 35; ≥ 35 kg/m2)
- Smoking habit (Never; Former; Current)

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

Disease characteristics at baseline

Provided for efficacy population,

- Time since diagnosis of the disease (years)
- Age at diagnosis of disease as quantitative variable (years) and in categories (< 18, ≥ 18 - < 40, ≥ 40 - < 60, ≥ 60 - ≤ 70 years)

- HS treatment history (biologic and small molecule immunosuppressive-naïve, TNF-experienced)
- Baseline lesion counts (by lesion type)
- Baseline Hurley stage (II, III)
- Baseline C-reactive protein
- Concomitant antibiotic therapy (yes, no)

Medical and surgical history

Medical and surgical history includes Alcohol, Nicotine, Substance usage, significant medical or surgical events (including tonsillectomy and history of hypertension and/or diabetes). Medical and surgical history will be coded to a LLT, PT, HLT, HLGT and associated primary SOC using the MedDRA version currently in effect at Sanofi at the time of database lock. All medical and surgical history will be summarized by primary SOC and PT using a frequency table (number and % of participants) by study intervention group.

Prior or concomitant medications

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

- Prior medications are those the participant received prior to first double-blinded 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 during the TE period.
- 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 medications and concomitant medication will be summarized for the randomized population. Participants will be counted once in each ATC category (anatomic or therapeutic) linked to the medications Concomitant medication will be presented for Period A and Period B separately.

Medications will be summarized by intervention group according to the WHO-DD dictionary, considering the first digit of the anatomic category (ATC) class (anatomic category) and the first 3 digits of the ATC class (therapeutic category). All ATC codes corresponding to a medication will be summarized, and participants will be counted once in each ATC category (anatomic or therapeutic) linked to the medication. Therefore, participants may be counted several times for the same medication.

The tables for prior medications will be sorted by decreasing frequency of ATC followed by all other therapeutic classes based on the overall incidence across intervention groups. In case of equal frequency regarding ATCs (anatomic or therapeutic categories), alphabetical order will be used.

The tables for concomitant medications will be sorted by decreasing frequency of ATC followed by all other therapeutic classes based on the incidence in the SAR442970 group in Period A or on the incidence in the overall group in Period B. In case of equal frequency regarding ATCs (anatomic or therapeutic categories), alphabetical order will be used.

4.4 APPENDIX 4 DATA HANDLING CONVENTIONS

Demographic formulas

- Age at onset of HS (years):
  - Year of first diagnosis of HS- Year of birth
- Time since first diagnosis of HS (years):
  - (Year of randomization - Year of first diagnosis of HS) + (Month of randomization - Month of first diagnosis of HS)/12 if at least year and month are available

    or
  - (Year of randomization - Year of first diagnosis of HS) if only year is available

Unscheduled visits

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

Biomarkers

- The baseline biomarker parameter is defined as the last non-missing value prior to the first IMP dose of IMP unless otherwise specified.
- Imputation of censored values: If any value below the lower limit of quantitation (LLOQ) is found, the values <LLOQ will be reported in tables and the associated values will be imputed by LLOQ/2 for data plotting and computation of summary statistics. If any value above the upper limit of quantitation (ULOQ) is found, the number of values >ULOQ will be reported in tables and the associated values will be imputed by the ULOQ for data plotting and computation of summary statistics. If the unit is %, the values >ULOQ will be imputed by (100+ULOQ)/2, instead of ULOQ. Whenever possible, the value of the LLOQ and ULOQ should be displayed in plots of absolute values, whereas it is not possible when plotting percent changes from baseline. If the value of any summary statistics will be itself <LLOQ (>ULOQ, respectively), it will not be reported as such but shown as ‘BLOQ’ (‘ALOQ’, respectively).

- Change and Percent change: For biomarkers, the change and the percent change from baseline are reported in addition to the analysis values. The percent change from baseline is defined as $100 \times \frac{X-B}{B}$, with X the analysis value at a given timepoint and B the baseline analysis value for the same participant. The change from baseline is defined as $X - B$.

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, safety, PK and ADA variables.

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

After applying these time windows, if multiple assessments are associated to the same time point, the closest from the targeted study day will be used. If the difference is a tie, the value after the targeted study day will be used. If multiple valid values exist within a same day, then the first value of the day will be selected. For procedures planned on Visit 2, if it is done on the same date as the first IMP injection but the performance time is missing, it will belong to the Visit 2 window.

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

Table 12 - Analysis window definition for safety analysis

Analysis visits	Targeted study day[a]	Time window				
		Vital signs	Fasting lipid panel	Non-fasting laboratory tests	Urinalysis	12-lead ECG
Period A						
Screening	-28 to -14	<-14	<-14	<-14	<-14	<-14
Baseline	1	-14 - 1	-14 - 1	-14 - 1	-14 - 1	-14 - 1
Week 2	15	2 - 21	2 - 21	2 - 21	2 - 21	2 - 21
Week 4	29	22 - 35	22 - 35	22 - 35	22 - 35	22 - 35
Week 6	43	36 - 49	36 - 49	36 - 49	36 - 49	36 - 49
Week 8	57	50 - 63	50 - 63	50 - 63	50 - 63	50 - 63
Week 10	71	64 - 77	64 - 77	64 - 77	64 - 77	64 - 77
Week 12	85	78 - 91	78 - 91	78 - 91	78 - 91	78 - 91
Week 14	99	92 - 105	92 - 105	92 - 105	92 - 105	92 - 105
Week 16	113	106 - D[b]	106 - D[b]	106 - D[b]	106 - D[b]	106 - D[b]
Period B						
Week 18	15	2 - 21	2 - 21	2 - 21	2 - 21	2 - 21
Week 20	29	22 - 35	22 - 35	22 - 35	22 - 35	22 - 35
Week 22	43	36 - 49	36 - 49	36 - 49	36 - 49	36 - 49
Week 24	57	50 - 63	50 - 63	50 - 63	50 - 63	50 - 63
Week 26	71	64 - 77	64 - 77	64 - 77	64 - 77	64 - 77
Week 28	85	78 - 112	78 - 112	78 - 112	78 - 112	78 - 112
Week 36	141	>112	>112	>112	>112	>112

a Day 1 in Period A is the day of the first blinded IMP administration (or the day of randomization for participant not exposed). Day 1 in Period B is the day of the first open-label IMP administration.

b Last window in Period A is the 1st dose of open-label IMP administration.

Table 13 - Analysis window definition for efficacy endpoints

Analysis visit	Targeted study day[a]	Time windows		
		HS clinical parameters	Dermatology Life Quality Index	Hidradenitis Suppurativa Quality of Life
Period A				
Screening	-28 to -14	<-14	<-14	<-14
Baseline	1	-14 - 1	-14 - 1	-14 - 1
Week 2	15	2 - 21	2 - 21	2 - 21
Week 4	29	22 - 42	22 - 42	22 - 42
Week 6	43			
Week 8	57	43 - 70	43 - 70	43 - 70
Week 10	71			
Week 12	85	71 - 98	71 - 98	71 - 98
Week 14	99			
Week 16	113	99 - D[b]	99 - D[b]	99 - D[b]
Period B				
Week 18	15			
Week 20	29	2 - 42	2 - 42	2 - 42
Week 22	43			
Week 24	57	43 - 70	43 - 70	43 - 70
Week 26	71			
Week 28	85	>70	>70	>70

a Day 1 in Period A is the day of the first blinded IMP administration (or the day of randomization for participant not exposed). Day 1 in Period B is the day of the first open-label IMP administration.

b Last window in Period A is the 1st dose of open-label IMP administration.

Table 14 - Analysis window definition for daily questionnaires

Analysis visit	Targeted study day[a]	Time windows		
		Daily Diary HS-Skin Pain NRS	Daily Diary PP-NRS	Daily diary analgesic use
Period A				
Screening	-28 to -7	<-7	<-7	<-7
Baseline	1	-7 - <1	-7- <1	-7- <1
Week 2	15	8 - 14	8 - 14	8 - 14
Week 4	29	22 - 28	22 - 28	22 - 28
Week 6	43	36 - 42	36 - 42	36 - 42
Week 8	57	50 - 56	50 - 56	50 - 56
Week 10	71	64 - 70	64 - 70	64 - 70
Week 12	85	78 - 84	78 - 84	78 - 84
Week 14	99	92 - 98	92 - 98	92 - 98
Week 16	113	106 - D[b]	106 - D[b]	106 - D[b]
Period B				
Week 18	15	8 - 14	8 - 14	8 - 14
Week 20	29	22 - 28	22 - 28	22 - 28
Week 22	43	36 - 42	36 - 42	36 - 42
Week 24	57	50 - 56	50 - 56	50 - 56
Week 26	71	64 - 70	64 - 70	64 - 70
Week 28	85	78 - 84	78 -84	78 - 84

a Day 1 in Period A is the day of the first blinded IMP administration (or the day of randomization for participant not exposed). Day 1 in Period B is the day of the first open-label IMP administration.

b D = minimum (Day 112, the day prior to the first open-label IMP)

Table 15 - Analysis windows for pharmacokinetics/pharmacodynamics variables

Analysis visit	Targeted study day[a]	Time windows				
		ADA	Blood biomarkers	PK	PD Biomarker	Skin Biopsy
Period A						
Screening	-28 to -14	<-14	<-14		<-14	
Baseline	1	-14 - 1	-14 - 1	≤1	-14 - 1	≤1
Week 2	15	2 - 21	2 - 21		2 - 21	
Week 4	29	22 - 42	22 - 42	2 - 49	22 - 42	
Week 6	43					
Week 8	57	43 - 70	43 - 70	50 - 63	43 - 70	
Week 10	71			64 - 77		
Week 12	85	71 - 98	71 - 98	78 - 98	71 - 98	
Week 14	99					
Week 16	113	99 - D[b]	99 - D[b]	99 - D[b]	99 - D[b]	> 1
Period B						
Week 18	15			2 - 21		
Week 20	29	2 - 42	2 - 42	22 - 70	2 - 42	
Week 22	43					
Week 24	57	43 - 70	43 - 70		43 - 70	
Week 26	71					
Week 28	85	71 - 112	> 70	71 - 112	71 - 112	
Week 36	141	> 112		> 112	> 112	

a Day 1 in Period A is the day of the first blinded IMP administration (or the day of randomization for participant not exposed). Day 1 in Period B is the day of the first open-label IMP administration.

b Last window in Period A is the 1st dose of open-label IMP administration.

5 REFERENCES

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