AMENDED CLINICAL TRIAL PROTOCOL 02

Protocol title:	**A randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of dupilumab in patients with uncontrolled, chronic rhinosinusitis without nasal polyposis (CRSsNP)**
Protocol number:	**EFC16723**
Amendment number	**02**
Compound number (INN/Trademark):	**SAR231893** **Dupilumab/Dupixent®**
Study phase:	**Phase 2**
Short title:	**Dupilumab in CRSsNP** **Acronym: Liberty CRSsNP ORION**
Sponsor name: **Legal registered address:**	**Sanofi-Aventis Recherche & Développement** **1 avenue Pierre Brossolette** **91380 Chilly-Mazarin, France**
Monitoring Team's Representative Name and Contact Information	

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PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY

Document	Country/ countries impacted by amendment	Date, version
Amended Clinical Trial Protocol 02	All	23 February 2023, version 1 (electronic 2.0)
Amended Clinical Trial Protocol 01	All	08 July 2021, version 1 (electronic 1.0)
Original Protocol		14 September 2020, version 1 (electronic 1.0)

Amended protocol 02 (23 February 2023)

This amended protocol 02 (amendment 02) is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

OVERALL RATIONALE FOR THE AMENDMENT

Due to difficulties in recruitment, the Sponsor is amending the Phase 2/3 (Part A and B) EFC16723 efficacy and safety study to be just a Part A Phase 2 study. The purpose of this protocol amendment is to remove Part B and for Part A to modify the number of participants to be enrolled, shorten treatment period, modify endpoints, and modify overall study phase. In addition, the primary analysis population is being updated to the elevated baseline eosinophils population, and consequently the sample size is updated so that we will have approximately 30 participants with elevated eosinophils ($\geq$300 cells/mm^3), which coupled to the existing low eosinophils population will bring the total sample size to 70. Other changes include the modification of treatment period and primary and secondary endpoints. The following table outlines the changes made to the protocol and the affected sections:

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Throughout	Deleted mentions of and relevant text for Part B of the study, including objectives and endpoints for Part B.	The original study design was Phase 2/3 with Part A (proof-of-concept Phase 2) and Part B (Phase 3) changed to a Phase 2 study with removal of Part B.
	Deleted nomenclature for Part A and Part B.	Clarification for removal of Part B.
	Deleted mentions of and relevant text for adolescents, parents, LAR, 200 mg dose, Week 48, and Week 52 at applicable instances.	As consequence of Part B removal, no adolescent participant will be enrolled.

Section # and Name	Description of Change	Brief Rationale
	The Part A treatment period has been changed from 52 weeks to at least 24 and no more than 52 weeks.	To align with the primary analysis timepoint at week 24 and to shorten the time to study completion while allowing for collection of endpoint data to evaluate efficacy in participants with CRSsNP.
	Updated sample size from: 140 participants (approximately 70 per arm) with approximately 100 participants with blood eosinophils >= 300 (approximately 50 per arm) To: 70 participants (approximately 35 per arm) with 30 participants with blood eosinophils>= 300 (approximately 15 per arm)	Due to enrollment difficulties, the Sponsor proposes a single part Phase 2 study with reduced sample size.
	Deleted the phrase "2-part" from the study title.	Due to protocol change, the Part B Phase 3 study will no longer be conducted. Part A is modified and remains a Phase 2 study.
	Updated study Phase from 2/3 to 2	
	Minor editorial and typographical changes wherever applicable	Formatting and typographical
	Updated patient to participant wherever applicable	Formatting and typographical
1.1 Synopsis	Deleted note with below text: *The primary analysis of Part A at Week 24 (details in Section 9.6) will be conducted both to provide initial evidence of efficacy of dupilumab in adult participants with severe or uncontrolled CRSsNP and inform the initiation and design of Part B.* Added new note with below text: *Modification of the treatment period will result in all patients who complete the treatment period being treated for a minimum of 24 weeks and a maximum of 52 weeks, or until the last patient randomized completes a minimum treatment period of 24 weeks.*	Since the purpose of the study has now changed from Phase 2/3 to a Phase 2 and there is no longer need to assess efficacy beyond 24 weeks, the 52-week treatment period for all participants in Part A is now variable between 24 weeks and 52 weeks. A minimum of 24-week treatment period for all participants allows for reliable assessment of the LMK endpoint in participants with CRSsNP.
1.1 Synopsis 3 Objectives and Endpoints	Updated the primary objective and endpoint from: Primary Objective To evaluate the efficacy of dupilumab as assessed by the reduction at Week 24 in sinus opacification on computerized tomography (CT) scan and sinus total symptom score (sTSS) compared to placebo To: To evaluate the efficacy of dupilumab as assessed by the reduction at Week 24 in sinus opacification on computerized tomography (CT) scan in the dupilumab group only	Because the reduction in sample size does not support reasonable power for the symptoms score sTSS and for placebo comparison.

Section # and Name	Description of Change	Brief Rationale
	Moved co-primary endpoint (sTSS) to secondary endpoint making LMK score a single primary endpoint with evaluation only in the dupilumab group: • Change from baseline to Week 24 in opacification of sinuses assessed by CT scan using the Lund Mackay (LMK) score To: • Change from baseline to Week 24 in opacification of sinuses assessed by CT scan using the Lund Mackay (LMK) score in the dupilumab group	To align with the new primary objective.
	Moved the following co-primary endpoint to a secondary endpoint: • Change from baseline to Week 24 in the sTSS*	
	For all the secondary objective and endpoints, deleted the Week 52 objective/endpoints and requalified to exploratory, except the following endpoints listed below. In addition, in the asthma subgroup objective and endpoints removed comparison to placebo, and for endpoints evaluating the ≥300 cells/mm^3 population changed to ITT. • Change from baseline to Week 24 in opacification of sinuses assessed by CT scan using LMK score • Change from baseline to Week 24 in sTSS	Given that 15 participants per arm (primary analysis population is patients with blood eosinophil count ≥300 cells/mm^3) does not support reasonable power, most endpoints moved to exploratory. Removed all 52-week endpoints as treatment duration shortened to 24 weeks. Certain endpoints modified to align with primary analysis population modification. Since the asthma subgroup will be a small subset of the primary analysis population, FEV1 and ACQ-6 will be evaluated in the dupilumab arm only.
	Deleted the following endpoints: Endpoints in the asthma subgroup evaluating LMK and sTSS. Endpoint in other secondary endpoints in the screening blood eosinophil count ≥300 cells/mm^3 subgroup Endpoints evaluating rescue therapy for worsening disease.	Endpoints removed to reflect changes in primary analysis population, reduced sample size, and shortened treatment duration.
	Added new exploratory objective and corresponding endpoint for three-Dimensional CT volumetric assessments	Additional data analysis relevant for evaluation of efficacy.
1.3 Schedule of Activities (SoA)	Added a note with below text for treatment duration: The treatment period will be variable between 24 to 52 weeks, V6 and V7 are optional for participants.	This allows flexibility for participants on study completion due to variable treatment period between 24 weeks and 52 weeks.

Section # and Name	Description of Change	Brief Rationale
	Added following text in footnote 'h' applicable to Study intervention and Efficacy Assessments: Questionnaires in paper form are not permitted; only electronic form is allowed.	The study employs exclusively eCROs and ePROs; the statement reflects the Sponsor's prohibition on use of questionnaire in paper copy.
	Added following text in footnote 'h' applicable to Study intervention and Efficacy Assessments: Physician assessment UPSIT may not be available at some sites for visits; in this case the investigator may omit the test for that visit.	To add flexibility in the UPSIT test performance.
3.1 Appropriateness of Measurements	Deleted text to reflect that sTSS is not a primary endpoint now and added "in the dupilumab group" for LMK primary endpoint. Added text to reflect that LMK and sTSS when comparing dupilumab to placebo are secondary endpoints.	Text adaptation to endpoint hierarchy change.
4.2 Scientific Rationale for Study Design	Updated the following text from: … participants regardless of screening blood eosinophil counts will be included. While the primary analysis population will be the ITT population, the treatment effect of dupilumab will also be evaluated on the screening blood eosinophil count of ≥300 cells/mm^3 population. To: … a subset of patients with blood eosinophil counts of <300 cells/mm^3 will be randomized while the primary analysis population will remain as patients who have peripheral blood eosinophil counts ≥300 cells/mm^3.	The primary analysis population will be participants with blood eosinophil count ≥300 cells/mm^3 as this is the population predicted to have most benefit with dupilumab.
4.4 End of Study Definition	Updated study completion definition for participants following original protocol, amended protocol 1 and 2	As consequence of treatment period shortening from 52 to 24 weeks.
5.4 Screen Failures	Added the below sentence: All other screening procedures must be repeated for rescreening.	To clarify to participating clinical sites that in case of rescreening all procedures need to be repeated, except CT scan if within the defined window period.
6.1 Study Intervention(s) Administered	Addition of the following sentence: 'During study visits, the IMP is administered on sites after all procedures.	In order to further clarify that IMP will be administered at sites at the time of Visits.
6.5.3 Rescue medicine	Changed from Short course OCS (prednisone or equivalent prednisolone up to 7 days; avoid use 4 weeks before Week 24 or Week 52, where applicable). To Short course OCS (prednisone or equivalent prednisolone up to 14 days; avoid use 4 weeks before Week 24 or Week 52, where applicable).	To clarify an inconsistency between Prohibited medications and Rescue medications, the short course of OCS is up to 14 days.

Section # and Name	Description of Change	Brief Rationale
8.6 Pharmacodynamics	Removed measurement of secreted P-glycoprotein.	Test is unable to be performed by the Sponsor due to assay limitations.
9.2 Sample size determination 9.3 Populations for analyses	Sample size determination updated. Primary population changed from ITT population to ITT population with screening blood eosinophil count ≥ 300 cells/mm^3.	To reflect changes in the study primary objective and endpoint.
9.1 Statistical hypotheses 9.4.1 General considerations 9.4.2 Primary endpoint(s)	Statistical hypotheses removed. Multiplicity consideration removed. Multiple imputation removed. Model-based analyses removed. Sensitivity and subgroup analyses removed. Use of descriptive statistics for all endpoints.	To apply more appropriate analysis methods based on the reduced sample size.
9.4.2 Primary endpoint(s)	The intercurrent events handling strategy for taking SCS for any reason prior to Week 24 was changed from 'all data collected after SCS use will be used in the analysis' to 'data after the IE will be set to missing and the worst post-baseline value on or before the time of the IE will be used to impute missing Week 24 value (WOCF)'.	To change handling of taking SCS for any reason in the primary estimand to an approach more appropriate for this clinical setting.
9.4.3 Secondary endpoint(s)	Description of secondary analyses for proportion and time-to-event endpoints removed.	To reflect changes in the secondary objectives and endpoints.
9.6 Timing of statistical analyses	Updated the timing of analyses to only one database lock after all participants have completed the study.	To reflect the removal of Part B and shortened treatment duration of Part A.
10.8 Appendix 8: Clinician-Reported Outcomes and Patient-Reported Outcomes	Added new appendices with samples for following questionnaires: 10.8.6 Morning Diary, 10.8.7 Healthcare Resource Utilization (HCRU) questionnaire	Addition of screenshots of patient reported outcome tools to allow clarification to sites.

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1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Protocol title: A randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of dupilumab in patients with uncontrolled, chronic rhinosinusitis without nasal polyposis (CRSsNP)

Short title: Dupilumab in CRSsNP
Liberty CRSsNP ORION

Rationale:

Chronic rhinosinusitis (CRS) is an inflammatory disease of the nasal cavity and paranasal sinuses characterized by 2 or more symptoms (lasting for ≥12 weeks), one of which is nasal obstruction or nasal discharge (anterior and/or posterior), and may also include facial pressure/pain and/or reduced sense of smell. It is estimated to affect approximately 10% of the population in the United States (US) and Europe (1, 2). Chronic rhinosinusitis phenotypically is broadly divided into 2 types based on the presence or absence of nasal polyps: CRS with nasal polyposis (CRSwNP) and CRS without nasal polyposis (CRSsNP) (3). Chronic rhinosinusitis without nasal polyposis is the most common type of CRS, accounting for approximately two-thirds of the overall CRS population (3, 4).

While the underlying etiopathogenesis of CRSsNP is likely multifactorial, there is a subset of CRSsNP patients, representing nearly one-third of the overall CRSsNP population, where the disease process appears to be predominantly driven by type-2 inflammation. In this subset of type-2 CRSsNP patients, transcriptomic and proteomic analyses of surgical sinonasal tissues reveal elevated levels of type-2 inflammatory markers, such as interleukin (IL)-5, immunoglobulin E (IgE), eosinophilic cationic protein (ECP), Charcot-Leyden crystal galectin (CLC), etc (5, 6, 7). The type-2-associated molecular signature identified in these type-2 CRSsNP patients suggests that the underlying pathophysiological disease process is similar to that found in CRSwNP patients where it is well known that type-2 inflammation with prominent eosinophilia and elevated levels of type-2 cytokines, such as IL-4, IL-5, and IL-13, plays a key role in the disease process (5, 6, 7, 8, 9, 10). Consistent with the implication of type-2 inflammation underlying the disease process in these CRS patients, asthma is a common comorbid condition for both CRSsNP and CRSwNP patients, 20% to 40% in the former and 50% to 60% in the latter (4, 11) and about 52% of CRSsNP patients have comorbid allergic rhinitis (4). Clinical features more commonly reported in CRSsNP patients with type-2 endotype include loss of sense of smell/reduced taste (5). Comorbid asthma and peripheral blood eosinophilia have been associated with higher risk of need for recurrent sinonasal surgery (12, 13).

Standard medical therapies, including topical and oral corticosteroids (OCS), and antibiotics, do not provide adequate or lasting control of the symptoms in many patients with CRSsNP. In a study of CRSsNP, 45% of patients “failed” medical therapy, defined as persistent symptoms and 31% remained symptomatic enough to elect to pursue surgery (14). In the GA^{2}LEN study, 70% to 80% of patients did not have lasting benefits from the medical therapies (including OCS,

antibiotics, and intranasal corticosteroids [INCS]) (11). Also, many CRSsNP patients have reported at least one prior surgery or are planning to have surgery in the near future for better control of symptoms (11). In patients who have undergone sinonasal surgery, comorbid asthma and peripheral blood eosinophilia are risk factors for recurrence of CRS post-operatively (12, 13), suggesting that type-2 CRSsNP patients may be more at risk for disease recurrence after surgery. Consequently, because of the chronic and unremitting nature of the condition in many patients, CRS is associated with a substantial socioeconomic burden that results from the costs of diagnostic tests, medical and surgical therapies, lost and reduced school and work productivity, and a detrimental impact on physical and emotional health (15).

Dupilumab blockade of IL-4 and IL-13 signaling has demonstrated a favorable efficacy and safety profile for the treatment of a variety of atopic disease states, including atopic dermatitis (AD) (16), asthma (17), eosinophilic esophagitis (EoE) (18), and CRSwNP (19); diseases where type-2 inflammation is a key driver of the underlying disease process.

This study will evaluate the clinical efficacy and safety profile of dupilumab administered to type-2 CRSsNP patients who are inadequately controlled by or have intolerance/contraindication to INCS, systemic corticosteroids (SCS), and antibiotics or sinonasal surgery.

This study consists of:

A screening period of up to 4 weeks, followed by a randomized, double-blind, placebo-controlled, 2-arm, parallel-group, 24 to 52 -week treatment period. The primary endpoint will be assessed at Week 24. Participants who complete treatment will continue to a 12-week post-treatment follow-up period.

Note: Modification of the treatment period will result in all patients who complete the treatment period being treated for a minimum of 24 weeks and a maximum of 52 weeks, or until the last patient randomized completes a minimum treatment period of 24 weeks.

Objectives and endpoints

Objectives	Endpoints
Primary	
• To evaluate the efficacy of dupilumab as assessed by the reduction at Week 24 in sinus opacification on computerized tomography (CT) scan in the dupilumab group only	• Change from baseline to Week 24 in opacification of sinuses assessed by CT scan using the Lund-Mackay (LMK) score in the dupilumab group
Secondary	
• To evaluate the efficacy of dupilumab as assessed by the reduction at Week 24 in sinus opacification on CT scan and sinus total symptom score (sTSS) compared to placebo	• Change from baseline to Week 24 in opacification of sinuses assessed by CT scan using the LMK score • Change from baseline to Week 24 in sTSS* **Composite severity score consisting of nasal congestion, anterior/posterior rhinorrhea, facial pain/pressure items of the CRSsNP sinonasal symptom e-diary*
• To evaluate the safety and tolerability of dupilumab in CRSsNP patients compared to placebo	• Incidence of treatment-emergent adverse events (TEAEs), of treatment-emergent serious AEs (TESAEs), and TEAEs leading to treatment discontinuation, abnormal laboratory values, and vital signs
• To evaluate the pharmacokinetics (PK) of dupilumab in CRSsNP patients compared to placebo	• Dupilumab concentration in serum
• Assessment of immunogenicity to dupilumab over time compared to placebo	• Assessment of immunogenicity to dupilumab as determined by the incidence, titer, and neutralizing antibody (NAb) status of treatment-emergent anti-drug antibody (ADA) response over time compared to placebo

Overall design:

This is a Phase 2 multicenter-study to evaluate the efficacy and safety of dupilumab compared to placebo, in participants with uncontrolled CRSsNP. This is a randomized, double-blind, placebo-controlled study in adult participants regardless of screening eosinophil count to evaluate the treatment effect of dupilumab on sinus opacification as assessed by the Lund-Mackay (LMK) sinus computed tomography (CT) scan total score, and to provide data on safety.

All participants in the study (adults only) will enter a screening period (2 to 4 weeks), with a 24 to 52 -week treatment period, followed by post-treatment follow-up (12 weeks).

Approximately 70 adult participants will be randomized 1:1 (approximately 35 participants per arm) into 2 treatment groups as follows:

- Arm A: Dupilumab 300 mg every 2 weeks (q2w),
- Arm B: Matching placebo.

Randomization will be stratified by screening blood eosinophil count (≥300 cells/mm^3 or <300 cells/mm^3), background INCS use (yes or no) and region.

To ensure enrollment according to the intended distribution of screening blood eosinophil count, alerts will be built into the IRT to control the number of participants in each stratification group as follows:

- ≥300 cells/mm^3: approximately 15 participants per arm,
- <300 cells/mm^3: approximately 20 participants per arm.

In addition, in order to have an adequate number of participants with comorbid asthma, alerts will be built into the IRT to limit the number of participants without comorbid asthma to no more than 70% of the randomized population.

During the study, participants who report deterioration requiring medical/surgical intervention may come to the site for clinical evaluation. An unscheduled visit may be used for this purpose and, if necessary, the Investigator may consider one of the treatment alternatives described in Section 6.

Disclosure Statement:

This is an interventional study with 2 study treatment arms and the study treatment assignment is blinded to the Participant and Investigator.

Number of participants:

Approximately 35 participants will be enrolled to each study intervention arm for an estimated total of study enrollment of approximately 70 participants.

Note: "Enrolled" means a participant's, or their legally acceptable representative's, agreement to participate in a clinical study following completion of the informed consent process and is randomized into the study at Visit 2. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol.

Intervention groups and duration:

Study interventions

Participants who satisfy the inclusion and exclusion criteria will be randomized (1:1) to one of the following investigational medicinal product (IMP) treatment groups:

- Dupilumab 300 mg q2w
- Matching placebo

Duration of study period (per participant):

- Screening period (2 to 4 weeks)
- Randomized IMP intervention period (24 up to 52 weeks)
- Follow-up period (12 weeks)

Note: The treatment will stop for all participants when the LPI has completed 24 weeks of treatment. Therefore, all participants following Amendment 02 will be treated for at least 24 weeks and the other participants (enrolled before Amendment 02) will have variable treatment period and may continue up to 52 weeks.

Investigational medicinal products:

- Dupilumab 300 mg and placebo matching dupilumab 300 mg supplied in pre-filled syringes that are visually indistinguishable.

Dupilumab

Formulation:

- Dupilumab 300 mg: a 150 mg/mL dupilumab solution in a pre-filled syringe to deliver 300 mg in a 2 mL injection.

Route of administration: Subcutaneous (SC) injection.

Dose regimen:

- One injection of 300 mg q2w for all adult

Placebo

Formulation:

- Placebo matching dupilumab 300 mg: identical formulation to the active 300 mg formulation without dupilumab, in a pre-filled syringe to deliver placebo in a 2 mL injection.

Route of administration: SC injection

Dose regimen:

- One injection of placebo matching dupilumab 300 mg q2w

Post-trial access to study medication:

Post-trial access to study medication will not be provided.

Statistical considerations:

The primary efficacy analysis population will be the ITT population with screening blood eosinophil count ≥ 300 cells/mm^3 (see Section 9.3).

- **Primary endpoint:**

  In the primary analysis approach for the primary endpoint, for participants who undergo sinonasal surgery for CRSsNP or take SCS for any reason, data collected after surgery or initiation of SCS will be set to missing and the worst post-baseline value on or before the time of surgery or SCS will be used to impute missing Week 24 value (ie, worst observation carried forward [WOCF] approach). For participants with no post-baseline values, the baseline value will be used. Participants who discontinue the study intervention prematurely are encouraged to follow the planned clinical visits and, in these participants, who did not undergo surgery or receive SCS, all data collected after study intervention discontinuation will be used in the analysis. No missing data will be imputed. Descriptive statistics and 95% CI in the dupilumab group will be provided.

  Main secondary endpoints:

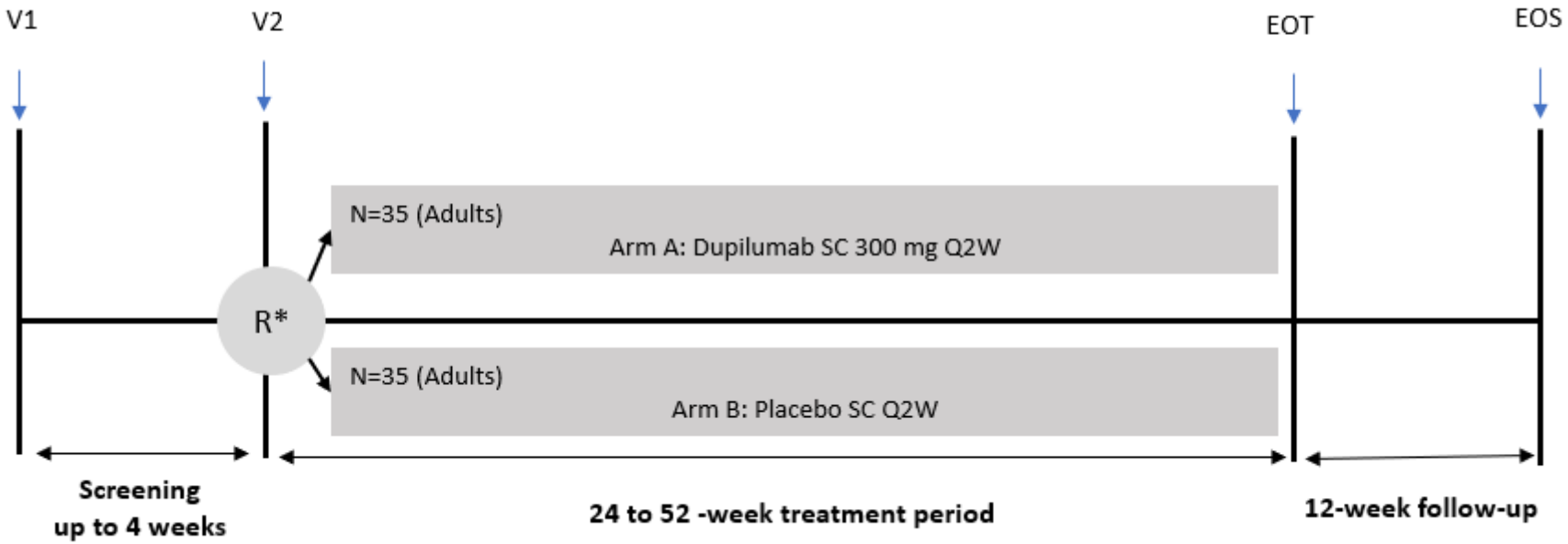
  The change from baseline to Week 24 in the secondary efficacy endpoints will be analyzed using the same analysis approach as for the primary endpoint. For endpoints comparing dupilumab to placebo, 95% CI of the treatment difference will be provided

  The safety variables, including adverse events (AEs), laboratory parameters, and vital signs, will be summarized using descriptive statistics.

Data Monitoring Committee: Due to the extensive safety record of the post-marketed IMP (dupilumab), it is not planned to have a Data Monitoring Committee for this study.

1.2 SCHEMA

Figure 1 - Graphical study design



1.3 SCHEDULE OF ACTIVITIES (SOA)

Procedure	Screening (2 to 4 weeks before Day 1) D-28	Intervention Period (Weeks)						Follow-up W36 to W64 (12 weeks)[a]	Notes
		W0	W2	W12	W24	W40	W52		
Visit	1	2[b]	3	4	5	6[a]	7 (EoT)[a c]	8 (EOS)	Visit window: +3 days for Visit 2, ±3 days for visits 3 to EOT, and ±5 days for EOS
Informed consent[d]	X								
Inclusion and exclusion criteria	X	X							Recheck clinical status before randomization
Participant demographics	X								
Full physical examination	X	X			X		X		Including skin (full body skin exam), nasal cavities, eyes, ears, respiratory, cardiovascular, gastrointestinal, neurological, lymphatic, and musculoskeletal systems
Medical/surgical history[e]	X								
Record planned endoscopic sinus surgery[f]	←----------							----------→	
Nasal endoscopy[g]	X								Central reading for excluding polyps and local reading for excluding purulent discharge
Prior/concomitant/rescue medications	X	X	X	X	X	X	X	X	Check INCS background medication at screening and throughout the study period. Record rescue therapy if applicable
Randomization		X							
Log-in to IRT	X	X	X	X	X	X	X	X	
Study intervention[h,i]									
IMP administration[j]		←----------						----------→	IMP will be administered every 14 ±3 days (q2w). Between visits at site home administration is allowed after

									appropriate training of the participant (or caregiver). The planned last dose is up to Week 50.
Efficacy assessments[h]									
CT scan[k]	X				X		X		Initial CT scan to be done during screening period, results should be available prior to randomization (Visit 2).
Dispense or download daily diary for symptoms[l]	X	X	X	X	X	X	X	X	Device will be dispensed at screening (including instructions for use). At EOS, the e-diary will be returned to the site.
CRSsNP Symptom Diary (includes nasal congestion/obstruction, facial pain/pressure, anterior and posterior rhinorrhea; sTSS derived from these 4 items, as well as loss of smell and headache)[l,m]	←---------- Daily Diary----------→								Every day (morning assessment) as of screening. Participant will continue to assess daily symptoms during follow-up (important to assess disease relapse after treatment)
Sino-Nasal Outcome Test-22 item (SNOT-22)[m]		X			X	X	X	X	
University of Pennsylvania Smell Identification Test (UPSIT)		X	X		X	X	X	X	Baseline value to be collected ahead of first dose IMP
Rhinosinusitis Severity Visual Analog Scale[m]		X	X		X	X	X	X	
EQ-5D-5L[m]		X			X	X	X		
Spirometry[n]	X	X		X	X		X	X	At Visit 1, all participants will have spirometry to confirm exclusion criteria. Afterwards spirometry will be locally collected and read in participants with asthma only.
Asthma Control Questionnaire ([ACQ-6] participants with comorbid asthma)[m]		X		X	X	X	X	X	

Health Care Resource Utilization/Productivity (HCRU/P)		X		X	X	X	X		Health Care Resource Utilization/Productivity will be captured in the eCRF
Patient global impression of severity (PGIS)[m]		X		X	X	X	X		
Patient global impression of change (PGIC)[m]				X	X	X	X		
Safety assessments[h]									
Vital signs[o]	X	X	X	X	X	X	X		Height at V1 only
12-Lead ECG	X								Locally collected and read
AE review	←----------							----------→	
SAE review[p]	←----------							----------→	
Laboratory testing									
Laboratory assessments[q]	X	X		X	X	X	X		Includes hematology, serum chemistry, liver function tests
Urinalysis (urine dipstick) [q]	X	X		X	X	X	X		For participants enrolled in China, the urine analysis will be performed at laboratory (not dipstick)
HBV, HCV, HIV, TB testing[r]	X								TB test (performed locally if required and results noted in the eCRF)
Pregnancy test (WOCBP only)[s]	X	X		X	X	X	X		Serum pregnancy test at screening and then urine pregnancy test at Visit 2 and every 4 weeks thereafter. It can be done by participant at home between on-site visits and after training
Sampling for serum drug concentration (PK)[p]		X		X	X		X		
Antidrug antibody (ADA) sampling[p]		X		X	X		X		
[redacted]		X		X	X		X		
[redacted]		X		X	X		X		Spot urine test, if applicable
[redacted]		X		X	X		X		

Nasal brushing for RNA and cytology[u]		X			X		X		
[redacted]		X			X		X		Optional
[redacted]		X							Optional
[redacted]		X			X		X		Optional for adults only

ACQ-6:Asthma Control Questionnaire 6-question version, ADA: anti-drug antibody, AE: adverse event, AESI: adverse event of special interest, CRSsNP: chronic rhinosinusitis without nasal polyposis, CT: computerized tomography, COVID-19: Coronavirus Disease 2019, D: day, DBP: diastolic blood pressure, ECG: electrocardiogram, eCRF: electronic case report form, EOS: end of study, EOT: end of treatment, EQ-5D-5L: 5-level version of the EuroQol 5 dimensions European quality of life-5D scale, FEF: forced expiratory flow, FEV_1: forced expiratory volume, FVC: forced vital capacity, HBcAb: hepatitis B core antibody, HBsAb: hepatitis B surface antibody, HBsAg: hepatitis B surface antigen, HBV: hepatitis B virus, HCRU/P: Healthcare Resource Utilization/Productivity, HCV: hepatitis C virus, HCVAb: hepatitis C virus antibodies, HIV: Human Immunodeficiency Virus, IEC: independent ethics committee, Ig: immunoglobulin, IRB: institutional review board, IMP: investigational medicinal product, IRT: interactive response technology, INCS: intranasal corticosteroids, LABA: long-acting beta-agonists; LAMA: long-acting muscarinic acetylcholine, LTE4: leukotriene 4, PGDM: prostaglandin D2 metabolite, PGIS: patient global impression of severity, PGIC: patient global impression of change, PK: pharmacokinetic, PRO: patient-reported outcome, q2w: every 2 weeks, SAE: serious adverse event, SBP: systolic blood pressure, SC: Subcutaneous, SCS: systemic corticosteroids, sTSS: sinus Total Symptom Score, SNOT-22: Sino-Nasal Outcome Test – 22 item, TB: tuberculosis, TARC: thymus-and activation-regulated chemokine, UPSIT: University of Pennsylvania smell identification test, VAS: visual analog scale, V: Visit, W: week, WOCBP: women of childbearing potential.

a The treatment period will be variable between 24 to 52 weeks; therefore, follow up may be between 36 to 64 weeks. V6 and V7 are optional for participants given variable treatment period.

b All assessments at Randomization Visit (V2) are to be conducted pre-IMP dose with the exception of the assessment of local tolerability of subcutaneous (SC) injections.

c Participants who discontinue the study treatment prematurely (prior to completing Week 24 of treatment period) will perform the end of treatment (EOT) assessments at the time of discontinuation to assure a complete clinical assessment in close temporal proximity to the premature termination of study treatment. In addition, to allow assessment of participant outcomes over the stipulated study period, participants will be asked and encouraged to complete all remaining study visits and participate in all assessments according to the visit schedule.

d Consent to be obtained for optional procedures (whole blood DNA, whole blood RNA sampling, and serum/plasma sampling for archival; human immunodeficiency virus (HIV) test if specific consent locally required).

e Past medical history including allergic comorbidities (asthma, aspirin sensitivity, allergic rhinitis etc). Surgeries will be assessed including type and dates of sinonasal surgeries in the past. Systemic corticosteroids (SCS) use (number of courses, doses, way of administration and duration) in the past 2 years before V1 and/or contraindication/intolerance to SCS, as well as long-term antibiotics use (>2 weeks) in the previous year will be entered in the electronic case report form (eCRF).

f Details on actual or planned date for surgery type and outcome (whenever possible) of surgery will be recorded in a specific eCRF page. If surgery is performed during the study treatment period or follow-up an adverse event (AE) or serious adverse event (SAE) page will be completed. Participants will be discontinued from study treatment and assessed as soon as possible using the procedures normally planned for the EOT Visit. If surgery is scheduled after the planned end of study, a follow-up contact(s) may be required to document the surgery date and outcome.

g Nasal endoscopy: Endoscopy (including use of decongestants before the procedure) will be performed at Screening Visit only for eligibility confirmation. At V2, Investigator will review V1 results from central reader to confirm entry criteria and reconfirm eligibility based on review of inclusion/exclusion criteria.

h Assessments/procedures should be conducted in the following order: Patient-Reported outcome (PRO) assessments, Investigator assessments, safety and laboratory assessments (including sample collection for ADA, PK, biomarker, and optional DNA and RNA), and administration of IMP. Questionnaires in paper form are not permitted; only electronic form is allowed. Physician assessment UPSIT may not be available at some sites for visits; in this case the investigator may omit the test for that visit.

i In case of emergency (eg, natural disaster, pandemic) remote visit could be considered (eg, homenursing, telehealth, except for baseline and Week 24) and will be documented in the participant's study file. Arrangements could also be made for qualified site personnel and/or health care professionals (eg, visiting nurse service) to collect study samples, administer IMP at participant's home or perform study examinations as needed. "Coronavirus Disease 2019" (COVID-19) pandemic will have an impact on the conduct of clinical trials, some laboratory tests and clinical assessment procedures can be considered to conduct locally per local regulatory requirement.

j Refer to Section 4 for details on treatment arms. The IMP will be administered after completion of all scheduled clinical assessments and sample collections at the visit or at home.

k A CT scan should be performed during screening period (before first administration of IMP), at V5 (Week 24), , and central reading will be used for comparison of baseline to Week 24 for the primary analysis. In countries for which a specific approval procedure for the CT scan is required by a different committee than the IEC/IRB, these countries will be exempted from all the planned study CT scans until approval from these committees is received. A 4-month window must be required between 2 CT scans. It is recommended to avoid use of OCS as rescue therapy during the Week 20 to Week 24 or the Week 48 to Week 52. If a participant must use OCS during this period to control CRSsNP worsening/acute sinusitis based on Investigator judgment the site should make every effort to schedule the Week 24th CT scan prior to OCS rescue therapy.

l An electronic diary (ie, CRSsNP sinonasal symptom diary) is used for daily recording of nasal symptoms (from V1 to EOS): 1) nasal congestion/obstruction 2) anterior rhinorrhea (runny nose), 3) posterior rhinorrhea (post-nasal drip), 4) loss of sense of smell, 5) facial pain/pressure, and 6) headache. This device is dispensed at V1, and information is downloaded from this device on the other indicated days. For sTSS (nasal congestion, anterior/posterior rhinorrhea, facial pain/pressure), a score of ≥5 at Visit 1 (day score) and at Visit 2 (weekly average score) is required.

m During the study the PROs should be completed by the participants in the e-diary before seeing the physician, in the following order: The CRSsNP sinonasal symptom diary (Nasal congestion, loss of sense of smell, rhinorrhea, facial pain/pressure) and a headache symptom; SNOT-22; rhinosinusitis severity VAS; PGIS, PGIC, EQ-5D-5L, and ACQ-6 (in participants with asthma)

n Spirometry (FEV_1, FVC, and FEF 25 to 75): should be performed before randomization for all participants, locally after withholding the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for 6 hours and long-acting muscarinic acetylcholine (LAMA) receptor antagonists and Long-Acting Beta-Agonists for 24 hours. All participants should have the result of FEV_1 (% of predicted normal) recorded in eCRF before V2. Participants with FEV_1 of 50% or less (of predicted normal) will not be randomized. For the other scheduled visits during the randomized treatment period, spirometry will be performed only in participants with asthma; and the result of FEV_1, FVC, and FEF 25 to 75 will be recorded in the eCRF at the study scheduled visits.

o Vital signs, including blood pressure (mmHg), heart rate (beats per minute), respiratory rate (breaths per minute), body temperature (degrees Celsius), and body weight (kg), will be measured at the screening (V1), randomization visits (V2) and subsequent visits prespecified in the flow-chart. Height (cm) will be measured at V1 only. Vital signs will be measured in a semi-supine or sitting position using preferably the same arm at each visit prior to receiving IMP at the clinic visits..

p At indicated visit serum dupilumab concentration and ADA assessment samples will be collected and archived prior to administration of IMP during the randomized treatment period. In the event of a suspected SAEs or AESIs like anaphylaxis or hypersensitivity, AE of severe injection site reaction lasting longer than 24 hours, or systemic allergic reaction that is related to IMP and that requires treatment, additional PK and ADA samples may be collected closer to the event, based on the judgment of the medical Investigator and/or Sponsor or Sponsor representative(s). Pharmacokinetic and ADA samples will be collected unless restricted due to local regulation. However, the PK and ADA sample will be collected for safety assessment in the event of a SAE.

q Refer to Section 10.2 and central laboratory manual for collection details.

r Clinical laboratory testing at V1 includes hepatitis screen covering hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (HBsAb), hepatitis B core antibody (HBcAb) including total HBcAb, hepatitis C virus antibodies (HCVAb), HIV screen (anti-HIV-1 and HIV-2 antibodies). In case of results showing HBsAg (negative) and HBcAb (positive), an HBV DNA testing will be performed and should be confirmed negative prior to randomization. In case of results showing HCVAb (positive), HCV RNA testing will be performed and should be confirmed negative prior to randomization.

s Serum pregnancy test at V1 and urine pregnancy tests at Visit 2 and every 4 weeks thereafter. A negative result must be obtained between V1 and V2 prior to randomization. Urine pregnancy test could be performed at home with or without the assistance of a home care provider. In case of positive urine test, the study treatment will be withheld and a serum pregnancy test should be performed as soon as possible, to confirm the pregnancy. Pregnancy will lead to definitive treatment discontinuation in all cases.

[redacted]

2 INTRODUCTION

Dupilumab is a fully human monoclonal antibody directed against the interleukin 4 receptor alpha subunit (IL-4Rα), which is a component of IL-4 receptors type-1 and Type-2, as well as the IL-13 Type-2 receptor. The binding of dupilumab to IL-4Rα results in blockade of IL-4 and IL-13 intracellular signaling.

As a targeted/specific immunomodulatory agent, dupilumab is expected to selectively inhibit Type-2 inflammation and is designed to achieve the desired therapeutic effect without the side effects typically associated with the use of less selective immunosuppressants.

Both IL-4 and IL-13 signaling pathways are implicated in atopic diseases; and by blocking the activity of these cytokines, dupilumab has been shown to be an effective treatment for atopic conditions, including CRSwNP, AD, and asthma (eosinophilic phenotype) in adults.

2.1 STUDY RATIONALE

Dupilumab blockade of IL-4 and IL-13 signaling has demonstrated a favorable efficacy and an acceptable safety profile for the treatment of a variety of atopic disease states, including AD (16), asthma (17), EoE (18), and CRSwNP (19), where Type-2 inflammation is a key driver of the underlying disease process. Notably in the dupilumab CRSwNP clinical development program, two Phase 3 studies in adult participants with severe CRSwNP have demonstrated that dupilumab 300 mg q2w is significantly better than placebo for the reduction of polyp size, sinus opacification, and severity of symptoms, and is generally well tolerated (19). Similarly, in the dupilumab asthma Phase 3 study that included both adult and adolescent participants, dupilumab significantly reduced the adjusted annualized rate of severe asthma exacerbations compared to placebo in pre-specified subgroups of participants with elevated blood eosinophil counts and high Fractional exhaled nitric oxide (FeNO) levels, both markers of Type-2 inflammation (17). Of note, in the asthma Phase 3 study EFC13579 (QUEST), a subset of asthma patients with CRSsNP, treated, with dupilumab appeared to have greater improvement in Sino-Nasal Outcome Test-22-item (SNOT-22) from baseline to Week 24 compared with placebo-treated participants. Compared with placebo, dupilumab also led to greater suppression of markers of Type-2 inflammation, including FeNO, IgE, and thymus-and activation-regulated chemokine (TARC) levels, in the subset of asthma patients with CRSsNP in EFC13579 (20). The totality of the data from the completed AD, asthma, and CRSwNP clinical development programs indicates that dupilumab has broad therapeutic benefit in various conditions with strong Type-2 immunologic signatures.

The key objective of this study will be to evaluate the clinical efficacy and safety profile of dupilumab administered to type-2 CRSsNP patients with difficult-to-treat disease.

A detailed description of the chemistry, pharmacology, efficacy, and safety of dupilumab is provided in the Investigator's Brochure (IB).

2.2 BACKGROUND

Chronic rhinosinusitis is an inflammatory disease of the nasal cavity and paranasal sinuses characterized by 2 or more symptoms (lasting for ≥12 weeks), one of which is nasal obstruction or nasal discharge (anterior and/or posterior) and may also include facial pressure/pain and/or reduced sense of smell. It is estimated to affect approximately 10% of the population in the US and Europe (1, 2); based on real-world data a large majority of CRSsNP patients are adults (≥18 years old). However, lower estimates for symptomatic patients are reported; in the US, the percentage of the population that met the initial symptom criteria compatible with a diagnosis of CRS was reported at 2.1% (21). Chronic rhinosinusitis phenotypically is broadly divided into 2 types based on the presence or absence of nasal polyps: CRSwNP and CRSsNP (3). Chronic rhinosinusitis without nasal polyposis is the most common type of CRS, accounting for approximately two-thirds of the overall CRS population (3, 4).

While the underlying etiopathogenesis of CRSsNP is likely multifactorial, there is a subset of CRSsNP patients, representing nearly one-third of the overall CRSsNP population, where the disease process appears to be predominantly driven by type-2 inflammation. In this subset of type-2 CRSsNP patients, transcriptomic and proteomic analyses of surgical sinonasal tissues reveal elevated levels of Type-2 inflammatory markers, such as IL-5, IgE, ECP, CLC, etc (5, 6, 7). The Type-2-associated molecular signature identified in these Type-2 CRSsNP patients suggest that the underlying pathophysiological disease process is similar to that found in CRSwNP patients, where it is well known that Type-2 inflammation with prominent eosinophilia and elevated levels of Type-2 cytokines, such as IL-4, IL-5, and IL-13, plays a key role in the disease process (5, 6, 7, 8, 9, 10).

Several reports suggest peripheral blood eosinophilia is well correlated with tissue Type-2 inflammation (sinus tissue eosinophilia) in CRS patients with or without nasal polyps (22, 23, 24, 25, 26). In one cohort, receiver operating characteristic (ROC) curve analysis predicted high tissue eosinophilia from ethmoid sinus biopsies (>10/high power field [HPF]) using a peripheral blood eosinophil cutoff level of 240 cells/mm^3 (sensitivity 70.9%, specificity 78.4%, AUC: 0.792, $p<0.01$). This cutoff level produced a positive predictive value (PPV) of 83.0%, negative predictive value (NPV) of 64.5%, positive likelihood ratio (LR+) of 3.28 (24). Similarly, in another cohort, a cutoff value of 215 cells/mm^3 for the absolute blood eosinophil count yielded a sensitivity of 74.2% and a specificity of 86.5%, PPV of 80.3% and NPV of 81.9%, LR+ of 5.51 (25). Generally, a higher cutoff for peripheral blood eosinophil count is associated with greater specificity, but correspondingly lesser sensitivity, for identifying Type-2 inflammation (eosinophilia) in sinus tissue.

Consistent with the implication of type-2 inflammation underlying the disease process in these CRS patients, asthma is a common comorbid condition for both CRSsNP and CRSwNP patients: 20% to 40% in the former and 50% to 60% in the latter (4, 11), and about 52% of CRSsNP patients are reported to have comorbid allergic rhinitis (4). Fractional exhaled nitric oxide has been reported to be significantly correlated with other markers of type-2 inflammation, including elevated peripheral blood eosinophil counts and tissue eosinophilia, which also correlates with LMK scores in patients with CRS (27). Fractional exhaled nitric oxide has been noted to be elevated in CRSwNP patients with tissue eosinophilia independent of a diagnosis of asthma (27). Further peripheral blood eosinophilia, ≥300 cells/mm^3 (sensitivity 70%, specificity 70%), has been reported as a predictor of bronchial hyperresponsiveness in CRSsNP patients without a diagnosis of asthma (22). Comorbid asthma and peripheral blood eosinophilia have been associated with a higher risk of need for recurrent sinonasal surgery and need for systemic therapy after sinus surgery (12, 13, 28). Other clinical features more commonly reported in CRSsNP patients with type-2 endotype include loss of sense of smell/reduced taste; the type-2 CRSsNP patients also have more complaints of headache/migraine as compared with the non-type-2 CRSsNP patients (5).

The pathological hallmark of CRSsNP-associated upper airway disease is mucus secretion and goblet cell and glandular hyperplasia. Goblet cells are responsible for the production of mucin 5AC, one of the main secreted mucins in the human airway (29). The increase in mucous gland density that occurs in patients with severe CRSsNP is in contrast to those with CRSwNP who show a significant decrease in mucous gland density (30, 31, 32, 33). Glandular hypertrophy and mucous secretion in the airway mucosa are likely to be mediated by various cytokines, including IL-13 (34, 35, 36).

Standard medical therapies, including topical and oral corticosteroids, and antibiotics, do not provide adequate or lasting control of the symptoms in many patients with CRSsNP. In a study, 45% of patients “failed” medical therapy, defined as persistent symptoms; and 31% remained symptomatic enough to elect to pursue surgery (14). In the GA²LEN study, 70% to 80% of patients do not sustain adequate benefits from the medical therapies (including OCS, antibiotics and INCS) (11). Also, many CRSsNP patients have reported at least 1 prior surgery or are planning to have surgery in the near future for better control of symptoms (11). In patients who have undergone sinonasal surgery, comorbid asthma and peripheral blood eosinophilia are risk factors for the recurrence of CRS post-operatively (12, 13), suggesting that CRSsNP patients with type-2 inflammation (as indicated by increased peripheral blood eosinophilia and comorbid asthma) may be more at risk for disease recurrence after surgery. Consequently, because of the chronic and unremitting nature of the condition in many patients, CRS is associated with substantial socioeconomic burden that results from the costs of diagnostic tests, medical and surgical therapies, lost and reduced school and work productivity, and detrimental impact on physical and emotional health (15). Therefore, a high unmet medical need for efficacious therapy remains for CRSsNP patients who are inadequately treated by currently available treatment options, and dupilumab may become a novel effective treatment option for CRSsNP patients with peripheral blood eosinophilia (a marker of type-2 inflammation) who are inadequately controlled with available therapies.

2.3 BENEFIT/RISK ASSESSMENT

COVID-19 Benefit-risk assessment

Dupilumab has shown clinical benefit in several type-2 driven immunological disorders, such as AD, asthma, and CRSwNP.

To date, more than 8000 participants have been treated with dupilumab during the clinical development program in several indications, of which AD, asthma, and CRSwNP are licensed in some countries.

Currently, there are insufficient data in participants with Coronavirus Disease-2019 (COVID-19) who are being treated with dupilumab. Thus, the safety and efficacy of dupilumab in COVID-19 patients are unknown. During the course of the clinical trial program, respiratory infections including viral infections were monitored and these events are not listed as adverse drug reactions (ADRs) with dupilumab

The target population of EFC16723 is patients with uncontrolled, CRSsNP who have evidence of type-2 inflammation. These patients have failed medical therapies and/or surgical intervention and have active disease that causes significant impairment in function and quality of life. Therefore, these patients have a high unmet medical need for novel effective treatment. Participation in EFC16723 will provide an opportunity for these patients to be treated with a novel therapy that has proven efficacy in certain other disease states (ie, AD, asthma, and CRSwNP) where type-2 inflammation is the underlying driver of the disease process.

Based on the aforementioned potential benefits to patients participating in EFC16723, the Sponsor's assessment is that the benefit-risk remains favorable for patients to participate in this trial.

The Sponsor also recognizes that the COVID-19 pandemic may have an impact on the conduct of clinical trials. The Sponsor will monitor the situation closely and ensure the integrity of the trial conduct and data (see Section 8).

More detailed information about the known and expected benefits and risks and reasonably expected AEs of dupilumab is available in the IB.

2.3.1 Risk assessment

No tissue targets or specific hazards to humans were identified in nonclinical general and reproductive toxicology studies.

Dupilumab has an extensive safety database. As of 28 March 2020, 10 191 participants were enrolled into the development program for dupilumab and included in the safety population: 382 as healthy volunteers, 4405 from AD studies, 3614 from asthma studies, 782 from CRSwNP studies, 232 from EoE studies, 103 from the grass allergy study, 145 from peanut allergy studies, 511 from the chronic obstructive pulmonary disease (COPD) study, 5 from prurigo nodularis (PN) studies, and 12 from the chronic spontaneous urticaria (CSU) study. The number of participants

exposed to dupilumab in clinical studies was 8720 (356 in healthy volunteer studies, 4052 in AD studies, 3263 in asthma studies, 470 in CRSwNP studies, 166 in EoE studies, 52 in the grass allergy study, 96 in peanut allergy studies, 256 in the COPD study, 3 in PN studies, and 6 in the CSU study. For the latest information, please refer to the current IB.

Based on the information retrieved from Intercontinental Marketing Services Health and using the World Health Organization's defined daily dose for dupilumab of 21.4 mg/day, the cumulative post marketing exposure to dupilumab is estimated to be 161 582 patient-years (01 January 2017 through 31 March 2020).

Dupilumab was generally well tolerated in all populations tested in clinical development programs consistent with a favorable benefit/risk profile. The adverse drug reactions (ADR) identified to date for dupilumab include injection site reactions, conjunctivitis (including allergic and bacterial), oral herpes, herpes simplex, blepharitis, keratitis, dry eye, eye pruritus, eosinophilia, serum sickness, anaphylactic reaction, angioedema, and arthralgia. These ADRs were generally mild or moderate, transient, and manageable. These ADRs were not observed consistently in all indications (see IB for greater details). More significant serious allergic reactions were very rare. Importantly, no increased overall infection risk was observed in patients treated with dupilumab.

Systemic hypersensitivity is established as an important identified risk with dupilumab. As protein therapeutics, all monoclonal antibodies are potentially immunogenic. Rare serious and systemic hypersensitivity reactions have been observed in the dupilumab program including serum sickness/serum sickness-like reaction in the adult AD program and anaphylaxis related to dupilumab in the adult asthma clinical trials.

The important potential risk for dupilumab is "eosinophilia associated with clinical symptoms in asthma patients." The observed increase in eosinophil count is transient, which is consistent with the current understanding of the mechanism of action of dupilumab. In dupilumab asthma studies, a small number of patients with asthma experienced serious systemic eosinophilia presenting with clinical features of eosinophilic pneumonia or vasculitis consistent with eosinophilic granulomatosis with polyangiitis, conditions which are often treated with systemic corticosteroid therapy. These events have been seen in other drug development programs for severe asthma and usually, but not always, have been associated with the reduction of oral corticosteroid therapy suggesting possible unmasking of these conditions with tapering of corticosteroids during dupilumab therapy. The association of dupilumab treatment and these events has not been established. Health care providers should be alert to eosinophilia associated with vasculitic rash, worsening of pulmonary symptoms, pulmonary infiltrate, cardiac complications, and/or neuropathy presenting in their patients, especially upon reduction of SCS.

Patients with known helminth infections were excluded from participation in clinical studies; therefore, it is not known if dupilumab will influence the immune response against helminth infections. Consequently, patients with pre-existing helminth infections should be treated for their helminth infection before initiating therapy with dupilumab.

The common ADR across all indications is injection site reactions. Other potential risks based on the safety profile in particular indications are discussed in the IB.

While long-term data are still accumulating, data from randomized, placebo-controlled trials and open-label extension studies to date have not identified any new safety concern in these populations. It is anticipated that dupilumab in patients with type-2 CRSsNP will have a favorable safety profile as observed across other type-2 driven immunological disorders.

2.3.2 Benefit assessment

Dupixent® (dupilumab) is authorized for marketing in over 60 countries worldwide including the US, European Union (EU) (Centralized Procedure), Japan, Canada, and Australia for the adult AD indication. Dupilumab is also authorized in the US, EU, and other jurisdictions for the adolescent AD indication, in the US for children 6 to 12 years old with AD, and in the US, EU, Japan, and other jurisdictions for the adult and adolescent asthma indication. Dupilumab also has approval for its CRSwNP indication in the US, EU, and Japan. For the latest information, please refer to the current IB.

There are no treatments specifically approved for CRSsNP in the US. Standard medical therapies, such as those based on EPOS 2020 guidelines, which include topical and oral corticosteroids, and antibiotics, do not provide adequate or lasting control of the symptoms in many patients with CRSsNP. A high unmet medical need exists for therapies that target underlying inflammatory processes in type-2 CRSsNP patients who are inadequately treated by the current standard of care.

Considering this unmet medical need and the known mechanism of action of dupilumab, the Sponsor is proposing to develop dupilumab for the treatment of type-2 CRSsNP for the following reasons:

1. There is a subset of CRSsNP patients with an underlying pathophysiology that is driven primarily by Type-2 inflammatory processes and is characterized by increased type-2 biomarkers such as blood eosinophils, type-2 comorbidities or recurrence after surgery. Dupilumab has demonstrated favorable safety and efficacy profiles across a broad range of diseases including AD, asthma, and CRSwNP where type-2 inflammation is a key driver of the underlying disease process.
2. Dupilumab has demonstrated significant efficacy in reducing sinus opacification, severity of CRS symptoms and nasal polyp burden in CRSwNP, a disease that shares several clinical and molecular features with CRSsNP with evidence of Type-2 inflammation.
3. A post-hoc analysis of the LIBERTY ASTHMA QUEST study demonstrated that dupilumab treatment improved sinonasal symptoms and health-related quality of life (HRQoL), as assessed by SNOT-22, in patients with CRS (20) and suppressed airway (FeNO) and systemic (total IgE, TARC) type-2 inflammatory biomarkers versus placebo (20). Furthermore, clinically meaningful improvement from baseline in SNOT-22 was observed primarily in patients who had peripheral blood eosinophil counts $\geq$300 cells/mm^3.

2.3.3 Overall benefit: risk conclusion

Therefore, based on the totality of evidence to support the potential therapeutic benefit in CRSsNP, a patient population with an unmet medical need, the favorable benefit/risk profile across multiple indications, and the extensive safety database for dupilumab, the Sponsor is proposing to conduct a Phase 2 program with dupilumab for the treatment of CRSsNP with evidence of type-2 inflammation.

3 OBJECTIVES AND ENDPOINTS

Table 1 - Objectives and endpoints

Objectives	Endpoints
Primary	
• To evaluate the efficacy of dupilumab as assessed by the reduction at Week 24 in sinus opacification on computerized tomography (CT) scan in the dupilumab group only	• Change from baseline to Week 24 in opacification of sinuses assessed by CT scan using the Lund-Mackay (LMK) score in the dupilumab group
Secondary	
• To evaluate the efficacy of dupilumab as assessed by the reduction at Week 24 in sinus opacification on CT scan and sinus total symptom score (sTSS) compared to placebo	• Change from baseline to Week 24 in opacification of sinuses assessed by CT scan using the LMK score • Change from baseline to Week 24 in sTSS* **Composite severity score consisting of nasal congestion, anterior/posterior rhinorrhea, facial pain/pressure items of the CRSsNP sinonasal symptom e-diary*
• To evaluate the safety and tolerability of dupilumab in CRSsNP patients compared to placebo	• Incidence of treatment-emergent adverse events (TEAEs), of treatment-emergent serious AEs (TESAEs), and TEAEs leading to treatment discontinuation, abnormal laboratory values, and vital signs
• To evaluate the pharmacokinetics (PK) of dupilumab in CRSsNP patients compared to placebo	• Dupilumab concentration in serum
• Assessment of immunogenicity to dupilumab over time compared to placebo	• Assessment of immunogenicity to dupilumab as determined by the incidence, titer, and neutralizing antibody (NAb) status of treatment-emergent anti-drug antibody (ADA) response over time compared to placebo
Exploratory	
• [redacted]	[redacted]

Objectives	Endpoints
• [redacted]	[redacted]

3.1 APPROPRIATENESS OF MEASUREMENTS

The primary efficacy assessment of change from baseline in the LMK CT scan score at Week 24 in the dupilumab group, will provide objective imaging-based measurement of benefit of CRSsNP patients. The LMK and a related total symptom score (TSS), as secondary endpoint with dupilumab group comparison to placebo, are 2 of the key assessments that have been successfully implemented and have provided clinically meaningful evidence of therapeutic benefit of dupilumab treatment after 24 weeks in the completed clinical development program of dupilumab in CRSwNP (19). The sTSS in this trial is a total score composed of three common, cardinal symptoms of CRSsNP, including nasal congestion, rhinorrhea (anterior/posterior), and facial pain/pressure that are daily assessed by the participant. This score will provide a comprehensive clinical assessment of the impact of dupilumab on the key symptoms of CRSsNP, and will complement the objective assessment provided by the well-validated LMK score. Other supportive assessments, including individual scores for the main symptoms in CRSsNP (NC/obstruction, loss of sense of smell, facial pain/pressure, and rhinorrhea) and visual analog scale (VAS) for rhinosinusitis severity will also be assessed. The SNOT-22 will also be collected to provide additional evidence of therapeutic benefit.

4 STUDY DESIGN

4.1 OVERALL DESIGN

This is a Phase 2 multicenter study to evaluate the efficacy and safety of dupilumab, in participants with uncontrolled CRSsNP. This is a randomized, double-blind, placebo-controlled study in adult participants regardless of screening eosinophil count to evaluate the treatment effect of dupilumab on sinus opacification as assessed by the LMK sinus CT scan total score and to provide data on safety.

All participants (adults only) will enter a screening period (2 to 4 weeks), with a 24 to 52-week treatment period, followed by post-treatment follow-up (12 weeks).

Approximately 70 adult participants will be randomized 1:1 (approximately 35 participants per arm) into 2 treatment groups as follows:

- Arm A: Dupilumab 300 mg q2w,
- Arm B: Matching placebo.

Randomization will be stratified by screening blood eosinophil count (≥300 cells/mm^3 or <300 cells/mm^3), background INCS use (yes or no) and region.

To ensure enrollment according to the intended distribution of screening blood eosinophil count, alerts will be built into the IRT to control the number of participants in each stratification group as follows:

- ≥300 cells/mm^3: approximately 15 participants per arm,
- <300 cells/mm^3: approximately 20 participants per arm.

Note: The treatment will stop for all participants when the LPI has completed 24 weeks of treatment. Therefore, all participants following Amendment 02 will be treated for at least 24 weeks and the other participants (enrolled before Amendment 02) will have variable treatment period and may continue up to 52 weeks.

In addition, in order to have an adequate number of participants with comorbid asthma, alerts will be built into the IRT to limit the number of participants without comorbid asthma to no more than 70% of the randomized population.

During the study**,** participants who report deterioration requiring medical/surgical intervention may come to the site for clinical evaluation. An unscheduled visit may be used for this purpose and, if necessary, the Investigator may consider one of the treatment alternatives described in Section 6.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

EFC16723 is designed as a double-blind, randomized, placebo-controlled, study to minimize bias in data collection and interpretation. The presence of a placebo arm is appropriate for the objectives of this study since it will provide the most robust assessment of the efficacy and safety

of dupilumab. The study has a 24 to 52 -week study treatment period to provide initial evidence related to the treatment effect of dupilumab in patients with Type-2 inflammation (as indicated by peripheral blood eosinophil counts ≥300 cells/mm^3) CRSsNP and to provide safety information. In addition, a post-hoc analysis to assess the efficacy of dupilumab on upper airway symptoms as measured by SNOT-22 in the subset of asthma patients with CRS from the dupilumab Phase 3 asthma study EFC13579 (QUEST) was performed. Clinically meaningful improvement from baseline in SNOT-22 was observed only in patients who had peripheral blood eosinophil counts ≥300 cells/mm^3 and not in those with <300 cells/mm^3. In the study, to further evaluate the predictive value of baseline peripheral blood eosinophil counts as a potential marker of treatment response to dupilumab, a subset of participants with blood eosinophil counts of <300 cells/mm^3 will be randomized while the primary analysis population will remain as participants who have peripheral blood eosinophil counts ≥300 cells/mm^3.

The 24-week treatment duration should be sufficient for the demonstration of the efficacy with dupilumab based on the efficacy results seen in CRSwNP. This duration is also sufficient for safety assessment given the extensive safety experience with dupilumab including in the related condition of CRSwNP.

Rescue medications and/or surgery for CRSsNP deemed necessary by Investigators will be allowed~~,~~ which mirror the expected future therapeutic paradigm of dupilumab in this population in clinical practice.

The primary efficacy assessment will be change from baseline in the LMK at Week 24 in the dupilumab group. Other supportive assessments, including sTSS scores for the main symptoms in CRSsNP (nasal congestion [NC]/obstruction, loss of sense of smell, rhinorrhea, facial pain/pressure), VAS for rhinosinusitis severity, and SNOT-22 will also be collected, to provide additional evidence of therapeutic benefit.

Changes in the LMK and sTSS, as secondary endpoint, will provide both objective imaging measure of benefit and evidence of symptomatic improvement in the cardinal clinical manifestations of CRSsNP patients, respectively other secondary and exploratory measures, including individual scores for the main symptoms in CRSsNP, VAS for rhinosinusitis severity, and SNOT-22, that assess other disease manifestations of CRSsNP and the associated impact on the quality of life in participants.

4.2.1 Participant input into design

Participants were not involved in the design of the clinical trial.

4.3 JUSTIFICATION FOR DOSE

Based on the known pharmacokinetics (PK), safety, and efficacy of dupilumab, the selected dosing regimen for EFC16723 study is dupilumab 300 mg q2w.

This dose regimen is expected to achieve concentrations in serum that saturate the target-mediated clearance pathway and has demonstrated similar efficacy in adult patients with asthma and AD,

and in adults with CRSwNP. The PK of dupilumab have been found to be consistent across populations of patients with AD, asthma, and CRSwNP, as well as healthy volunteers. Furthermore, the sources of variability of dupilumab PK identified in each population and the magnitude of the covariate effects indicate that body weight is the most influential factor, whereas other covariates identified as being statistically significant have no meaningful impact on dupilumab PK. Overall, it is expected that the PK of dupilumab is similar in healthy adults and participants with a range of type-2 diseases, with body weight being the most influential covariate affecting exposure. The immunogenicity of dupilumab is also comparable in these populations (see approved Dupixent prescribing information).

The 300 mg q2w dose regimen has been proven to be effective with an acceptable safety profile in patients with moderate-to-severe AD, moderate-to-severe asthma, and CRSwNP. The 300 mg q2w without a loading dose has been demonstrated to be efficacious for adult participants with severe CRSwNP, where differential treatment responses between dupilumab- and placebo-treated patents were observed as early as after 4 weeks of study treatment. Consistent with the observed PK and pharmacodynamic (PD) profile of nasal polyp score (NPS) response (gradual development of response during the treatment period as well as slow offset of response during off-treatment period) in patients with CRSwNP, PK/PD simulation of the co-primary endpoints of NPS and NC showed minimal difference in the development of treatment effect and steady-state response of NPS and NC in the presence and absence of the loading dose of 600 mg on Day 1 in patients with CRSwNP. Therefore, no loading dose is included in the present study for CRSsNP adult participants.

The collective PK/PD, clinical efficacy, and safety data of dupilumab across diverse disease populations suggest that the selected dose regimens for EFC16723 will be efficacious and safe for the treatment of adult CRSsNP patients.

4.4 END OF STUDY DEFINITION

A participant is considered to have completed the study if he/she has completed all phases of the study including the Follow-up visit (EOS Visit).

- For participants actively followed under original protocol or Amendment 1, if a participant discontinues study intervention prematurely before Week 40 but completes follow-up to Week 52, he/she will be considered to have completed the study.
- For participants actively followed under Amendment 2, if a participant discontinues study intervention prematurely before Week 12 but completes follow-up to Week 24, he/she will be considered to have completed the study.

The end of the study is defined as the date of the last visit of the last participant in the study.

5 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 INCLUSION CRITERIA

Participants are eligible to be included in the study only if all of the following criteria apply:

Age

I 01. Participant must be at least 18 years of age at the time of signing the informed consent form (ICF).

Type of participant and disease characteristics

I 02. Participants must have bilateral inflammation of paranasal sinuses in CT scan with LMK ≥8 and bilateral ethmoid opacification before randomization.

I 03. Participants must have ongoing symptoms of loss of smell and rhinorrhea (anterior/posterior) of any severity, with or without facial pain/pressure for at least 12 consecutive weeks by Visit 1.

I 04. Participants must have ongoing symptoms of NC/obstruction at least 12 consecutive weeks before Visit 1 and a NC score of ≥2 at Visit 1 (day score) and Visit 2 (weekly average score).

I 05. Participants must have sTSS (NC, rhinorrhea, facial pain/pressure) ≥5 at Visit 1 (day score) and Visit 2 (weekly average score).

I 06. Participants must have at least one of the 2 following features:

a) Prior sinonasal surgery (see note at end of section 5.2 for definitions of sinonasal surgery) for CRS,

b) Treatment with SCS therapy for CRS as defined by any dose and duration within the prior 2 years before screening (Visit 1) or intolerance/contraindication to SCS.

I 07. No restrictions on eosinophil count.

Weight

I 08. Body weight ≥30 kg.

Sex

I 09. Male or female

Contraceptive use by women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

- A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least 1 of the following conditions applies:
  - Is not a woman of childbearing potential (WOCBP).

  OR

  - Is a WOCBP and agrees to use a contraceptive method that is highly effective, with a failure rate of <1%, as described in Appendix of the protocol during the study (up to 12 weeks after the last administration of the study treatment).
- A WOCBP must have a negative highly sensitive pregnancy test (urine or serum as required by local regulations) on Day 1 before the first dose of study intervention,
- If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive,
- Additional details can be found in Appendix 4 (Section 10.4) of the protocol,
- The Investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

Informed Consent

~~I 10.~~ Capable of giving signed informed consent as described in Appendix 1 (Section 10.1.3) of the protocol which includes compliance with the requirements and restrictions listed in the ICF and in this protocol. In countries where the legal age of majority is above 18 years, a specific ICF must also be signed by the participant's legally authorized representative.

5.2 EXCLUSION CRITERIA

Participants are excluded from the study if any of the following criteria apply:

Medical conditions

E 01. Participants with conditions/concomitant diseases making them non-evaluable at Visit 1 or for the primary efficacy endpoint such as:

a) Participants with nasal polyposis observed during nasal endoscopy at Visit 1,

b) Participants with past history of nasal polyposis,

c) Nasal septal deviation that would cause complete occlusion of at least one nostril,

d) Acute sinusitis or purulent drainage or nasal infection, or upper respiratory infection at Visit 1 or Visit 2,

e) Ongoing rhinitis medicamentosa,

f) Eosinophilic granulomatous polyangitis (Churg-Strauss syndrome), granulomatosis with polyangiitis (Wegener's granulomatosis), microscopic polyangiitis, Young's syndrome, Kartagener's syndrome or other dyskinetic ciliary syndromes, cystic fibrosis.

E 02. Participants with nasal cavity malignant tumor and benign tumors (eg, papilloma, hemangioma).

E 03. Participants with Forced expiratory volume (FEV_1) ≤50% of predicted normal at Visit 1.

E 04. Radiologic suspicion or confirmed invasive or expansive fungal rhinosinusitis.

E 05. Diagnosed with, suspected of, or at high risk of endoparasitic infection, and/or use of antiparasitic drug within 2 weeks before the Screening Visit (Visit 1) or during the screening period.

E 06. History of human immunodeficiency virus (HIV) infection or positive HIV screen (anti-HIV-1 and HIV-2 antibodies) serology at the Screening Visit (Visit 1).

E 07. Severe concomitant illness(es) that, in the Investigator's judgment, would adversely affect participation in the study. Examples include, but are not limited to, participants with short life expectancy, participants with uncontrolled diabetes (hemoglobin A1c ≥9%), participants with cardiovascular conditions (eg, Class III or IV cardiac failure according to the New York Heart Association classification), severe renal conditions (eg, participants on dialysis), hepato-biliary conditions (eg, Child-Pugh class B or C), neurological conditions (eg, demyelinating diseases), active major autoimmune diseases (eg, lupus, inflammatory bowel disease, rheumatoid arthritis), and other severe endocrinological, gastrointestinal, metabolic, pulmonary, or lymphatic diseases. The specific justification for participants excluded under this criterion will be noted in study documents (chart notes, electronic case report forms [eCRFs], etc).

E 08. Known or suspected immunodeficiency, including history of invasive opportunistic infections eg, tuberculosis (TB), histoplasmosis, listeriosis, coccidioidomycosis, pneumocystosis, and aspergillosis), despite infection resolution, or otherwise recurrent infections of abnormal frequency or prolonged duration suggesting an immune-compromised status, as judged by the Investigator.

E 09. Participants with active TB, non-tuberculous mycobacterial infection, or a history of incompletely treated TB will be excluded from the study unless it is well documented by a specialist that the participant has been adequately treated and can now start treatment with a biologic agent, in the medical judgment of the Investigator and/or infectious disease specialist. Tuberculosis testing would be performed on a country-by-country basis according to local guidelines if required by regulatory authorities or ethics boards.

E 10. Active chronic or acute infection requiring treatment with systemic antibiotics, antivirals, or antifungals within 2 weeks before the Screening Visit (Visit 1) or during the screening period.

E 11. History of malignancy within 5 years before Visit 1, except completely treated in situ carcinoma of the cervix, and completely treated and resolved nonmetastatic squamous or basal cell carcinoma of the skin.

E 12. Known or suspected alcohol and/or drug abuse.

E 13. History of systemic hypersensitivity or anaphylaxis to dupilumab or any of its excipients.

E 14. Planned major surgical procedure during the patient’s participation in this study.

E 15. Participant with any other medical or psychological condition including relevant laboratory or electrocardiogram abnormalities at screening that, in the opinion of the Investigator, suggest a new and/or insufficiently understood disease, may present an unreasonable risk to the study participant as a result of his/her participation in this clinical trial, may make patient's participation unreliable, or may interfere with study assessments. The specific justification for participants excluded under this criterion will be noted in study documents (chart notes, eCRF, etc).

Prior/concomitant therapy

E 16. Participation in prior dupilumab clinical study or have been treated with commercially available dupilumab within 12 months or who discontinued dupilumab use due to adverse event.

E 17. Participants who have taken:

- Biologic therapy/systemic immunosuppressant such as methotrexate, cyclosporine, mycophenolate, tacrolimus, etc to treat inflammatory disease (including CRSsNP) or autoimmune disease (eg, rheumatoid arthritis, inflammatory bowel disease, primary biliary cirrhosis, systemic lupus erythematosus, multiple sclerosis) within 4 weeks before Visit 1 or 5 half-lives, whichever is longer,

- Any investigational monoclonal antibody (mAb) within 5 half-lives or within 6 months before Visit 1 if the half-life is unknown,
- Anti-immunoglobulin E therapy (omalizumab) within 4 months prior to Visit 1.

E 18. Treatment with a live (attenuated) vaccine within 4 weeks before the Screening Visit (Visit 1).

NOTE: For participants who have vaccination with live, attenuated vaccines planned during the course of the study (based on national vaccination schedule/local guidelines), it will be determined, after consultation with a physician, whether the administration of vaccine can be postponed until after the end of study (EOS), or preponed to before the start of the study without compromising the health of the participant:

Participants for whom administration of live (attenuated) vaccine can be safely postponed would be eligible to enroll into the study.

Participants who have their vaccination preponed can enroll in the study only after a gap of 4 weeks following administration of the vaccine.

E 19. Leukotriene antagonists/modifiers unless participant is on a continuous treatment for at least 30 days prior to Visit 1.

E 20. Initiation of allergen immunotherapy within 3 months prior to Visit 1 or a plan to begin therapy or change its dose during the screening period or the randomized treatment period.

E 21. Sinus surgery within 6 months before screening (Visit 1) or sinonasal surgery (see note at end of Section 5.2 for definitions of sinonasal surgery) changing the lateral wall structure of the nose making the evaluation of LMK impossible.

E 22. Participants on unstable dose of INCS spray 4 weeks prior to Screening Visit (Visit1) and during screening period.

E 23. Participants treated with intranasal corticosteroid drops, intranasal steroid emitting devices/stents, nasal spray using exhalation delivery system, such as Xhance™ during screening period.

E 24. Participants who received SCS during screening period (between Visit 1 and Visit 2).

E 25. Either intravenous immunoglobulin (IVIG) therapy and/or plasmapheresis within 30 days prior to Screening Visit (Visit 1).

Diagnostic assessments

E 26. Participants with any of the following results at the Screening Visit (Visit 1):

a) Positive (or indeterminate) hepatitis B surface antigen (HBsAg) or,

b) Positive total HBcAb and a negative HBsAg confirmed by positive hepatitis B virus (HBV) DNA or,

c) Positive hepatitis C virus antibody (HCVAb) confirmed by positive HCV RNA.

Noncompliance to completion of the e-diary

E 27. Participants must demonstrate at least the following for acceptable compliance: Completing the e-diary for any 4 in the 7 days immediately preceding the Baseline Visit (Visit 2).

Other exclusions

E 28. Individuals accommodated in an institution because of regulatory or legal order; prisoners or participants who are legally institutionalized.

E 29. Any country-related specific regulation that would prevent the participant from entering the study.

E 30. Participant not suitable for participation, whatever the reason, as judged by the Investigator, including medical or clinical conditions or participants potentially at risk of noncompliance to study procedures.

E 31. Participants are employees of the clinical study site or other individuals directly involved in the conduct of the study, or immediate family members of such individuals (in conjunction with Section 1.61 of ICH-GCP Ordinance E6).

E 32. Not applicable as per Amended protocol 02.

E 33. Sensitivity to any of the study interventions, or components thereof, or drug or other allergy that, in the opinion of the Investigator, contraindicates participation in the study.

Note: Definitions of sinonasal surgery

- Endoscopic sinus surgery (ESS), include all the current procedural terminology (CPT) codes used for sinus surgery, which implies restitution of physiology and is used to create a sinus cavity opening that incorporates the natural ostium; allows adequate sinus ventilation; facilitates mucociliary clearance; facilitates instillation of topical therapies:
  - ESS may include also balloon sinuplasty: endoscopic nasal surgery that uses small balloon catheters that inflate to drain the large nasal sinuses.

- Or “Full ESS’ defined as complete sinus opening including anterior and posterior ethmoidectomy, maxillary antrostomy (could be large), sphenoidotomy and frontal sinusotomy in the same context as ‘full’ (eg, Draf III) but could also include extension beyond the confines of sinuses ie, skull base, orbit, pterygopalatine and infratemporal fossa.
- Or radical Functional endoscopic sinus surgery which includes significant removal of inflamed/dysfunctional mucosa.

5.3 LIFESTYLE CONSIDERATIONS

No restrictions.

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study intervention/entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure reasons, eligibility criteria, and any serious adverse event (SAE).

In the case of technical malfunction of equipment, the participants may be rescreened.

Individuals who do not meet the inclusion criteria or fail the exclusion criteria may be rescreened once as per Investigator decision. Rescreened participants will be assigned a new participant number versus the one received for the initial Screening Visit (Visit 1).

There is no requirement for a waiting period between the screen failure date and the rescreening date. The interactive response technology (IRT) report will flag rescreened participants. Participants that are rescreened must sign a new consent form.

If certain dynamic laboratory tests do not meet the eligibility criteria at the screening period, these laboratory assessments may be repeated at the discretion of the Investigator, if it is judged to be likely to return to the acceptable range for study inclusion within the screening window prior to Day 1. A baseline CT scan must be repeated for these rescreened participants if the previous CT scan done between Visit 1 and Visit 2 is more than 31 days in the past (28 days+3 days). If, the rescreening cannot be done within 31 days (28 days + 3 days), then these rescreened participants must wait for 4 months to repeat CT scan to prevent over exposure to CT radiation. All other screening procedures must be repeated for rescreening.

6 STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a participant according to the study protocol.

6.1 STUDY INTERVENTION(S) ADMINISTERED

Table 2 - Overview of study interventions administered

ARM name	Dupilumab	Placebo
Intervention name	Dupilumab 300 mg	Placebo
Type	Biological	Other
Dose formulation	Dupilumab 300 mg: A 150 mg/mL dupilumab solution in a pre-filled syringe to deliver 300 mg in 2 mL	Placebo matching dupilumab 300 mg will be supplied as an identical formulation to the active 300 mg formulation without dupilumab, in a pre-filled syringe to deliver placebo in 2 mL
Unit dose strength(s)	300 mg	0 mg
Dosage level(s)	One injection of 300 mg q2w for all adults	One injection of placebo matching 300 mg q2w for all adults
Route of administration	Subcutaneous injection	Subcutaneous injection
Use	Experimental	Experimental
IMP	IMP	IMP
Packaging and labeling	Each dose of dupilumab will be supplied as 1 glass pre-filled syringe packed in a participant kit box. Both glass pre-filled syringe and box will be labeled as required per country requirement	Each dose of placebo will be supplied as 1 glass pre-filled syringe packed in a participant kit box. Both glass pre-filled syringe and box will be labeled as required per country requirement

Abbreviations: q2w: every 2 weeks, IMP: investigational medicinal product.

Investigational medicinal product(s)

The IMP is administered every 14 ± 3 days (q2w) during the treatment period (with the last IMP administration at Week 22-50).

During study visits, the IMP is administered on sites after all procedures. For the doses that are not scheduled to be given at the study site, home administration of IMP is allowed after appropriate training of the participant or caregiver). Investigator or delegate will prepare and inject the first dose of IMP at Visit 2, in front of the participant (or caregiver). The participant (or caregiver) will prepare and inject the IMP under the supervision of the Investigator or delegate at Visit 3. The training must be documented in the participant's study file. In case of emergency (eg, natural disaster, pandemic, etc) different training ways (eg, training remotely with instruction provided by phone, etc) can be performed (and will be documented in the participant's study file).

If the participant (or caregiver) is unable or unwilling to prepare and inject IMP, injections can be performed at the study site by way of unscheduled visits; or arrangements can be made for qualified site personnel and/or health care professionals (eg, visiting nurse service) to administer IMP at participant's home.

In case of emergency (eg, natural disaster, pandemic, etc), IMP may be supplied from the site to the participant via a Sponsor-approved courier company where allowed by local regulations and approved by the participant. When the participant has a study visit, the IMP will be administered after clinical procedures and blood collection are performed. Participants should be monitored for at least 30 minutes following injection. The monitoring period may be extended as per country-specific or local site-specific requirements.

The participant/parent/legally authorized representative/caregiver should be trained by the site staff to recognize potential signs and symptoms of hypersensitivity reaction in order to self-monitor/monitor at home for at least 30 minutes (or longer per country-specific or local site-specific requirements) following injection. In case of hypersensitivity symptoms, the participant should contact healthcare provider/emergency.

Subcutaneous injection sites should be alternated among the 4 quadrants of the abdomen (avoiding navel and waist areas), the upper thighs or the upper arms, so that the same site is not injected between two q2w injections. Injections in the upper arms could be done only by a trained person (caregiver trained by Investigator or delegate) or health care professional but not the participants themselves.

For doses not given at the study site, paper diaries will be provided to the participant to record information related to the home injections. The paper diary will be kept as source data in the participant's study file.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 Storage and Handling

1. The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. At site, all study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.
3. The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

6.2.2 Responsibilities

Any quality issue noticed with the receipt or use of an IMP (deficiency in condition, appearance, pertaining documentation, labeling, expiration date, etc) must be promptly notified to the Sponsor. Some deficiencies may be recorded through a complaint procedure (see Section 8.3.7).

A potential defect in the quality of IMP may be subject to the initiation of a recall procedure by the Sponsor. In this case, the Investigator will be responsible for promptly addressing any request made by the Sponsor in order to recall the IMP and eliminate potential hazards.

Under no circumstances will the Investigator supply IMP to a third party (except for direct mail to participant shipment, for which a courier company has been approved by the Sponsor), allow the IMP to be used other than as directed by this clinical trial protocol, or dispose of the IMP in any other manner.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

The randomized intervention kit number list is generated centrally by Sanofi, and IMPs are packaged in accordance with this list. The randomization and intervention allocation are performed centrally by IRT. The IRT generates the participant randomization list and allocates the intervention number and the corresponding intervention kits to the participants according to it. Before the study is initiated, the log-in information and directions for the IRT will be provided to each site.

Participants will be randomized in a 1:1 ratio treatment arm described in Table 2.

Randomization will be stratified by screening blood eosinophil count (≥300 cells/mm^3 or <300 cells/mm^3), background INCS use (yes or no) and region.

At Screening (Visit 1), the Investigator or designee will contact the IRT to receive the participant number. If a participant who had previously failed screening is approached for re-screening, a new ICF must be signed. In such case, a new participant number will be assigned by IRT.

A randomized participant is defined as a participant who has been allocated to a randomized intervention regardless of whether the treatment was administered or not (ie, participant registered by the IRT). A participant cannot be randomized more than once in the study.

Study intervention will be dispensed at the study visits summarized in the SoA (Section 1.3). Returned study intervention should not be re-dispensed to the participants.

Methods of blinding

Dupilumab 300 mg and placebo 300 mg will be provided in identically matched 2 mL pre-filled syringes that are visually indistinguishable for each dose. Syringes and box will be labeled with a treatment kit number.

Code breaking

The IRT will be programmed with blind-breaking instructions. In case of an emergency, the Investigator has the sole responsibility for determining if unblinding of a participant's intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the Investigator decides that unblinding is warranted, he/she may, at his/her discretion, contact the Sponsor to discuss the situation prior to unblinding a participant's intervention assignment unless this could delay emergency treatment of the participant. If a participant's intervention assignment is unblinded, the Sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and eCRF, as applicable.

If the code is broken at the site level, the participant must withdraw permanently from IMP administration.

6.4 STUDY INTERVENTION COMPLIANCE

- The Investigator or his/her delegate must ensure that IMP is administered to each participant according to the labeling instructions.
- IMPs accountability:
  - Intervention units are returned by the participant at each visit. In case of direct mail to participant process, the intervention units can be returned by the carrier (if defined in the contract),
  - The Investigator or his/her delegate counts the number of remaining kits/pre-filled syringes and fills in the Intervention Log Form,
  - The Investigator or his/her delegate records the dosing information on the appropriate pages of the eCRF,
  - The monitor in charge of the study then checks the eCRF data by comparing them with the IMP that he/she has retrieved, and the intervention log forms.

When participants are dosed at the site, they will receive study intervention directly from the Investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the eCRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

When participants self-administer study intervention(s) at home, compliance with study intervention will be assessed at each visit. Compliance will be assessed by checking participant home-dosing diary and used/unused kits/pre-filled syringes during the site visits and documented

in the source documents and eCRF. Changes(s) from the prescribed dosage regimen should be recorded in the eCRF.

Detailed instructions for transport, storage, preparation, and administration of IMP are provided to the participant. For doses not given at the study site, participants will complete a dosing diary to document compliance with self-injection (or caregiver) of IMP, location of injection, and any symptoms. The diary will be kept as source data in the participant's study file.

A record of the number of kits/pre-filled syringes dispensed to and taken by each participant must be maintained and reconciled with study intervention and compliance records. Relevant data from the dosing diary will be recorded in the eCRF.

6.5 CONCOMITANT THERAPY

Any medication or vaccine (including over the counter or prescription medicines, vitamins, and/or herbal supplements or other specific categories of interest) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use.
- Dates of administration including start and end dates.
- Dosage information including dose and frequency.

The Sponsor or Sponsor representative(s) should be contacted if there are any questions regarding concomitant or prior therapy.

6.5.1 Background treatments

Participants should continue their permitted background INCS spray during the study, if they were on stable dose of INCS (except for Xhance™) for at least 4 weeks prior to screening. From the time of screening, they should not change their background medications.

Permitted concomitant medication

The following treatments are allowed:

- Intranasal corticosteroid spray (except for Xhance™) is permitted as background medication that it should be on the stable dose for at least 4 weeks prior to study screening, and participants must maintain the same INCS throughout the study treatment period if initiated before enrollment.
- Single dose of topical decongestants administration, for example, oxymetazoline hydrochloride (to reduce the swelling and widen the path for the endoscope) as well as a topical anesthetic (eg, lidocaine) are allowed before nasal brushing or before endoscopy.
- Administration of short courses antibiotics for a concurrent infection or CRSsNP worsening /acute sinusitis, is allowed during the study (reason for and duration of treatment should be documented in the eCRF) (see Section 6.5.3).

- Short-acting β2-adrenergic receptor agonists (SABA), long-acting β2-adrenergic receptor agonists (LABA), and long-acting muscarinic acetylcholine receptor antagonists (LAMA).
- Methylxanthines (eg, theophylline, aminophylline).
- Inhaled corticosteroids.
- Systemic antihistamines.
- Leukotriene antagonists/modifiers are only permitted during the study, for participants who have been on a continuous treatment for ≥30 days prior to Visit 1.
- Allergen immunotherapy in place for ≥3 months and dose stable for 1 month prior to Visit 1 is permitted.
- Short courses of SCS to treat other serious co-existing diseases (such as asthma exacerbation) or for AEs are allowed (see Section 6.5.3).

Other concomitant medication may be considered on a case-by-case basis by the Investigator in consultation with the Sponsor or Sponsor representative(s) if required.

6.5.2 Prohibited medications

The following concomitant treatments are not permitted during the screening period and the randomized treatment period:

- Any systemic immunosuppressive treatment, such as methotrexate, cyclosporine, mycophenolate, tacrolimus, etc.
- Initiation of allergen immunotherapy.
- Intranasal corticosteroid drops; intranasal steroid emitting devices/stents; nasal spray using Exhalation Delivery System such as Xhance™.
- All forms of SCS are prohibited during screening and study treatment period except for short-term courses (≤2 weeks) of OCS can be used as rescue during treatment period (see Section 6.5.3).
- Live attenuated vaccines.
- Intravenous immunoglobulin (IVIG) therapy.
- Other monoclonal antibodies (biological immunomodulators), including but not limited to anti-IgE, anti-IL-5, and anti-tumor necrosis factor (TNF), etc.
- Systemic antibiotics are prohibited during screening and study treatment period except for rescue use (see Section 6.5.3).

6.5.3 Rescue medicine

During the study treatment and follow-up periods, based on clinical evaluation, in case of worsening of signs and/or symptoms/acute sinusitis requiring medical intervention, the Investigator may consider rescue treatment with:

- Systemic antibiotics (up to 2 weeks) in case of acute infection.
- Short course OCS (prednisone or equivalent prednisolone up to 14 days; avoid use 4 weeks before Week 24 or Week 52, where applicable).
- Sinonasal surgery for CRSsNP (8 weeks of IMP treatment is recommended prior to surgery to allow onset of treatment effect).
- Intranasal corticosteroids spray (initiation of INCS spray or change in dosing of a background INCS during the study period).

Participants receiving rescue treatment other than surgery during the study should continue on study drug unless the Investigator decides to withdraw the study treatment. Before starting treatment with OCS participants should come to the study site for the clinical assessments. It is recommended to avoid use of OCS as rescue therapy during the Week 20 to Week 24 or the Week 48 to Week 52. If a participant must use OCS during this period to control worsening of symptoms based on Investigator judgment the site should make every efforts to schedule the Week 24 CT scan or the Week 52 CT scan prior to OCS rescue therapy.

For participants who undergo or are planned for surgery for CRSsNP the Investigator may decide to continue IMP up to the time of surgery or end of treatment (EOT) whichever date comes first. At the time of surgery participants will be permanently discontinued from study treatment and assessed as soon as possible using the procedures normally planned for the EOT Visit. In any case participants who prematurely discontinued the treatment will be encouraged to return to the study site for the efficacy and safety assessments planned at EOT Visit and for additional visits.

Additional appropriate medical/therapy per local guideline or per Investigators decision may be considered to use as rescue medicine. The date and time of rescue medication administration as well as the name and dosage regimen of the rescue medication must be recorded in the eCRF.

6.6 DOSE MODIFICATION

No IMP dose modification is allowed.

6.7 INTERVENTION AFTER THE END OF THE STUDY

Sponsor will not be responsible for intervention after the EOS Visit. Study intervention after the EOS Visit will be at the discretion of Investigator or treating physician.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

7.1.1 Definitive discontinuation

In rare instances, it may be necessary for a participant to permanently discontinue study intervention. If study intervention is permanently discontinued, the participant will remain in the study to be evaluated for safety and efficacy. See the SoA (Section 1.3) for data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed.

The participants may withdraw from treatment with the IMP if he or she decides to do so at any time for any reason, or based on the Investigator's decision. All efforts should be made to document the reason(s) for study intervention discontinuation and recorded in the eCRF.

Participants must be permanently withdrawn from the study intervention for the following reasons:

- At their own request or at the request of their legally authorized representative (legally authorized representative means an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective participant to participate in the procedure(s) involved in the research).
- If, in the Investigator's opinion, continuation in the study would be detrimental to the participant's well-being.
- At the specific request of the Sponsor.
- If the participant is treated with the specific prohibited medications mentioned in Section 6.5.
- If the participant misses 2 consecutive IMP doses.
- In the event of a protocol deviation, at the discretion of the Investigator or the Sponsor.
- Any code broken at the requested of the Investigator.
- Pregnancy.
- Anaphylactic reactions or systemic allergic reactions that are related to IMP and require treatment (see Section 10.9).
- Diagnosis of a malignancy during the study, excluding carcinoma in situ of the cervix, or squamous or basal cell carcinoma of the skin.
- Any opportunistic infection or other infections whose nature or course may suggest an immunocompromised status (see Section 10.10).
- Serum alanine aminotransferase (ALT) >3 ×upper limit of normal (ULN) and total bilirubin >2 × ULN (see Section 10.6).

- Serum ALT >5 ×ULN if baseline ALT ≤2 ×ULN, or ALT >8 × ULN if baseline ALT >2 × ULN (see Section 10.6).

If a clinically significant finding is identified (including, but not limited to changes from baseline in QT interval corrected using Fridericia's formula [QTcF] after enrollment), the Investigator or qualified designee will determine if the participant can continue in the study and if any change in participant management is needed. This review of the electrocardiogram (ECG) printed at the time of collection must be documented. Any new clinically relevant finding should be reported as an AE.

Any abnormal laboratory value or ECG parameter will be immediately rechecked for confirmation within a reasonable timeframe as assessed by the Investigator before making a decision of definitive discontinuation of the IMP for the concerned participant.

Handling of participants after definitive intervention discontinuation

If participants no longer wish to take the IMP, they will be encouraged to remain in the study.

The Investigators should discuss with them key visits to attend. The value of all their study data collected during their continued involvement will be emphasized as important to the public health value of the study.

Participants who withdraw from the study intervention should be explicitly asked about the contribution of possible AEs to their decision, and any AE information elicited must be documented.

Participants will be followed-up according to the study procedures specified in this protocol up to the scheduled date of study completion, or up to recovery or stabilization of any AE to be followed-up as specified in this protocol, whichever comes last.

Participants who discontinue the study intervention prematurely (prior to completing the treatment period) will perform, as soon as possible, the Early Termination Visit with all the assessments normally planned for the EOT Visit (refer to Section 8.1.1), to assure a complete clinical assessment in close temporal proximity to the premature termination of study intervention is available. A CT scan can be done at time of Early Termination Visit if the previous CT scan is performed at least 4 months ago. Otherwise, the CT scan should be performed at the next scheduled timepoint (ie, Week 24).

In addition, and to allow assessment of participant outcomes over the stipulated study period, participants will be asked and encouraged to complete all remaining study treatment visits and participate in all assessments according to the visit schedule with a ±3 days window. Under exceptional circumstances when a participant cannot come to the site for a scheduled visit, a phone contact can be made. During the phone contact, at least information about AEs, concomitant medication, and the status of CRSsNP should be collected.

All cases of definitive intervention discontinuation must be recorded by the Investigator in the appropriate pages of the eCRF when considered as confirmed.

7.1.2 Temporary discontinuation

Temporary intervention discontinuation may be considered by the Investigator because of suspected AEs. For all temporary intervention discontinuations, duration should be recorded by the Investigator in the appropriate pages of the eCRF.

Temporary intervention discontinuation decided by the Investigator corresponds to at least 1 dose not administered to the participant. Following a temporary interruption or missed dose, the study intervention should be reinitiated at the next scheduled administration, maintaining the planned dose.

If 2 consecutive IMP doses have been missed, the study intervention will be definitively discontinued (see Section 7.1.1). Investigator must contact the participant to instruct not to take any subsequent injection.

7.1.2.1 Rechallenge

Reinitiation of intervention with the IMP will be done under close and appropriate clinical/and or laboratory monitoring once the Investigator considers this to be appropriate according to his/her best medical judgment that the responsibility of the IMP(s) in the occurrence of the concerned event was unlikely and if the selection criteria for the study are still met (refer to Section 5).

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

- A participant may withdraw from the study at any time at his/her own request or if his/her caregiver(s) or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons. This is expected to be uncommon.
- At the time of discontinuing from the study, if possible, an early follow-up/EOS Visit should be conducted, as shown in the SoA (Section 1.3).
- The participant will be permanently discontinued both from the study intervention and from the study at that time.
- If the participant withdraws consent for the disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested; and the Investigator must document this in the site study records.
- All study withdrawals should be recorded by the Investigator in the appropriate screens of the eCRF and in the participant's medical records. In the medical record, at least the date of the withdrawal and the reason should be documented.
- In addition, a participant may withdraw his/her consent to stop participating in the study. A participant's decision to discontinue intervention should be distinguished from withdrawal of consent for follow-up visits and from withdrawal of consent for non-participant contact follow-up, eg, medical record checks. The site should document any case of withdrawal of consent.

Participants who have withdrawn from the study cannot be rerandomized (treated) in the study. Their inclusion and intervention numbers must not be reused.

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- If the participant continues to be unreachable, he/she will be considered to have withdrawn from the study.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 1 (Section 10.1).

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA (Section 1.3). Protocol waivers or exemptions are not allowed.
- Adherence to the study design requirements, including those specified in the SoA (Section 1.3), is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA (Section 1.3).
- Assessments/procedures should be conducted in the following order:
  - CRSsNP sinonasal symptom diary (nasal congestion, loss of sense of smell, rhinorrhea, facial pain/pressure, and headache symptoms);
  - SNOT-22;
  - Rhinosinusitis severity VAS;
  - PGIS; PGIC; EQ-5D-5L;
  - ACQ-6 (in participants with asthma);
  - Investigator assessments (smell test [UPSIT], HCRU/P, spirometry [baseline and subsequently in participants with asthma], physical examination, AE/SAEs, concomitant medications, nasal endoscopy (V1 only), nasal secretion, nasal brushing, sinus CT scan);
  - Laboratory assessments (including sample collection for ADA, PK, biomarker, and optional DNA and RNA);
  - And, administration of IMP.
- Patient-Reported Outcome (PRO) questionnaires should be completed by the participants before the consultation and/or clinical tests in a quiet place (at home in e-diary and at clinic). The questionnaires should be completed by the participants themselves, independently from their physician, the study nurse, or any other medical personnel, and without any help from friends or relatives.
- The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed approximately 179 mL. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.
- In light of the public health emergency related to COVID-19 (or in case of any other public health emergency), the continuity of clinical study conduct and oversight may require implementation of temporary or alternative mechanisms, such as phone contact,

virtual visits, online meetings, use of local clinic or laboratory locations, and home visits by skilled staff. Implementation of such mechanisms may differ country by country, depending on country regulations and local business continuity plans. Additionally, no waivers to deviate from protocol enrollment criteria due to COVID-19 (or any other pandemic) will be granted. All temporary mechanisms utilized, and deviations from planned study procedures are to be documented as being related to COVID-19 (or any other public health emergency) and will remain in effect only for the duration of the public health emergency.

8.1 EFFICACY ASSESSMENTS

8.1.1 Computerized Tomography Scans using Lund-Mackay

Computerized tomography scans using the LMK allows the assessment of sinus opacification (37).

The CT scan LMK staging system represents the most widely established method of sinus CT scoring in clinical trials. The LMK total score is based on assessment of the CT scan findings for each sinus area (maxillary, anterior ethmoid, posterior ethmoid, sphenoid, and frontal sinus on each side). The extent of mucosal opacification is rated on a 3-point scale ranging from 0 = normal to 2 = total opacification. In addition, the ostiomeatal complex is graded as 0 = not occluded or 2 = occluded. The maximum score is therefore 12 per side for a maximum total score of 24, corresponding to the sum of all sinuses and the ostiomeatal unit.

This scoring system has been validated in several studies (37, 38, 39).

The CT scans should be performed anytime during the screening period before first administration of IMP at Visit 2 (baseline CT data), Visit 5 (Week 24). The Visit 7 (Week 52) CT scan is optional due to variable treatment period. Whenever possible a cone beam CT scan should be utilized. In countries for which a specific approval procedure for the CT scan is required by a different committee than the local IEC/IRB, a 4-month window is required between 2 CT scans. If a participant needs to be rescreened or is terminated early from the study intervention, the repeated CT scan or following CT scan must be done over a 4-month restriction window. If Participant who discontinue the study intervention prematurely, the CT scan will be performed as soon as possible, with all other assessments normally planned in EOT Visit as long as between 2 CT scans can meet a 4-month restriction window. Otherwise, the CT scan can be done in next scheduled visit.

It is recommended to avoid use of OCS as rescue therapy during the Week 20 to Week 24 or the Week 48 to Week 52. If a participant must use OCS during this period to control CRSsNP worsening/acute sinusitis based on Investigator judgment the site should make every efforts to schedule the Week 24 CT scan or the Week 52 CT scan prior to OCS rescue therapy.

The CT scan will be performed locally and reviewed centrally in a pre-specified manner as described in the Image Acquisition Standards (IAS) and Image Interpretation Standards (IIS) (refer Section 1.3).

8.1.2 CRSsNP Sinonasal Symptom Diary, including nasal congestion/obstruction, loss of sense of smell, anterior and posterior rhinorrhea, facial pain/pressure and headache symptoms

The CRSsNP sinonasal symptom diary is designed to assess the severity of CRS sinonasal symptoms on a daily basis. These symptoms include NC/obstruction, anterior rhinorrhea and posterior rhinorrhea, and facial pain/pressure, and loss of smell (39). Each of the individual items of the diary are scored from 0 ("No symptoms") to 3 ("Severe symptoms – symptoms that are hard to tolerate, cause interference with activities or daily living"). Higher scores on the items of the individual symptoms denote greater symptom severity.

The CRSsNP sinus Total Symptom Score (sTSS) is a composite score derived from the following individual items: NC, anterior/posterior rhinorrhea, and facial pain/pressure. The total score ranges from 0 to 9 and consists of the sum of NC, the averaged rhinorrhea item scores, and facial pain/pressure scores. Higher scores on sTSS indicate greater overall symptom severity.

The CRSsNP sinonasal symptom diary also includes an individual item about headache. Headache severity is scored on a scale ranging from 0 ("No symptoms") to 3 ("Severe symptoms – symptoms that are hard to tolerate, cause interference with activities or daily living"). The score is not a part of sTSS.

The CRSsNP sinonasal symptom diary will be administered electronically. The e-diary is used for daily recording of participant's answers to the questionnaires. This device will be dispensed at the Screening Visit (Visit 1), including instructions for use. Participants will be instructed on the use of the device. Recorded information will be downloaded from this device daily. At EOS Visit, the e-diary will be downloaded and returned to the site. On regular basis, the site staff should review on the vendor's website the information downloaded from participants' e-diary. They should particularly check status of the disease as well as compliance to background/rescue therapy and overall e-diary compliance. The site should follow-up with the participant as appropriate.

Participants will complete the CRSsNP sinonasal symptom diary as described in the SoA (Section 1.3).

8.1.3 University of Pennsylvania Smell Identification Test (UPSIT)

The UPSIT is a rapid and easy-to-administer method to quantitatively assess human olfactory function. The test consists of 4 booklets, each containing 10 odorants with one odorant per page. Above each odorant strip is a multiple-choice question with 4 alternative words to describe the odor that the participant is asked to indicate which word best describes the odor. The score ranges from 0 to 40, with 40 being the best possible score. Participant's olfactory function can be classified based on their scores (40). The UPSIT will be procured and used to match to each culture easing participants identifications of the odorant depending on degree of loss of sense of smell.

The clinician will administer and score the UPSIT as described in the SoA (Section 1.3).

8.1.4 Sino-Nasal Outcome Test-22-Items

The SNOT-22 is a PRO questionnaire designed to assess the impact of CRS on participants' HRQoL (41). SNOT-22 has 22 items covering symptoms, social/emotional impact, productivity, and sleep consequences of CRS. The recall period is past 2 weeks. Each item is rated on a 6-point Likert scale response option, ranging from 0 ('No problem') to 5 ('Problem as bad as it can be'). A global score ranging from 0 to 110 is calculated by summing the responses to all items; higher score indicates greater rhinosinusitis-related health burden. The questionnaire is an easy, valid, and reliable tool (41). The minimally important difference that is the smallest change in SNOT-22 score that can be detected by a participant was found to be 8.9 points (41).

The SNOT-22 is provided in Appendix 8 (Section 10.8).

Participants will complete the SNOT-22 as described in the SoA (Section 1.3).

8.1.5 Three-dimensional volumetric measurement of the sinuses

This method is used to calculate: (42)

- The volume of the air (mL)
- The volume of mucosa (mL)
- % occupied by disease
- Thickness of lateral wall

For the analysis, central reading at baseline will be used for comparison with EOT reading. The sites will remove participant-identifying information from the imaging data header prior to sending the imaging data to the central reader. The % change in opacification from baseline to EOT will be calculated.

8.1.6 Rhinosinusitis Severity Visual Analog Scale

The rhinosinusitis severity VAS is used to evaluate the overall severity of the rhinosinusitis (41). It is a recommended scale to determine the participant's disease severity and to guide the treatment for CRS. The participant is asked to answer the following question: "How troublesome are your symptoms of your rhinosinusitis" on a 10-cm VAS from 0 ('not troublesome') to 10 ('worst thinkable troublesome'). Based on their score on the VAS, the severity of rhinosinusitis can be divided into 3 categories as follows:

- Mild = VAS 0 to 3
- Moderate = VAS >3 to 7
- Severe = VAS >7 to 10

The rhinosinusitis severity VAS is provided in in Appendix 8 (Section 10.8).

Participants will complete the rhinosinusitis severity VAS as described in the SoA (Section 1.3).

8.1.7 Asthma Control Questionnaire 6-item version

The asthma control questionnaire 6-items (ACQ-6) was designed to measure both the adequacy of asthma control and the change in asthma control that occurs either spontaneously or as a result of treatment (43). The ACQ-6 has 6 questions that assess the most common asthma symptoms: 1) Frequency in past week awoken by asthma during the night, 2) Severity of asthma symptoms in the morning, 3) Limitation of daily activities due to asthma, 4) Shortness of breath due to asthma, 5) Frequency of wheezing, and 6) Short-acting bronchodilator use.

Participants are asked to recall how their asthma has been during the previous week and to respond to the symptom questions on a 7-point scale (0 = no impairment, 6 = maximum impairment). The questions are equally weighted; and the ACQ-6 global score is the mean of the 6 questions ranging from 0 (totally controlled) to 6 (severely uncontrolled). A higher score indicates lower asthma control. On the 7-point scale of the ACQ-6, a change or difference in score of 0.5 is the smallest change that can be considered clinically important, corresponding to the minimal clinically important difference (MCID) defined by the developer (44). Measurement properties such as reliability and the ability to detect change have been documented in the literature (44).

The ACQ-6 is provided in Appendix 8 (Section 10.8).

Participants with comorbid asthma will complete the ACQ-6 as described in the SoA (Section 1.3).

8.1.8 Patient Global Impression of Severity of CRSsNP and Patient Global Impression of Change of CRSsNP

The Patient Global Impression of Change (PGIC) is a 1-item questionnaire that asks the participant to provide the overall self-assessment of change in their CRSsNP on a 7-point scale compared to just before the participant started taking the study treatment. The response choices are: 0 = “Very much better”, 1 = “Moderately better”, 2 = “A little better”, 3 = “No change”, 4 = “A little worse”, 5 = “Moderately worse”, and 6 = “Very much worse”.

The Patient Global Impression of Severity (PGIS) is a 1-item questionnaire that asks participants to provide the overall self-assessment of their CRSsNP severity on a 4-point scale for the past week. Response choices are: 1 = “None”, 2 = “Mild”, 3 = “Moderate”, and 4 = “Severe”.

The PGIS and PGIC are provided in Appendix 8 (Section 10.8).

Participants will complete the 2 items as described in the SoA (Section 1.3).

8.1.9 EuroQol-5 dimensions questionnaire

The EuroQol-5 dimensions (EQ-5D) is a standardized PRO measure of health status developed by the EuroQol Group in order to provide a simple, generic measure of health for clinical and economic appraisal. The adult version of the questionnaire is adapted to participants age 16 and older and can be used for participants aged 12-15 as stated in the EQ-5D user guide. The EQ-5D

consists of 2 parts: the descriptive system and the EuroQol-VAS. The EQ-5D-5L descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 levels of perceived problems: "no problem", "slight problems", "moderate problems", "severe problems", and "extreme problems" (45). The respondent is asked to indicate his/her health state by ticking (or placing a cross) in the box against the most appropriate statement in each of the 5 dimensions; this results in a 1-digit number expressing the level for that dimension. The digits for 5 dimensions can be combined in a 5-digit number describing the respondent's health state. The EQ-VAS records the respondent's self-rated health on a vertical, VAS where the endpoints are labeled "best imaginable health state (100)" and "worst imaginable health state (0)". This information can be used as a quantitative measure of health outcome as judged by the individual respondents. The recall period of the questionnaire is "today".

The EQ-5D-5L is provided in Appendix 8 (Section 10.8).

Participants will complete the questionnaire as described in the SoA (Section 1.3).

8.1.10 Health care resource utilization and missed days at work/missed days at school

A questionnaire about health care resource utilization and productivity (missed days of school/workdays) will be collected by the Investigator for all participants throughout the study through eCRF.

8.1.11 CRSsNP Worsening/Acute Sinusitis

The CRSsNP worsening/acute sinusitis is defined as worsening of any of CRS symptoms that requires initiation of rescue therapy as assessed by Investigator.

8.1.12 Spirometry

Spirometry will be performed at the local level (study site or another facility) in the morning after withholding the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours and LAMA and LABA for 24 hours. The FEV_1, forced vital capacity (FVC), and forced expiratory flow at 25% to 75% of forced vital capacity (FEF 25 to 75) will be determined at the designated treatment visits. The results of FEV1 (% of predicted normal), FVC and FEF 25 to 75 should be recorded in the eCRF during the screening period (before V2) for all participants and in participants with asthma for the other scheduled visits during the randomized treatment period. Whenever possible, the same spirometer and standard spirometric techniques, including calibration, will be used to perform spirometry at all visits and, the same person should perform the measurements.

8.1.13 [redacted]

[redacted]

[redacted] (Section 1.3).

8.2 SAFETY ASSESSMENTS

Planned time points for all safety assessments are provided in the SoA (Section 1.3).

8.2.1 Physical examinations

- A complete physical examination will include, at a minimum, assessments of the skin (full body skin examination), nasal cavities, eyes, ears, respiratory, cardiovascular, gastrointestinal, neurological, lymphatic, and musculoskeletal systems.
- Participants should be disrobed and provided with a hospital gown before the skin examination.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.
- Any new finding or worsening of previous finding should be reported as a new adverse event.

8.2.2 Vital signs

Vital signs will be measured in a semi-supine or sitting position after 5 minutes rest and will include temperature, systolic and diastolic blood pressure, pulse, and respiratory rate.

Blood pressure and pulse measurements should be assessed using the same arm with a completely automated device. Manual techniques will be used only if an automated device is not available.

Body weight (kg) will be measured at Screening (Visit 1), Baseline (Visit 2) and following visits. Height (cm) will be measured only at Screening (Visit 1).

8.2.3 Electrocardiograms

As defined in SoA (Section 1.3), single 12-lead ECG will be obtained for screening purpose only.

8.2.4 Clinical safety laboratory assessments

- See Appendix 2 (Section 10.2) for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.
- The Investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those that are not associated with the underlying disease,

unless judged by the Investigator to be more severe than expected for the participant's condition.

- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 12 weeks after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator or Sponsor or Sponsor representative(s).
  - If such values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified, and the Sponsor notified,
  - All protocol-required laboratory assessments, as defined in Appendix 2 (Section 10.2), must be conducted in accordance with the laboratory manual and the SoA (Section 1.3),
  - If laboratory values from non-protocol-specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the Investigator (eg, SAE, AE or dose modification), then the results must be recorded in the eCRF.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

Adverse event will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study intervention (see Section 7).

8.3.1 Time period and frequency for collecting AE and SAE information

All SAEs will be collected from the signing of the informed consent form (ICF) until the EOS Visit at the time points specified in the SoA (Section 1.3).

All AEs will be collected from the signing of the ICF at the time points specified in the SoA (Section 1.3).

All SAEs and AESI will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3 (Section 10.3). The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AEs or SAEs after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably

related to the study intervention or study participation, the Investigator must promptly notify the Sponsor.

8.3.2 Method of detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3 (Section 10.3).

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3 Follow-up of AEs and SAEs

After the initial AE/AESI/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. At the prespecified study end-date, all SAEs, and AEs of special interest (as defined in Section 8.3.6), will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Appendix 3 (Section 10.3).

8.3.4 Regulatory reporting requirements for SAEs

- Prompt notification by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and Investigators.
- Adverse events that are considered expected will be specified in the reference safety information.
- Suspected unexpected serious adverse reactions (SUSARs) are reported to regulatory authorities, Investigators, and IRBs/IECs as follows:
- For SUSARs that are life-threatening or result in death, reporting is no later than 7 days after first knowledge by the Sponsor, with all relevant follow-up information subsequently reported within an additional 8 days,
- For SUSARs, other than those that are life-threatening or result in death, reporting is no later than 15 days after first knowledge by the Sponsor.
- An Investigator who receives an Investigator safety report describing an SAE, SUSAR or any other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements. It is the responsibility of the Sponsor to assess whether an event meets the criteria for a SUSAR and, therefore, is expedited to regulatory authorities.

8.3.5 Pregnancy

- Details of all pregnancies in female participants and female partners of male participants will be collected after the start of study intervention and until the outcome has been determined.
- If a pregnancy is reported, the Investigator should inform the Sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4 (Section 10.4).
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs

8.3.6 Adverse event of special interest

Adverse event of special interest

An adverse event of special interest (AESI) is an AE (serious or nonserious) of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and immediate notification by the Investigator to the Sponsor is required. Such events may require further investigation in order to characterize and understand them. Adverse events of special interest may be added, modified, or removed during a study by protocol amendment.

For these AESIs, the Sponsor will be informed immediately (ie, within 24 hours), per SAE notification described in Section 10.3, even if not fulfilling a seriousness criterion, using the corresponding pages in the eCRF (to be sent) or screens in the eCRF. Adverse event of special interests for this study include:

- Anaphylactic reactions.
- Systemic hypersensitivity reactions.
- Helminthic infections.
- Any severe type of conjunctivitis or blepharitis.
- Keratitis.
- Clinically symptomatic eosinophilia (or eosinophilia associated with clinical symptoms).
- Pregnancy of a female participant entered in a study as well as pregnancy occurring in a female partner of a male participant entered in the study with IMP:
  - Pregnancy occurring in a female participant entered in the clinical trial or in a female partner of a male participant entered in the clinical trial will be qualified as an SAE only if it fulfills one of the seriousness criteria,
  - In the event of pregnancy in a female participant, IMP should be discontinued,
  - Follow-up of the pregnancy in a female participant or in a female partner of a male participant is mandatory until the outcome has been determined,
  - Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

- Significant ALT elevation:
  - ALT >5 × ULN in participants with baseline ALT ≤2 × ULN,
  - OR
  - ALT >8 × ULN if baseline ALT >2 × ULN.
- Symptomatic overdose (serious or nonserious) with IMP/NIMP
  - An overdose (accidental or intentional) with the IMP is an event suspected by the Investigator or spontaneously notified by the participant and defined as at least twice the intended dose during an interval of less than 11 days. The circumstances (ie, accidental or intentional) should be clearly specified in the verbatim and symptoms, if any, entered on separate AE forms,
  - An overdose (accidental or intentional) with any NIMP is an event suspected by the Investigator or spontaneously notified by the participant and defined as at least twice the maximum prescribed daily dose, within the intended therapeutic interval. The circumstances (ie, accidental or intentional) should be clearly specified in the overdose form.

8.3.7 Guidelines for reporting product complaints

Any defect in the IMP must be reported as soon as possible by the Investigator to the monitoring team that will complete a product complaint form within required timelines.

Appropriate information (eg, samples, labels or documents like pictures or photocopies) related to product identification and to the potential deficiencies may need to be gathered. The Investigator will assess whether or not the quality issue has to be reported together with an AE or SAE.

8.4 TREATMENT OF OVERDOSE

Overdose is an AESI (defined in Section 8.3.6). No antidote is available for dupilumab. The Sponsor does not recommend specific treatment for an overdose.

In the event of an overdose, the Investigator/treating physician should:

1. Provide symptomatic care.
2. Contact the Sponsor or Sponsor representative(s) immediately.
3. Closely monitor the participant for any AE/SAE and laboratory abnormalities until dupilumab can no longer be detected systemically.
4. Obtain a plasma sample for PK analysis as soon as possible if requested by the Sponsor or Sponsor representative(s) (determined on a case-by-case basis).
5. Document appropriately in the eCRF.

Decisions regarding dose interruptions or modifications will be made by the Investigator in consultation with the Sponsor or Sponsor representative(s) based on the clinical evaluation of the participant.

8.5 PHARMACOKINETICS AND IMMUNOGENICITY ASSESSMENTS

8.5.1 Systemic drug concentration and anti-drug antibodies

8.5.1.1 Sampling time

Blood samples will be collected for determination of functional dupilumab and anti-dupilumab antibodies in serum as specified in the SoA (Section 1.3). Special procedures for collection, storage, and shipping of serum are described in separate operational manuals. The date of collection should be recorded in the eCRF.

8.5.1.2 Handling procedures

Special procedures for collection, storage, and shipping of serum are described in separate operational manuals. An overview of handling procedure for samples used in the determination of systemic drug concentration and anti-drug antibody (ADA) is provided in Table 3.

Table 3 - Summary of handling procedures

Sample type	Functional dupilumab	Anti-dupilumab antibody
[redacted]		

8.5.1.3 Bioanalytical method

Serum PK and ADA samples will be analyzed using validated methods as described in Table 4.

Table 4 - [redacted]

[redacted]

Note: In the event of any suspected SAE, any AE of severe injection site reaction lasting longer than 24 hours, or any AESI like anaphylactic reaction hypersensitivity, PK and ADA samples will be collected at or near the onset of the event. The exact date and time of sample collection must be recorded and entered into the database by the central laboratory. An unscheduled systemic drug concentration page in the eCRF must be completed as well.

Specifically for PK, any changes in the timing or addition of time points for any planned study assessments must be documented and approved by the relevant study team member and then archived in the Sponsor and site study files but will not constitute a protocol amendment. The IRB/IEC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICF.

8.6 PHARMACODYNAMICS

[redacted]

[redacted] (Section 1.3)

[redacted]

[redacted] (Section 1.3).

- [redacted]

[redacted]

Section 8.7.

8.7 GENETICS

Pharmacogenetic/pharmacogenomic testing from whole blood samples is optional and voluntary. Written informed consent must be obtained before sampling.

For those participants who consent to the optional pharmacogenetic/pharmacogenomic sample collection section of the ICF, blood samples for exploratory genetic analysis of DNA or RNA will be collected at the study visit as specified in the SoA (Section 1.3), and these samples will be stored for future analysis. Specific procedures for collection, storage and shipping of pharmacogenetic/pharmacogenomic samples will be provided in a lab manual.

In the event of DNA extraction failure, a replacement genetic blood sample may be requested from the participant. Signed informed consent will be required to obtain a replacement sample unless it was included in the original consent.

For participant(s) who have consented to it, the samples that are archived, unused or left over after planned testing may be used for additional research purposes refer to Appendix 5 (Section 10.5).

8.8 [redacted]

[redacted] Section 8.6 and Section 8.7.

[redacted]

[redacted]

8.9 MEDICAL RESOURCE UTILIZATION AND HEALTH ECONOMICS

Health care resource utilization and productivity (missed days of school/workdays) are described in Section 8.1.10.

8.10 USE OF BIOLOGICAL SAMPLES AND DATA FOR FUTURE RESEARCH

Future research may help further the understanding of disease subtypes, disease biology, related conditions, drug response and toxicity, and can help identify new drug targets or biomarkers that predict participant response to treatment. Therefore, data and biological samples will be stored and used for future research when consented to by participants (see Section 10.1.3) unless prohibited by local laws or IRBs/IECs (in such case, consent for future use of sample will not be included in the local ICF).

For participants who consent to the storage and use of their data and remaining and/or extra clinical samples, data and samples may be used after the study ends for future research related either to the drug, the mechanism of action, and the disease or its associated conditions. Such research may include, but is not limited to, performing assessments on DNA, RNA, proteins, or metabolites. If future research on genetic material is performed, this will also be limited to the purpose of addressing research questions related to the drug, the mechanism of action, the disease or its associated conditions.

In the event future research is conducted for other purposes, the study participants will be informed of those purposes and will be given means to object to those research projects.

Data and samples will be used in compliance with the information provided to participants in the ICF Part 2 (future research).

All study participant data and samples will be coded such that no participant direct identifiers will be linked to them. Coded data and samples may be transferred to a Sponsor site (or a subcontractor site), which may be located outside of the country where the study is conducted. The Sponsor adopts safeguards for protecting participant confidentiality and personal data (see Section 10.1.4).

The samples will be stored for a maximum of 15 years after the end of the study. Any samples remaining at the end of retention period will be destroyed. If a participant requests destruction of his/her samples before the end of the retention period, the Investigator must notify the Sponsor (or its contract organization) in writing. In such case, samples will be destroyed and related coded data will be anonymized unless otherwise required by applicable laws.

Study participant coded data will be stored for future research for up to 25 years after the end of the study. If data are still considered of important scientific value after this period, coded data already available will be anonymized unless otherwise required by applicable laws (the same will apply to the data of a study participant who has requested the destruction of his/her samples).

Participant's coded data sets provided to researchers for a specific research project will be available to the researchers for a maximum of 2 years after the end of their specific project (end of project is defined by publication of the results or finalization of the future research project report).

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

No statistical hypotheses will be tested in this study.

9.2 SAMPLE SIZE DETERMINATION

Sample size calculation was performed to ensure reasonable accuracy for the estimation of the primary endpoint in participants treated with dupilumab with screening blood eosinophil count ≥300 cells/mm^3. With a 1:1 randomization ratio, a standard deviation (SD) of 5 and a dropout rate of 10%, a sample size of approximately 30 participants with screening blood eosinophil count ≥300 cells/mm^3 will provide a half-width of approximately less than 3 for the 2-sided 95% CI in the dupilumab group which is deemed reasonable.

In addition, it is planned to include approximately 40 participants with screening blood eosinophil count <300 cells/mm^3. Thus, the planned total sample size is approximately 35 participants per arm.

9.3 POPULATIONS FOR ANALYSES

The following populations are defined in Table 5 for this study. The primary population of the efficacy endpoints will be the ITT population with screening blood eosinophil count ≥ 300 cells/mm^3.

Table 5 - Populations for analyses

Population	Description
Screened	All participants who sign the ICF.
Randomized	The randomized population includes all participants with a treatment kit number allocated and recorded in the IRT database, and regardless of whether the treatment kit was used or not. Participants treated without being randomized will not be considered randomized and will not be included in any efficacy population.
Intent-to-treat (ITT)	All randomized participants analyzed according to the treatment group allocated by randomization regardless if treatment kit is used or not.
ITT with screening blood eosinophil count ≥300 cells/mm^3	All randomized participants with screening blood eosinophil count ≥300 cells/mm^3 analyzed according to the treatment group allocated by randomization regardless if treatment kit is used or not.
Safety	All participants randomly assigned to study intervention and who take at least 1 dose of study intervention. 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 in the safety population as randomized. For participants who accidentally receive different study intervention from the planned, the actual intervention allocation for as-treated analysis will be the dupilumab group.

Population	Description
Pharmacokinetic (PK)	The PK population includes all participants in the safety population with at least 1 non-missing result for functional dupilumab concentration in serum after the first dose of the study intervention. Participants will be analyzed according to the intervention actually received.
Anti-drug antibody (ADA)	ADA population includes all participants in the safety population who have at least 1 non-missing result in the ADA assay after the first dose of the study intervention. Participants will be analyzed according to the intervention actually received.

ADA: anti-drug antibody; ICF: informed consent form; IRT: interactive response technology; ITT: intent-to-treat; PK: pharmacokinetic

9.4 STATISTICAL ANALYSES

The statistical analysis plan (SAP) will include more technical and detailed descriptions of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and secondary endpoints.

9.4.1 General considerations

The baseline value is defined generally as the last available value before randomization. For endpoints collected on the daily CRSsNP sinonasal symptom diary, baseline is defined as the average of the scores in the 7 days prior to randomization.

9.4.2 Primary endpoint(s)

The primary estimand for the primary endpoint is the hypothetical/treatment policy strategy as described in Table 6.

Table 6 - Summary of primary estimand for primary endpoint

Endpoint Category	Estimands			
	Endpoints	**Population**	**Intercurrent event(s) handling strategy and missing data handling**	**Population-level summary**
Primary objective: To evaluate the efficacy of dupilumab as assessed by the reduction at Week 24 in sinus opacification on computerized tomography (CT) scan in the dupilumab group only				
Primary endpoint	Change from baseline in LMK score at Week 24	ITT with screening blood eosinophil count ≥ 300 cells/mm^3	The intercurrent events (IEs) will be handled as follows: • Undergoing sinonasal surgery for CRSsNP or taking SCS for any reason prior to Week 24: data after the IE will be set to missing and the worst post-baseline value on or before the time of the IE will be used to impute missing Week 24 value (WOCF). For participants with no post-baseline values, the baseline value will be used (hypothetical strategy).	Descriptive statistics and 95% CI in the dupilumab group will be provided.

Endpoint Category	Estimands			
	Endpoints	Population	Intercurrent event(s) handling strategy and missing data handling	Population-level summary
			• Taking other prohibited/rescue medications: all data collected after use will be used in the analysis (treatment policy strategy). • Discontinuing the study intervention: all data collected after discontinuation will be used in the analysis (treatment policy strategy). Missing data will not be imputed.	

In the primary analysis approach for the primary endpoint, for participants who undergo sinonasal surgery for CRSsNP or take SCS for any reason, data collected after surgery or initiation of SCS will be set to missing and the worst post-baseline value on or before the time of surgery or SCS will be used to impute missing Week 24 value (ie, WOCF approach). For participants with no post-baseline values, the baseline value will be used. Participants who discontinue the study intervention prematurely are encouraged to follow the planned clinical visits and, in these participants, who did not undergo surgery or receive SCS, all data collected after study intervention discontinuation will be used in the analysis. No missing data will be imputed. Descriptive statistics (number of participants, mean, SD, median, minimum and maximum) and 95% CI in the dupilumab group, will be provided.

Supplementary analyses

Supplementary analyses to assess the robustness of intercurrent event handling may be performed. Details will be provided in the SAP.

9.4.3 Secondary endpoint(s)

- The change from baseline to Week 24 in the secondary endpoints will be analyzed using the same analysis approach as for the primary endpoint. For endpoints comparing dupilumab to placebo, 95% CI of the treatment difference will be provided.

9.4.4 Tertiary/exploratory endpoint(s)

Analysis of exploratory endpoints will be detailed in the SAP.

9.4.5 Other safety analyses

All safety analyses will be performed on the safety population. The summary of safety results will be presented by treatment group.

Analyses of Adverse Events

Adverse event incidence tables will present by system organ class (SOC) (sorted by internationally agreed order) and preferred term (PT), the number (n) and percentage (%) of participants experiencing an AE. Multiple occurrences of the same event in the same participant will be counted only once in the tables within a treatment phase. The denominator for computation of percentages is the safety population within each treatment group.

The proportion of participants with at least 1 treatment-emergent adverse event (TEAE), treatment-emergent serious adverse event (TESAE), TEAE leading to death, and TEAE leading to permanent study intervention discontinuation will be tabulated by treatment group. In addition, TEAEs will be described according to maximum intensity and relation to the study intervention. Serious AEs and AEs leading to study discontinuation that occur outside the treatment-emergent period will be summarized separately.

The incidence of each type of AESI and other AE groupings will be tabulated by treatment group. For each type of AESI, the following analysis will be generated:

- A summary of the number (%) of participants with:
  - Any TEAE,
  - Any SAE (regardless of treatment-emergent status),
  - Any TESAE,
  - Any AE leading to death,
  - Any TEAE leading permanent study intervention discontinuation,
  - Any TEAE related to study intervention reported by the Investigator,
  - Any TEAE by maximum intensity, corrective treatment, and final outcome.

The method to identify AESIs and other AE groupings will be specified in the SAP.

The following death summaries will be generated:

- Number (%) of participants who died by study period (TEAE, on study) summarized on the safety population by treatment received.
- Death in nonrandomized participants or randomized and not treated participants.
- TEAE leading to death (death as an outcome on the AE eCRF page as reported by the Investigator) by primary SOC and PT showing number (%) of participants.

Analyses of laboratory and vital signs parameters

Results and change from baseline for the laboratory and vital signs parameters will be summarized by treatment group for baseline and each post baseline time point, endpoint,

minimum and maximum value. Summary statistics will include number of participants, mean, standard deviation, median, Q1, Q3, minimum, and maximum.

The following definitions will be applied to laboratory and vital signs parameters.

- The potentially clinically significant abnormality (PCSA) values are defined as abnormal values considered medically important by the Sponsor according to predefined criteria/thresholds based on literature review and defined by the Sponsor.
- PCSA criteria will determine which participants had at least 1 PCSA during the treatment-emergent period, taking into account all evaluations performed during the treatment-emergent period, including unscheduled or repeated evaluations. The number of all such participants will be the numerator for the treatment-emergent PCSA percentage.

The proportion of participants who had at least one incidence of PCSA at any time during the treatment-emergent period will be summarized by treatment group. Shift tables showing changes with respect to the baseline status will be provided.

9.4.6 Other analyses

Pharmacokinetic, immunogenicity, PD, and biomarker exploratory analyses will be described in the SAP finalized before the database lock. The population PK and PD analyses might be presented separately from the main clinical study report (CSR).

Data collected regarding the impact of the COVID-19 or other pandemics on the participants will be summarized (eg, discontinuation due to COVID-19). Any additional analyses and methods required to investigate the impact of COVID-19 or other events requiring public health emergency on the efficacy (eg, missing data due to COVID-19) and safety will be detailed in the SAP.

9.5 INTERIM ANALYSES

No interim analysis is planned.

9.6 TIMING OF STATISTICAL ANALYSES

The database lock will be performed after all participants have completed the end of study visit. Final analyses in the CSR will be based on all data collected up to this database lock.

9.7 DATA MONITORING COMMITTEE (DMC)

Due to the extensive safety record of the post-marketed IMP (dupilumab), it is not planned to have a Data Monitoring Committee for this study.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 APPENDIX 1: REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 Regulatory and ethical considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and the applicable amendments and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines,
  - Applicable ICH Good Clinical Practice (GCP) Guidelines,
  - Applicable laws and regulations (eg, data protection law as General Data Protection Regulation - GDPR).
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The Investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC Determining whether an incidental finding should be returned to a participant and, if it meets the appropriate criteria, to ensure the finding is returned (an incidental finding is a previously undiagnosed medical condition that is discovered unintentionally and is unrelated to the aims of the study for which the tests are being performed). The following should be considered when determining the return of an incidental finding:
    - The return of such information to the study participant (and/or his/her designated healthcare professional, if so designated by the participant) is consistent with all applicable national, state, or regional laws and regulations in the country where the study is being conducted, and,
    - The finding reveals a substantial risk of a serious health condition or has reproductive importance, AND has analytical validity, AND has clinical validity,
    - The participant in a clinical study has the right to opt out of being notified by the Investigator of such incidental findings. In the event that the participant has opted out of being notified and the finding has consequences for other individuals, eg, the finding relates to a communicable disease, Investigators should seek independent ethical advice before determining next steps.

- In case the participant has decided to opt out, the Investigator must record in the site medical files that she/he does not want to know about such findings.

- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures,
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

As applicable, according to Directive 2001/20/EC, the Sponsor will be responsible for obtaining approval from the Competent Authorities of the EU Member States and/or Ethics Committees, as appropriate, for any amendments to the clinical trial that are deemed as "substantial" (ie, changes which are likely to have a significant impact on the safety or physical or mental integrity of the clinical trial participants or on the scientific value of the trial) prior to their implementation.

10.1.2 Financial disclosure

Investigators and sub-Investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3 Informed consent process

- The Investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

Participants who are rescreened are required to sign a new ICF.

The ICF contains 2 separate sections that addresses the use for research of participants' data and/or samples (remaining mandatory samples or new samples collected for optional research).

Optional exploratory research must be detailed in the section “Optional tests/procedures” and future research is to be defined in Core Study Informed Consent Form (CSICF) Part 2. Each option is subject to an independent consent and must be confirmed by ticking a checkbox in CSICF Part 3. The Investigator or authorized designee will explain to each participant the objectives of the exploratory research and why data and samples are important for future research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a participant's agreement to allow any remaining specimens to be used for exploratory research. Participants who decline to participate in this optional research will not provide this separate signature.

10.1.4 Data protection

All personal data collected related to participants, Investigators, or any person involved in the study, which may be included in the Sponsor’s databases, shall be treated in compliance with all applicable laws and regulations including the GDPR (General Data Protection Regulation). The study Sponsor is the Sanofi company responsible for ensuring compliance with this matter, when processing data from any individual who may be included in the Sanofi databases, including Investigators, nurses, experts, service providers, Ethics Committee members, etc.

When archiving or processing personal data pertaining to the Investigator and/or to the participants, the Sponsor takes all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

Protection of participant data

Data collected must be adequate, relevant and not excessive, in relation to the purposes for which they are collected. Each category of data must be properly justified and in line with the study objective.

Participant race and ethnicity will be collected in this study because these data are required by regulatory agencies (eg, on Afro American population for the FDA or on Japanese population for the Pharmaceuticals and Medical Devices Agency in Japan). They will not be collected in the countries where this is prohibited by local regulation.

- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor or its service providers will be identifiable only by the unique identifier; participant names or any information which would make the participant identifiable will not be transferred to the Sponsor.
- The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant as described in the informed consent.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

- Participants must be informed that their study-related data will be used for the whole "drug development program", ie, for this trial as well as for the following steps necessary for the development of the investigational product, including to support negotiations with payers and publication of results.

Protection of data related to professionals involved in the study

- Personal data (eg, contact details, affiliation(s) details, job title and related professional information, role in the study, professional resume, training records) are necessary to allow Sanofi to manage involvement in the study and/or the related contractual or pre-contractual relationship. They may be communicated to any company of the Sanofi group ("Sanofi") or to Sanofi service providers, where needed.
- Personal data can be processed for other studies and projects. At any time, objection to processing can be made by contacting the Sanofi Data Protection Officer (link available at Sanofi.com).
- In case of refusal to the processing of personal data by or on behalf of Sanofi, it will be impossible to involve the professionals in any Sanofi study. In case the professionals have already been involved in a Sanofi study, they will not be able to object to the processing of their personal data as long as they are required to be processed by applicable regulations. The same rule applies in case the professionals are listed on a regulatory agencies disqualification list.
- Personal data can be communicated to the following recipients:
  - Personnel within Sanofi or partners or service providers involved in the study,
  - Judicial, administrative and regulatory authorities, in order to comply with legal or regulatory requirements and/or to respond to specific requests or orders in the framework of judicial or administrative procedures. Contact details and identity may also be published on public websites in the interest of scientific research transparency.
- Personal data may be transferred towards entities located outside the Economic European Area, in countries where the legislation does not necessarily offer the same level of data protection or in countries not recognized by the European Commission as offering an adequate level of protection. Those transfers are safeguarded by Sanofi in accordance with the requirement of European law including, notably:
  - The standard contractual clauses of the European Commission for transfers towards our partners and service providers,
  - Sanofi's Binding Corporate Rules for intra-group transfers.
- Professionals have the possibility to lodge a complaint with Sanofi leading Supervisory Authority, the "Commission Nationale de l'Informatique et des Libertés" (CNIL) or with any competent local regulatory authority.
- Personal data of professionals will be retained by Sanofi for up to thirty (30) years, unless further retention is required by applicable regulations.

- In order to facilitate the maintenance of Investigators personal data, especially if they contribute to studies sponsored by several pharmaceuticals companies, Sanofi participates in the Shared Investigator Platform (SIP) and in the TransCelerate Investigator Registry (IR) project (https://transceleratebiopharmainc.com/initiatives/investigator-registry/). Therefore, personal data will be securely shared by Sanofi with other pharmaceutical company members of the TransCelerate project. This sharing allows Investigators to keep their data up-to-date once for all across pharmaceutical companies participating in the project, with the right to object to the transfer of the data to the TransCelerate project.
- Professionals have the right to request the access to and the rectification of their personal data, as well as their erasure (where applicable) by contacting the Sanofi Data Protection Officer: Sanofi DPO - 54 rue La Boétie - 75008 PARIS - France (to contact Sanofi by email, visit https://www.sanofi.com/en/our-responsibility/sanofi-global-privacy-policy/contact).

10.1.5 Committees structure

There will be no study committees.

10.1.6 Dissemination of clinical study data

Sanofi shares information about clinical trials and results on publicly accessible websites, based on company commitments, international and local legal and regulatory requirements, and other clinical trial disclosure commitments established by pharmaceutical industry associations. These websites include clinicaltrials.gov, EU clinicaltrialregister (eu.ctr), and sanofi.com, as well as some national registries.

In addition, results from clinical trials in participants are required to be submitted to peer-reviewed journals following internal company review for accuracy, fair balance and intellectual property. For those journals that request sharing of the analyzable data sets that are reported in the publication, interested researchers are directed to submit their request to vivli.org.

Individual participant data and supporting clinical documents are available for request at vivli.org. While making information available we continue to protect the privacy of participants in our clinical trials. Details on data sharing criteria and process for requesting access can be found at this web address: vivli.org.

Professionals involved in the study or in the drug development program

Sanofi undertakes the legal obligation to disclose the full name of the Investigator and his/her affiliated institute/ hospital's name and location on the China Trial Disclosure website as required by the National Medical Products Administration (NMPA) in its guidance "Implementation of Drug Clinical Trial Information Registration and Disclosure" ("Notification No. 28"), requesting name disclosure of Chinese and foreign investigational sites and Investigators in any eligible clinical trial.

Sanofi may publicly disclose, and communicate to relevant authorities/institutions, the funding, including payments and transfers of value, direct or indirect, made to healthcare organizations and professionals and/or any direct or indirect advantages and/or any related information or document if required by applicable law, by regulation or by a code of conduct such as the "EFPIA Code on Disclosure of Transfers of Value from Pharmaceutical Companies to Healthcare Professionals and Healthcare Organisations".

10.1.7 Data quality assurance

- All participant data relating to the study will be recorded on eCRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in separate study documents.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (eg, Contract Research Organizations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH-GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 25 years after the signature of the final study report unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.8 Source documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.

- Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Source data is all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Source documents are original documents, data and records such as hospital records, clinic and office charts, laboratory notes, memoranda, pharmacy dispensing records, recorded data from automated instruments, etc.

10.1.9 Study and site start and closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the first site open and will be the study start date.

The Sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed.

The Investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for study termination by the Sponsor, as well as reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

- For study termination:
  - Information on the product leads to doubt as to the benefit/risk ratio,
  - Discontinuation of further study intervention development.
- For site termination:
  - Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor’s procedures, or GCP guidelines,
  - Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the Investigator,
  - Total number of participants included earlier than expected.

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.10 Publication policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.
- The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2 APPENDIX 2: CLINICAL LABORATORY TESTS

- The tests detailed in Table 7 will be performed by the central laboratory.
- Local laboratory results are only required in the event that the central laboratory results are not available in time for either study intervention administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study intervention decision or response evaluation, the results must be entered into the eCRF.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.
- Additional serum or urine pregnancy tests may be performed, as determined necessary by the Investigator or required by local regulation, to establish the absence of pregnancy at any time during the participant's participation in the study.

Table 7 - Protocol-required laboratory assessments

Laboratory assessments	Parameters
Hematology	Platelet count
	Red blood cell (RBC) count
	Hemoglobin
	Hematocrit
	White blood cell (WBC) count with differential:
	Neutrophils
	Lymphocytes
	Monocytes
	Eosinophils
	Basophils
Clinical chemistry[a, b]	Blood urea nitrogen (BUN)
	Creatinine
	Glucose
	Lactate dehydrogenase
	Uric acid
	Total cholesterol
	Potassium
	Sodium
	Chloride
	Bicarbonate
	Aspartate aminotransferase (AST)/ Serum glutamic-oxaloacetic transaminase (SGOT)
	Alanine aminotransferase (ALT)/ Serum glutamic-pyruvic transaminase (SGPT)
	Alkaline phosphatase
	Total bilirubin
	Albumin

Laboratory assessments	Parameters
	Total protein
Routine urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, [bilirubin, urobilinogen, nitrite, leukocyte esterase] by dipstick[c] • Creatinine and leukotriene (central laboratory) • Microscopic examination (if blood or protein is abnormal) [f]
Other screening tests	• Highly sensitive serum (at screening) or urine (at other time points) hCG pregnancy test (as needed for WOCBP)[d] • Serology[e]: HBsAg, HBsAb, HBcAb, HCVAb, HIV screen (Anti-HIV-1 and HIV-2 antibodies). • Tuberculosis test • All study-required laboratory assessments will be performed by a central laboratory, with the exception of TB test, urine pregnancy test, and routine urine dipstick[c].

HBcAb: hepatitis B core antibody, HBsAb: hepatitis B surface antibody, HBsAg: hepatitis B surface antigen, HBV: hepatitis B virus, hCG: human chorionic gonadotropin, HCV: hepatitis C virus, HCVAb: hepatitis C virus antibodies, HIV: Human Immunodeficiency Virus, WOCBP: women of childbearing potential, ULN: upper limit of normal.

NOTES :

a Details of liver chemistry stopping criteria with suggested actions and follow-up assessments related to liver monitoring are given in Section 7.1 and Section 10.6. All events which may indicate severe liver injury (possible Hy's Law, ALT or AST >3 × ULN and total bilirubin >2 × ULN) must be reported as an SAE.

b All drug-induced liver injury (DILI) testing should be performed locally, unless there is no local support available in which case the analysis can be done at the central laboratory.

c For participants enrolled in China, the urine analysis will be performed at laboratory (not dipstick).

d After screening local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.

e In case of results showing HBsAg (negative) and HBcAb (positive), an HBV DNA testing will be performed and should be confirmed negative prior to randomization. In case of results showing HCVAb (positive), HCV RNA testing will be performed and should be confirmed negative prior to randomization.

f In case the urine dipstick test result is abnormal, a urine sample should be sent into the central laboratory for microscopic examination.

Investigators must document their review of each laboratory safety report.

Laboratory/analyte results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

10.3 APPENDIX 3: ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

10.3.1 Definition of AE

AE definition

- An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events meeting the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (ie, not related to progression of underlying disease).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.
- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE. Also, "lack of efficacy" or "failure of expected pharmacological action" also constitutes an AE or SAE.

Events NOT meeting the AE definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2 Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

A SAE is defined as any untoward medical occurrence that, at any dose:

a) Results in death

b) Is life-threatening

- The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c) Requires inpatient hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d) Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e) Is a congenital anomaly/birth defect

f) Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
  - Note: The following list of medically important events is intended to serve as a guideline for determining which condition has to be considered as a medically important event. The list is not intended to be exhaustive:
    - Intensive treatment in an emergency room or at home for:
      - Allergic bronchospasm,
      - Blood dyscrasias (ie, agranulocytosis, aplastic anemia, bone marrow aplasia, myelodysplasia, pancytopenia, etc),
      - Convulsions (seizures, epilepsy, epileptic fit, absence, etc).
    - Development of drug dependence or drug abuse,
    - ALT >3 × ULN + total bilirubin >2 × ULN or asymptomatic ALT increase >10 × ULN,
    - Suicide attempt or any event suggestive of suicidality,
    - Syncope, loss of consciousness (except if documented as a consequence of blood sampling),
    - Bullous cutaneous eruptions,
    - Cancers diagnosed during the study or aggravated during the study,
    - Chronic neurodegenerative diseases (newly diagnosed) or aggravated during the study.

10.3.3 Recording and follow-up of AE and/or SAE

AE and SAE recording

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information in the eCRF.
- It is **not** acceptable for the Investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the AE/SAE eCRF page.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor's representative. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the Sponsor's representative.

- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of intensity

The Investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

An event is defined as “serious” when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of causality

- The Investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The Investigator will also consult the Investigator’s Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report to the Sponsor’s representative. However, **it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to** the Sponsor’s representative**.**
- The Investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor's representative to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the Investigator will provide the Sponsor's representative with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed eCRF.
- The Investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

10.3.4 Reporting of SAEs

SAE reporting to the Sponsor via an electronic data collection tool

- The primary mechanism for reporting an SAE to the Sponsor's representative will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the Sponsor's representative by telephone.
- Contacts for SAE reporting can be found in the protocol.

SAE reporting to the Sponsor via paper CRF

- Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the Sponsor's representative.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts for SAE reporting can be found in the protocol.

10.4 APPENDIX 4: CONTRACEPTIVE GUIDANCE AND COLLECTION OF PREGNANCY INFORMATION

DEFINITIONS:

Woman of childbearing potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

If fertility is unclear (eg, amenorrhea athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP

1. Premenarchal.
2. Premenopausal female with one of the following:
   - Documented hysterectomy,
   - Documented bilateral salpingectomy,
   - Documented bilateral oophorectomy.

     For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, mullerian agenesis, androgen insensitivity), Investigator discretion should be applied to determining study entry.

   Note: Documentation can come from the site personnel's: review of the participant's medical records, medical examination, or medical history interview.
3. Postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
     - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

CONTRACEPTION GUIDANCE:

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described below.

Highly effective contraceptive methods that are user dependent[a] *Failure rate of <1% per year when used consistently and correctly.*
Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation • Oral • Intravaginal • Transdermal
Progestogen only hormonal contraception associated with inhibition of ovulation • Oral • Injectable
Highly effective methods that are user independent[a]
Implantable progestogen only hormonal contraception associated with inhibition of ovulation • Intrauterine device • Intrauterine hormone-releasing system • Bilateral tubal occlusion
Vasectomized partner *A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.*
Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.*

NOTES:
a Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies.

COLLECTION OF PREGNANCY INFORMATION:

Male participants with partners who become pregnant

- The Investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the partner's pregnancy. The

female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female participants who become pregnant

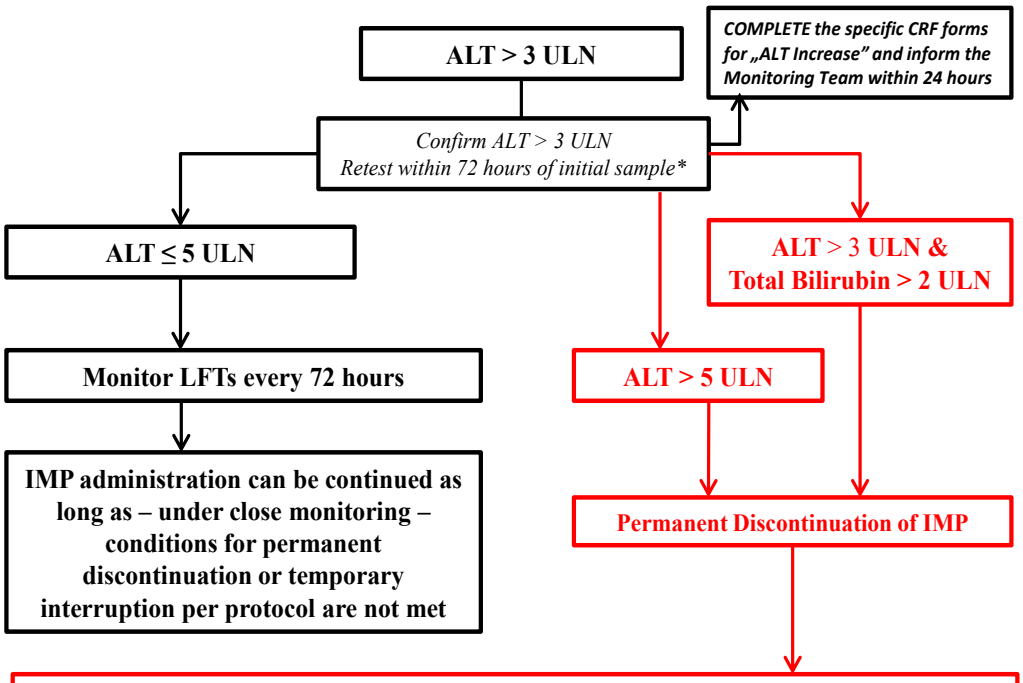
- The Investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. The initial information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a participant's pregnancy.
- The participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the Sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- Any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- A spontaneous abortion (occurring at <22 weeks gestational age) or still birth (occurring at >22 weeks gestational age) is always considered to be an SAE and will be reported as such.
- Any post-study pregnancy related SAE considered reasonably related to the study intervention by the Investigator will be reported to the Sponsor as described in Section 8.3.4. While the Investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study intervention.

10.5 APPENDIX 5: GENETICS

[redacted]

10.6 APPENDIX 6: LIVER AND OTHER SAFETY: ACTIONS AND FOLLOW-UP ASSESSMENTS

INCREASE IN ALT



In ANY CASE, FOLLOW the instructions listed in the box below:

1. **INFORM** the Site Monitor who will forward the information to the Study Manager
2. **INVESTIGATE** specifically for malaise with or without loss of consciousness, dizziness, and/or hypotension and/or episode of arrhythmia in the previous 72 hours; rule out muscular injury
3. **PERFORM** the following tests:
   - LFTs: AST, ALT, alkaline phosphatase, total and conjugated bilirubin and prothrombin time / INR
   - CPK, serum creatinine, complete blood count
   - Anti-HAV IgM, anti-HBc IgM, (HBV-DNA if clinically indicated), anti-HCV and HCV RNA, anti-CMV IgM and anti-HEV IgM antibodies
   - Depending on the clinical context, check for recent infection with EBV, herpes viruses, and toxoplasma
   - Hepatobiliary ultrasonography (or other imaging investigations if needed)
4. **CONSIDER** Auto-antibodies: antinuclear, anti-DNA, anti-smooth muscle, anti-LKM
5. **CONSIDER** consulting with hepatologist
6. **CONSIDER** patient hospitalisation if INR>2 (or PT<50%) and/or central nervous system disburbances suggesting hepatic encephalopathy
7. **MONITOR LFTs after discontinuation of IMP:**
   - As *closely as possible* (or **every 48 hours)** until stabilization, then every 2 weeks until return to normal/baseline or clinical resolution.
8. **FREEZE** serum sample (5ml x 2)
9. **In case of SUSPICION of GILBERT Syndrome,** a DNA diagnostic test should be done

*If unable to retest in 72 hours, use original lab results to decide on further reporting/monitoring/discontinuation.

Note:

"Baseline" refers to ALT sampled at baseline visit; or if baseline value unavailable, to the latest ALT sampled before the baseline visit. The algorithm does not apply to the instances of increase in ALT during screening.

See Section 10.3 for guidance on safety reporting.

Normalization is defined as ≤ULN or baseline value, if baseline value is >ULN.

10.7 APPENDIX 7: COUNTRY-SPECIFIC REQUIREMENTS

10.7.1 China

For participants enrolled in China, the urine analysis will be performed at laboratory (not dipstick).

10.8 APPENDIX 8: CLINICIAN-REPORTED OUTCOMES AND PATIENT-REPORTED OUTCOMES

10.8.1 Sino-Nasal Outcome Test

I.D.:_____ SINO-NASAL OUTCOME TEST (SNOT-22) DATE:_____

Below you will find a list of symptoms and social/emotional consequences of your rhinosinusitis. We would like to know more about these problems and would appreciate your answering the following questions to the best of your ability. There are no right or wrong answers, and only you can provide us with this information. Please rate your problems as they have been over the past two weeks. Thank you for your participation. Do not hesitate to ask for assistance if necessary.

1. Considering how severe the problem is when you experience it and how often it happens, please rate each item below on how "bad" it is by circling the number that corresponds with how you feel using this scale: →	No Problem	Very Mild Problem	Mild or slight Problem	Moderate Problem	Severe Problem	Problem as bad as it can be		5 Most Important Items
1. Need to blow nose	0	1	2	3	4	5		O
2. Nasal blockage	0	1	2	3	4	5		O
3. Sneezing	0	1	2	3	4	5		O
4. Runny nose	0	1	2	3	4	5		O
5. Cough	0	1	2	3	4	5		O
6. Post-nasal discharge	0	1	2	3	4	5		O
7. Thick nasal discharge	0	1	2	3	4	5		O
8. Ear fullness	0	1	2	3	4	5		O
9. Dizziness	0	1	2	3	4	5		O
10. Ear pain	0	1	2	3	4	5		O
11. Facial pain/pressure	0	1	2	3	4	5		O
12. Decreased sense of smell/taste	0	1	2	3	4	5		O
13. Difficulty falling asleep	0	1	2	3	4	5		O
14. Wake up at night	0	1	2	3	4	5		O
15. Lack of a good night's sleep	0	1	2	3	4	5		O
16. Wake up tired	0	1	2	3	4	5		O
17. Fatigue	0	1	2	3	4	5		O
18. Reduced productivity	0	1	2	3	4	5		O
19. Reduced concentration	0	1	2	3	4	5		O
20. Frustrated/restless/irritable	0	1	2	3	4	5		O
21. Sad	0	1	2	3	4	5		O
22. Embarrassed	0	1	2	3	4	5		O

2. Please mark the most important items affecting your health (maximum of 5 items)_____

SNOT-20 Copyright 1996 by Jay F. Piccirillo, M.D., Washington University School of Medicine, St. Louis, Missouri
SNOT-22 Developed from modification of SNOT-20 by National Comparative Audit of Surgery for Nasal Polyposis and Rhinosinusitis Royal College of Surgeons of England.

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10.8.2 Rhinosinusitis Severity Visual Analog Scale

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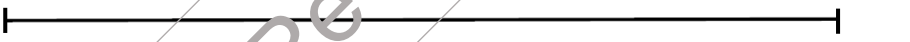
Rhinosinusitis Visual Analog Scale (Rhinosinusitis VAS)

Instructions: Please place a vertical mark on the line below to indicate how troublesome are your symptoms of rhinosinusitis.

How troublesome are your symptoms of rhinosinusitis?



Not troublesome 10 cm **Worst thinkable troublesome**

10.8.3 Asthma Control Questionnaire 6-item version

ASTHMA CONTROL QUESTIONNAIRE (ACQ)

ENGLISH FOR NORTH AMERICA VERSION
(QUESTIONS 1 – 6 ONLY: QUESTION 7 (FEV1) OMITTED)

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DECEMBER 2002

QUESTIONS 1 – 6 ONLY : MODIFIED JULY 2013 ENGLISH FOR NORTH AMERICA

ASTHMA CONTROL QUESTIONNAIRE© Page 1 of 2

Please answer questions 1 - 6.

Circle the number of the response that best describes how you have been during the past week.

1. On average, during the past week, how often were you **woken by your asthma** during the night?
   - 0 Never
   - 1 Hardly ever
   - 2 A few times
   - 3 Several times
   - 4 Many times
   - 5 A great many times
   - 6 Unable to sleep because of asthma

2. On average, during the past week, how **bad were your asthma symptoms when you woke up** in the morning?
   - 0 No symptoms
   - 1 Very mild symptoms
   - 2 Mild symptoms
   - 3 Moderate symptoms
   - 4 Quite severe symptoms
   - 5 Severe symptoms
   - 6 Very severe symptoms

3. In general, during the past week, how **limited were you in your activities** because of your asthma?
   - 0 Not limited at all
   - 1 Very slightly limited
   - 2 Slightly limited
   - 3 Moderately limited
   - 4 Very limited
   - 5 Extremely limited
   - 6 Totally limited

4. In general, during the past week, how much **shortness of breath** did you experience because of your asthma?
   - 0 None
   - 1 A very little
   - 2 A little
   - 3 A moderate amount
   - 4 Quite a lot
   - 5 A great deal
   - 6 A very great deal

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QUESTIONS 1 – 6 ONLY : MODIFIED JULY 2013 ENGLISH FOR NORTH AMERICA

ASTHMA CONTROL QUESTIONNAIRE© Page 2 of 2

5.	In general, during the past week, how much of the time did you **wheeze**?	0 Not at all 1 Hardly any of the time 2 A little of the time 3 A moderate amount of the time 4 A lot of the time 5 Most of the time 6 All the time
6.	On average, during the past week, how many **puffs/inhalations of short-acting bronchodilator** (eg. Ventolin/Bricanyl) have you used each day? *(If you are not sure how to answer this question, please ask for help)*	0 None 1 1 - 2 puffs/inhalations most days 2 3 - 4 puffs/inhalations most days 3 5 - 8 puffs/inhalations most days 4 9 - 12 puffs/inhalations most days 5 13 - 16 puffs/inhalations most days 6 More than 16 puffs/inhalations most days

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QUESTIONS 1 – 6 ONLY : MODIFIED JULY 2013 ENGLISH FOR NORTH AMERICA

10.8.4 Patient Global Impression of Severity (PGIS)/ Patient Global Impression of Change (PGIC)

Patient Global Impression of Change (PGIC) of

Chronic Rhinosinusitis Without Nasal Polyps

Please choose the response below that best describes the overall change in your chronic rhinosinusitis symptoms since you started taking the study injection.

☐ Very much better

☐ Moderately better

☐ A little better

☐ No change

☐ A little worse

☐ Moderately worse

☐ Very much worse

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Patient Global Impression of Severity (PGIS) of

Chronic Rhinosinusitis Without Nasal Polyps

Please choose the response below that best describes the severity of your chronic rhinosinusitis symptoms over the past week.

☐ None

☐ Mild

☐ Moderate

☐ Severe

10.8.5 EuroQol-5 dimensions

Health Questionnaire

English version for the USA

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Under each heading, please check the ONE box that best describes your health TODAY.

MOBILITY

I have no problems walking ❑
I have slight problems walking ❑
I have moderate problems walking ❑
I have severe problems walking ❑
I am unable to walk ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

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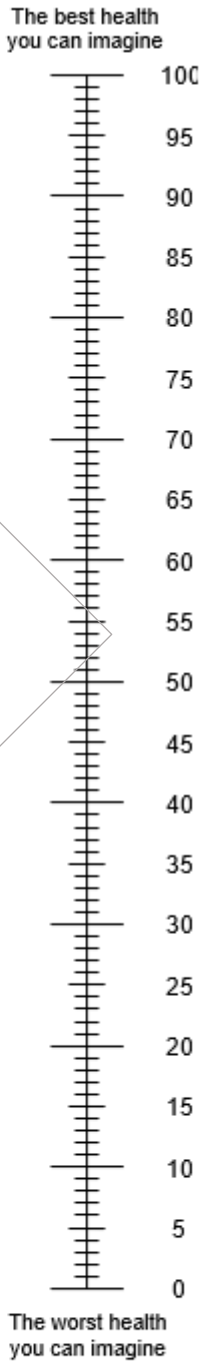
- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



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3

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10.8.6 CRSsNP Morning Diary

Sanofi_EFC16723 11JAN2023
English (US) v1.00

CRSsNP Morning Diary

Question Text	Response Values
The following questions will ask you to rate your nasal disorder symptoms over the past 24 hours. Please make sure you assess your nasal symptoms shortly after getting up in the morning (before 12:00 noon).	–
The following questions will ask you to rate your nasal disorder symptoms over the past 24 hours.	–
Rate the symptoms over the past 24 hours using the following ratings: 0 = No symptoms 1 = Mild symptoms (symptoms clearly present, but minimal awareness and easily tolerated) 2 = Moderate symptoms (definitive awareness of symptoms that is bothersome but tolerable) 3 = Severe symptoms (symptoms that are hard to tolerate, cause interference with activities of daily living)	–
Please rate your nasal congestion/obstruction symptoms over the past 24 hours	No symptoms=0 Mild symptoms=1 Moderate symptoms=2 Severe symptoms=3
Please rate your loss of sense of smell symptoms over the past 24 hours	No symptoms=0 Mild symptoms=1 Moderate symptoms=2 Severe symptoms=3
Please rate your runny nose symptoms over the past 24 hours	No symptoms=0 Mild symptoms=1 Moderate symptoms=2 Severe symptoms=3
Please rate your post-nasal drip (dripping at the back of your nose) symptoms over the past 24 hours	No symptoms=0 Mild symptoms=1 Moderate symptoms=2 Severe symptoms=3
Please rate your facial pain/pressure symptoms over the past 24 hours	No symptoms=0 Mild symptoms=1 Moderate symptoms=2 Severe symptoms=3
The following question will ask you to rate your headache over the past 24 hours. Please make sure you assess your headache shortly after getting up in the morning (before 12:00 noon).	–
The following question will ask you to rate your headache over the past 24 hours.	–
Rate the symptoms over the past 24 hours using the following ratings: 0 = No symptoms 1 = Mild symptoms (symptoms clearly present, but minimal awareness and easily tolerated) 2 = Moderate symptoms (definitive awareness of symptoms that is bothersome but tolerable)	–

For Review Only

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Question Text	Response Values
3 = Severe symptoms (symptoms that are hard to tolerate, cause interference with activities of daily living)	
Please rate <u>your headache</u> over the past 24 hours	No symptoms=0 Mild symptoms=1 Moderate symptoms=2 Severe symptoms=3
Since yesterday, did you decrease or increase your background rhinosinusitis nasal spray dose as prescribed below? {{{dt_INNmedicationND100}}}: {{{dt_INNsprayND100}}} spray(s)	Yes=1 No=0
Did you take any new medication not prescribed by your study doctor to treat your rhinosinusitis since yesterday?	Yes=1 No=0
Please remember to perform the monthly urine pregnancy test as directed by the study doctor.	–

For Review Only

2

10.8.7 Healthcare Resource Utilization (HCRU) questionnaire

The HCRU questionnaire presented below is the general one without specific visits. HCRU questionnaire versions with Baseline (Visit 1), Week 12 (Visit 4), Week 24 (Visit 5), Week 40 (Visit 6), and Week 52 (Visit 7) questions are displayed in the sub-headings below.

Chronic Rhinosinusitis without Nasal Polyps (CRSsNP) Healthcare Resource Utilization (HCRU) Questionnaire (Clinician-Reported)
EFC16723

This questionnaire will capture the patient's visits to health care professionals due to their chronic sinusitis, work and/or student status, and impact on work/school/daily activities due to their chronic rhinosinusitis.

When completing this health care resource use questionnaire (HCRU) please do not include any health care professional visits, impact on work/school/daily activities arising from the patient's participation in this study (including onsite visits), or from health conditions other than chronic rhinosinusitis.

HEALTH CARE PROFESSIONAL VISITS
Please do not include visits that are part of this study, or for health conditions other than CRSsNP

1. During the past four weeks, how many healthcare professional visits (general practitioner, specialist(s)) did this patient have due to his/her chronic rhinosinusitis?

   Number of visits to a general practitioner: ____ visits

   Number of visits to a specialist (e.g. otolaryngologist, allergist, ENT, psychiatrist):

   ____ visits

2. During the past four weeks, how many of these visits to a general practitioner or specialist(s) were unscheduled (not including planned, or regular checkup visits)?

   ____ unscheduled visits

WORK / STUDENT STATUS

3. During the past four weeks, which of the following best describes the patients' work/student status (please tick the corresponding box(es)):

   ☐ Working full time (4 days or more per week)

   ☐ Working part time (less than 4 days per week)

   ☐ Student full time (4 days or more per week)

   ☐ Student part time (less than 4 days per week)

   ☐ Neither working (unemployed, retired) nor a student

   ☐ On sick leave from work (paid/unpaid)

For patients who are working or on sick leave, please go to section WORK.

For Review Only

For patients who are studying, please go to section SCHOOL.
For patients who are working and studying please complete both sections WORK and SCHOOL.
For patients who are neither working nor studying please go to section DAILY ACTIVITIES.

Please include days on sick leave within the days missed from work/school.

WORK

Please do not include workdays missed due to participation in this study, or for health conditions other than CRSsNP.

4. During the past four weeks, how many days did this patient miss from work because of his/her chronic rhinosinusitis?
/
_____ days (half a day = 0.5 days)

5. During the past four weeks, how many days did this patient work while being bothered by his/her chronic rhinosinusitis?

_____ days (half a day = 0.5 days)

6. During the past four weeks, how much did this patient's chronic rhinosinusitis impact his/her performance in his/her work?

Please enter a number between 0 and 10, where 0 equals "not impacted", and 10 equals "extremely impacted".

_____ (score: range 0 (not impacted) to 10 (extremely impacted))

For Review Only

SCHOOL

Please do not include school days missed due to participation in this study, or for health conditions other than CRSsNP.

7. During the past four weeks, how many days did this patient miss from school because of his/her chronic rhinosinusitis?

_____ days (half a day = 0.5 days)

8. During the past four weeks, how many days did this patient go to school while being bothered by his/her chronic rhinosinusitis?

_____ days (half a day = 0.5 days)

9. During the past four weeks, how much did this patient's chronic rhinosinusitis impact his/her performance in his/her schoolwork?

Please enter a number between 0 and 10, where 0 equals "not impacted", and 10 equals "extremely impacted".

_____ (score range 0 (not impacted) to 10 (extremely impacted))

DAILY ACTIVITIES

Please do not include impact on daily activities due to participation in this study, or for health conditions other than CRSsNP

10. During the past four weeks, how many days did this patient perform his/her usual daily activities while being bothered by his/her chronic rhinosinusitis?

    _____days (half a day = 0.5 days)

11. During the past four weeks, how much did this patient's chronic rhinosinusitis impact his/her ability to do his/her usual daily activities (such as house chores, childcare, exercise etc.) other than working or studying?

    Please enter a number between 0 and 10, where 0 equals "not impacted", and 10 equals "extremely impacted".

    _____ (score range 0 (not impacted) to 10 (extremely impacted))

For Review Only

10.8.7.1 HCRU questionnaire at Visit 1

HCRU questionnaire version with Baseline (Visit 1) question is displayed below.

BASELINE HCRU: WEEK 0

Chronic Rhinosinusitis without Nasal Polyps (CRSsNP) Healthcare Resource Utilization (HCRU) Questionnaire (Clinician-Reported)
EFC16723: BASELINE VISIT (WEEK 0)

This questionnaire will capture the patient's visits to health care professionals due to their chronic sinusitis, work and/or student status, and impact on work/school/daily activities due to their chronic rhinosinusitis.

When completing this health care resource use questionnaire (HCRU) please do not include any health care professional visits, impact on work/school/daily activities arising from the patient's participation in this study (including onsite visits), or from health conditions other than chronic rhinosinusitis.

HEALTH CARE PROFESSIONAL VISITS
Please do not include visits that are part of this study, or for health conditions other than CRSsNP

1. During the past four weeks, how many healthcare professional visits (general practitioner, specialist(s)) did this patient have due to his/her chronic rhinosinusitis?

   Number of visits to a general practitioner: ____ visits

   Number of visits to a specialist (e.g. otolaryngologist, allergist, ENT, psychiatrist):

   ____ visits

2. During the past four weeks, how many of these visits to a general practitioner or specialist(s) were unscheduled (not including planned, or regular checkup visits)?

   ____ unscheduled visits

WORK / STUDENT STATUS

3. During the past four weeks, which of the following best describes the patients' work/student status (please tick the corresponding box(es)):

   ☐ Working full time (4 days or more per week)
   ☐ Working part time (less than 4 days per week)
   ☐ Student full time (4 days or more per week)
   ☐ Student part time (less than 4 days per week)
   ☐ Neither working (unemployed, retired) nor a student
   ☐ On sick leave from work (paid/unpaid)

For patients who are working or on sick leave, please go to section WORK.

For Review Only

For patients who are studying, please go to section SCHOOL.
For patients who are working and studying please complete both sections WORK and SCHOOL.
For patients who are neither working nor studying please go to section DAILY ACTIVITIES.

Please include days on sick leave within the days missed from work/school.

WORK

Please do not include workdays missed due to participation in this study, or for health conditions other than CRSsNP.

4. During the past four weeks, how many days did this patient miss from work because of his/her chronic rhinosinusitis?

   _____ days (half a day = 0.5 days)

5. During the past four weeks, how many days did this patient work while being bothered by his/her chronic rhinosinusitis?

   _____ days (half a day = 0.5 days)

6. During the past four weeks, how much did this patient's chronic rhinosinusitis impact his/her performance in his/her work?

   Please enter a number between 0 and 10, where 0 equals "not impacted", and 10 equals "extremely impacted".

   _____ (score: range 0 (not impacted) to 10 (extremely impacted))

SCHOOL

Please do not include school days missed due to participation in this study, or for health conditions other than CRSsNP.

7. During the past four weeks, how many days did this patient miss from school because of his/her chronic rhinosinusitis?

   _____ days (half a day = 0.5 days)

8. During the past four weeks, how many days did this patient go to school while being bothered by his/her chronic rhinosinusitis?

   _____ days (half a day = 0.5 days)

9. During the past four weeks, how much did this patient's chronic rhinosinusitis impact his/her performance in his/her schoolwork?

   Please enter a number between 0 and 10, where 0 equals "not impacted", and 10 equals "extremely impacted".

   _____ (score range 0 (not impacted) to 10 (extremely impacted))

For Review Only

DAILY ACTIVITIES

Please do not include impact on daily activities due to participation in this study, or for health conditions other than CRSsNP

10. During the past four weeks, how many days did this patient perform his/her usual daily activities while being bothered by his/her chronic rhinosinusitis?

    _____days (half a day = 0.5 days)

11. During the past four weeks, how much did this patient's chronic rhinosinusitis impact his/her ability to do his/her usual daily activities (such as house chores, childcare, exercise etc.) other than working or studying?

    Please enter a number between 0 and 10, where 0 equals "not impacted", and 10 equals "extremely impacted".

    _____ (score range 0 (not impacted) to 10 (extremely impacted))

For Review Only

10.8.7.2 HCRU questionnaire at Week 12

HCRU questionnaire version with Week 12 (Visit 4) question is displayed below.

POST-BASELINE HCRU: WEEK 12

Chronic Rhinosinusitis without Nasal Polyps (CRSsNP) Healthcare Resource Utilization (HCRU) Questionnaire (Clinician-Reported)
EFC16723 : POST-BASELINE VISIT (WEEK 12)

This questionnaire will capture the patient's visits to health care professionals due to their chronic sinusitis, work and/or student status, and impact on work/school/daily activities due to their chronic rhinosinusitis.

When completing this health care resource use questionnaire (HCRU) please do not include any health care professional visits, impact on work/school/daily activities arising from the patient's participation in this study (including onsite visits), or from health conditions other than chronic rhinosinusitis.

HEALTH CARE PROFESSIONAL VISITS

Please do not include visits that are part of this study, or for health conditions other than CRSsNP

1. Since this patient first started the treatment (about three months back), how many healthcare professional visits (general practitioner, specialist(s)) did this patient have due to his/her chronic rhinosinusitis?

   Number of visits to a general practitioner: ____ visits

   Number of visits to a specialist (e.g. otolaryngologist, allergist, ENT, psychiatrist):

   ____ visits

2. Since this patient first started the treatment (about three months back), how many of these visits to the general practitioner or specialist(s) were unscheduled (not including planned, or regular checkup visits)?

   ____ unscheduled visits

For Review Only

WORK / STUDENT STATUS

3. Since this patient first started the treatment (about three months back), which of the following best describes the patients' work/student status (please tick the corresponding box(es)):

   ☐ Working full time (4 days or more per week)

   ☐ Working part time (less than 4 days per week)

   ☐ Student full time (4 days or more per week)

   ☐ Student part time (less than 4 days per week)

   ☐ Neither working (unemployed, retired) nor a student

   ☐ On sick leave from work (paid/unpaid)

For patients who are working or on sick leave, please go to section WORK.
For patients who are studying, please go to section SCHOOL.
For patients who are working and studying please complete both sections WORK and SCHOOL.
For patients who are neither working nor studying please go to section DAILY ACTIVITIES.

Please include days on sick leave within the days missed from work/school.

WORK

Please do not include workdays missed due to participation in this study, or for health conditions other than CRSsNP.

4. Since this patient first started the treatment (about three months back), how many days did this patient miss from work because of his/her chronic rhinosinusitis?

   _____ days (half a day = 0.5 days)

5. Since this patient first started the treatment (about three months back), how many days did this patient work while being bothered by his/her chronic rhinosinusitis?

   _____ days (half a day = 0.5 days)

6. Since this patient first started the treatment (about three months back), how much did this patient's chronic rhinosinusitis impact his/her performance in his/her work?

   Please enter a number between 0 and 10, where 0 equals "not impacted", and 10 equals "extremely impacted".

   _____ (score range 0 (not impacted) to 10 (extremely impacted))

For Review Only

SCHOOL

Please do not include school days missed due to participation in this study, or for health conditions other than CRSsNP.

7. Since this patient first started the treatment (about three months back), how many days did this patient miss from school because of his/her chronic rhinosinusitis?

   _____ days (half a day = 0.5 days)

8. Since this patient first started the treatment (about three months back), how many days did this patient go to school while being bothered by his/her chronic rhinosinusitis?

   _____ days (half a day = 0.5 days)

9. Since this patient first started the treatment (about three months back), how much did this patient's chronic rhinosinusitis impact his/her performance in his/her schoolwork?

   Please enter a number between 0 and 10, where 0 equals "not impacted", and 10 equals "extremely impacted".

   _____ (score range 0 (not impacted) to 10 (extremely impacted))

DAILY ACTIVITIES

Please do not include impact on daily activities due to participation in this study, or for health conditions other than CRSsNP

10. Since this patient first started the treatment (about three months back), how many days did this patient perform his/her usual daily activities while being bothered by his/her chronic rhinosinusitis?

    _____days (half a day = 0.5 days)

11. Since this patient first started the treatment (about three months back), how much did this patient's chronic rhinosinusitis impact his/her ability to do his/her usual daily activities (such as house chores, childcare, exercise etc.) other than working or studying?

    Please enter a number between 0 and 10, where 0 equals "not impacted", and 10 equals "extremely impacted".

    _____ (score range 0 (not impacted) to 10 (extremely impacted))

For Review Only

10.8.7.3 HCRU questionnaire at Week 24

HCRU questionnaire version with Week 24 (Visit 5) question is displayed below.

POST-BASELINE HCRU: WEEK 24

Chronic Rhinosinusitis without Nasal Polyps (CRSsNP) Healthcare Resource Utilization (HCRU) Questionnaire (Clinician-Reported)
EFC16723 : POST-BASELINE VISIT (WEEK 24)

This questionnaire will capture the patient's visits to health care professionals due to their chronic sinusitis, work and/or student status, and impact on work/school/daily activities due to their chronic rhinosinusitis.

When completing this health care resource use questionnaire (HCRU) please do not include any health care professional visits, impact on work/school/daily activities arising from the patient's participation in this study (including onsite visits), or from health conditions other than chronic rhinosinusitis.

HEALTH CARE PROFESSIONAL VISITS
Please do not include visits that are part of this study, or for health conditions other than CRSsNP

1. Since the last assessment of HCRU (about three months back), how many healthcare professional visits (general practitioner, specialist(s)) did this patient have due to his/her chronic rhinosinusitis?

   Number of visits to a general practitioner: ___ visits

   Number of visits to a specialist (e.g. otolaryngologist, allergist, ENT, psychiatrist):

   ____ visits

2. Since the last assessment of HCRU (about three months back), how many of these visits to the general practitioner or specialist(s) were unscheduled (not including planned, or regular checkup visits)?

   ____ unscheduled visits

WORK / STUDENT STATUS

3. Since the last assessment of HCRU (about three months back), which of the following best describes the patients' work/student status (please tick the corresponding box(es)):

   ☐ Working full time (4 days or more per week)

   ☐ Working part time (less than 4 days per week)

   ☐ Student full time (4 days or more per week)

   ☐ Student part time (less than 4 days per week)

   ☐ Neither working (unemployed, retired) nor a student

   ☐ On sick leave from work (paid/unpaid)

For Review Only

For patients who are working or on sick leave, please go to section WORK.
For patients who are studying, please go to section SCHOOL.
For patients who are working and studying please complete both sections WORK and SCHOOL.
For patients who are neither working nor studying please go to section DAILY ACTIVITIES.

Please include days on sick leave within the days missed from work/school.

WORK

Please do not include workdays missed due to participation in this study, or for health conditions other than CRSsNP.

4. Since the last assessment of HCRU (about three months back), how many days did this patient miss from work because of his/her chronic rhinosinusitis?

_____ days (half a day = 0.5 days)

5. Since the last assessment of HCRU (about three months back), how many days did this patient work while being bothered by his/her chronic rhinosinusitis?

_____ days (half a day = 0.5 days)

6. Since the last assessment of HCRU (about three months back), how much did this patient's chronic rhinosinusitis impact his/her performance in his/her work?

Please enter a number between 0 and 10, where 0 equals "not impacted", and 10 equals "extremely impacted".

_____ (score range 0 (not impacted) to 10 (extremely impacted))

SCHOOL

Please do not include school days missed due to participation in this study, or for health conditions other than CRSsNP.

7. Since the last assessment of HCRU (about three months back), how many days did this patient miss from school because of his/her chronic rhinosinusitis?

_____ days (half a day = 0.5 days)

8. Since the last assessment of HCRU (about three months back), how many days did this patient go to school while being bothered by his/her chronic rhinosinusitis?

_____ days (half a day = 0.5 days)

9. Since the last assessment of HCRU (about three months back), how much did this patient's chronic rhinosinusitis impact his/her performance in his/her schoolwork?

Please enter a number between 0 and 10, where 0 equals "not impacted", and 10 equals "extremely impacted".

_____ (score range 0 (not impacted) to 10 (extremely impacted))

For Review Only

DAILY ACTIVITIES

Please do not include impact on daily activities due to participation in this study, or for health conditions other than CRSsNP

10. Since the last assessment of HCRU (about three months back), how many days did this patient perform his/her usual daily activities while being bothered by his/her chronic rhinosinusitis?

_____days (half a day = 0.5 days)

11. Since the last assessment of HCRU (about three months back), how much did this patient's chronic rhinosinusitis impact his/her ability to do his/her usual daily activities (such as house chores, childcare, exercise etc.) other than working or studying?

Please enter a number between 0 and 10, where 0 equals "not impacted", and 10 equals "extremely impacted"

_____ (score range 0 (not impacted) to 10 (extremely impacted))

For Review Only

10.8.7.4 HCRU questionnaire at Week 40

HCRU questionnaire version with Week 40 (Visit 6) question is displayed below.

POST-BASELINE HCRU: WEEK 40

Chronic Rhinosinusitis without Nasal Polyps (CRSsNP) Healthcare Resource Utilization (HCRU) Questionnaire (Clinician-Reported) EFC16723: POST-BASELINE VISIT (WEEK 40)

This questionnaire will capture the patient's visits to health care professionals due to their chronic sinusitis, work and/or student status, and impact on work/school/daily activities due to their chronic rhinosinusitis.

When completing this health care resource use questionnaire (HCRU) please do not include any health care professional visits, impact on work/school/daily activities arising from the patient's participation in this study (including onsite visits), or from health conditions other than chronic rhinosinusitis.

For Review Only

HEALTH CARE PROFESSIONAL VISITS

Please do not include visits that are part of this study, or for health conditions other than CRSsNP

1. Since the last assessment of HCRU (about four months back), how many healthcare professional visits (general practitioner, specialist(s)) did this patient have due to his/her chronic rhinosinusitis?

   Number of visits to a general practitioner: ____ visits

   Number of visits to a specialist (e.g. otolaryngologist, allergist, ENT, psychiatrist):

   ____ visits

2. Since the last assessment of HCRU (about four months back), how many of these visits to the general practitioner or specialist(s) were unscheduled (not including planned, or regular checkup visits)?

   ____ unscheduled visits

WORK / STUDENT STATUS

3. Since the last assessment of HCRU (about four months back), which of the following best describes the patients' work/student status (please tick the corresponding box(es)):

   ☐ Working full time (4 days or more per week)

   ☐ Working part time (less than 4 days per week)

   ☐ Student full time (4 days or more per week)

   ☐ Student part time (less than 4 days per week)

   ☐ Neither working (unemployed, retired) nor a student

   ☐ On sick leave from work (paid/unpaid)

For patients who are working or on sick leave, please go to section WORK.
For patients who are studying, please go to section SCHOOL.
For patients who are working and studying please complete both sections WORK and SCHOOL.
For patients who are neither working nor studying please go to section DAILY ACTIVITIES.

Please include days on sick leave within the days missed from work/school.

WORK

Please do not include workdays missed due to participation in this study, or for health conditions other than CRSsNP.

4. Since the last assessment of HCRU (about four months back), how many days did this patient miss from work because of his/her chronic rhinosinusitis?

   _____ days (half a day = 0.5 days)

5. Since the last assessment of HCRU (about four months back), how many days did this patient work while being bothered by his/her chronic rhinosinusitis?

   _____ days (half a day = 0.5 days)

6. Since the last assessment of HCRU (about four months back), how much did this patient's chronic rhinosinusitis impact his/her performance in his/her work?

   Please enter a number between 0 and 10, where 0 equals "not impacted", and 10 equals "extremely impacted".

   _____ (score range 0 (not impacted) to 10 (extremely impacted))

For Review Only

SCHOOL

Please do not include school days missed due to participation in this study, or for health conditions other than CRSsNP.

7. Since the last assessment of HCRU (about four months back), how many days did this patient miss from school because of his/her chronic rhinosinusitis?

   _____ days (half a day = 0.5 days)

8. Since the last assessment of HCRU (about four months back), how many days did this patient go to school while being bothered by his/her chronic rhinosinusitis?

   _____ days (half a day = 0.5 days)

9. Since the last assessment of HCRU (about four months back), how much did this patient's chronic rhinosinusitis impact his/her performance in his/her schoolwork?

   Please enter a number between 0 and 10, where 0 equals "not impacted", and 10 equals "extremely impacted".

   _____ (score range 0 (not impacted) to 10 (extremely impacted))

DAILY ACTIVITIES

Please do not include impact on daily activities due to participation in this study or for health conditions other than CRSsNP

10. Since the last assessment of HCRU (about four months back), how many days did this patient perform his/her usual daily activities while being bothered by his/her chronic rhinosinusitis?

_____days (half a day = 0.5 days)

11. Since the last assessment of HCRU (about four months back), how much did this patient's chronic rhinosinusitis impact his/her ability to do his/her usual daily activities (such as house chores, childcare, exercise etc.) other than working or studying?

Please enter a number between 0 and 10, where 0 equals "not impacted", and 10 equals "extremely impacted".

_____ (score range 0 (not impacted) to 10 (extremely impacted))

For Review Only

10.8.7.5 HCRU questionnaire at Week 52

HCRU questionnaire version with Week 52 (Visit 7) question is displayed below.

POST-BASELINE HCRU: WEEK 52

Chronic Rhinosinusitis without Nasal Polyps (CRSsNP) Healthcare Resource Utilization (HCRU) Questionnaire (Clinician-Reported) EFC16723: POST-BASELINE VISIT (WEEK 52)

This questionnaire will capture the patient's visits to health care professionals due to their chronic sinusitis, work and/or student status, and impact on work/school/daily activities due to their chronic rhinosinusitis.

When completing this health care resource use questionnaire (HCRU) please do not include any health care professional visits, impact on work/school/daily activities arising from the patient's participation in this study (including onsite visits), or from health conditions other than chronic rhinosinusitis.

For Review Only

HEALTH CARE PROFESSIONAL VISITS

Please do not include visits that are part of this study, or for health conditions other than CRSsNP

1. Since the last assessment of HCRU (about three months back), how many healthcare professional visits (general practitioner, specialist(s)) did this patient have due to his/her chronic rhinosinusitis?

   Number of visits to a general practitioner: ____ visits

   Number of visits to a specialist (e.g. otolaryngologist, allergist, ENT, psychiatrist):

   ____ visits

2. Since the last assessment of HCRU (about three months back), how many of these visits to the general practitioner or specialist(s) were unscheduled (not including planned, or regular checkup visits)?

   ____ unscheduled visits

WORK / STUDENT STATUS

3. Since the last assessment of HCRU (about three months back), which of the following best describes the patients' work/student status (please tick the corresponding box(es)):

   ☐ Working full time (4 days or more per week)

   ☐ Working part time (less than 4 days per week)

   ☐ Student full time (4 days or more per week)

   ☐ Student part time (less than 4 days per week)

   ☐ Neither working (unemployed, retired) nor a student

□ On sick leave from work (paid/unpaid)

For patients who are working or on sick leave, please go to section WORK.
For patients who are studying, please go to section SCHOOL.
For patients who are working and studying please complete both sections WORK and SCHOOL.
For patients who are neither working nor studying please go to section DAILY ACTIVITIES.

Please include days on sick leave within the days missed from work/school.

WORK

Please do not include workdays missed due to participation in this study, or for health conditions other than CRSsNP.

4. Since the last assessment of HCRU (about three months back), how many days did this patient miss from work because of his/her chronic rhinosinusitis?

_____ days (half a day = 0.5 days)

5. Since the last assessment of HCRU (about three months back), how many days did this patient work while being bothered by his/her chronic rhinosinusitis?

_____ days (half a day = 0.5 days)

6. Since the last assessment of HCRU (about three months back), how much did this patient's chronic rhinosinusitis impact his/her performance in his/her work?

Please enter a number between 0 and 10, where 0 equals "not impacted", and 10 equals "extremely impacted".

_____ (score range 0 (not impacted) to 10 (extremely impacted))

SCHOOL

Please do not include school days missed due to participation in this study, or for health conditions other than CRSsNP.

7. Since the last assessment of HCRU (about three months back), how many days did this patient miss from school because of his/her chronic rhinosinusitis?

_____ days (half a day = 0.5 days)

8. Since the last assessment of HCRU (about three months back), how many days did this patient go to school while being bothered by his/her chronic rhinosinusitis?

_____ days (half a day = 0.5 days)

9. Since the last assessment of HCRU (about three months back), how much did this patient's chronic rhinosinusitis impact his/her performance in his/her schoolwork?

Please enter a number between 0 and 10, where 0 equals "not impacted", and 10 equals "extremely impacted".

_____ (score range 0 (not impacted) to 10 (extremely impacted))

For Review Only

For Review Only

DAILY ACTIVITIES

Please do not include impact on daily activities due to participation in this study, or for health conditions other than CRSsNP

10. Since the last assessment of HCRU (about three months back), how many days did this patient perform his/her usual daily activities while being bothered by his/her chronic rhinosinusitis?

_____days (half a day = 0.5 days)

11. Since the last assessment of HCRU (about three months back), how much did this patient's chronic rhinosinusitis impact his/her ability to do his/her usual daily activities (such as house chores, childcare, exercise etc.) other than working or studying?

Please enter a number between 0 and 10, where 0 equals "not impacted", and 10 equals "extremely impacted".

_____ (score range 0 (not impacted) to 10 (extremely impacted))

10.9 APPENDIX 9: DEFINITION OF ANAPHYLAXIS

"Anaphylaxis is a serious allergic reaction that is rapid in onset and may cause death (48)".

Clinical criteria for diagnosing anaphylaxis

Anaphylaxis is highly likely when any one of the following 3 criteria are fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula)
   AND AT LEAST ONE OF THE FOLLOWING
   a. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   b. Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure *to a likely allergen for that patient* (minutes to several hours):
   a. Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)
   b. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   c. Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)
   d. Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)
3. Reduced BP after exposure to *known allergen for that patient* (minutes to several hours):
   a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP*
   b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

PEF, Peak expiratory flow; *BP*, blood pressure.
*Low systolic blood pressure for children is defined as less than 70 mm Hg from 1 month to 1 year, less than (70 mm Hg + [2 × age]) from 1 to 10 years, and less than 90 mm Hg from 11 to 17 years.

10.10 APPENDIX 10: LIST OF OPPORTUNISTIC INFECTIONS

- Aspergillosis
- Blastomyces dermatitidis (endemic in the south-eastern and south-central states US, along Mississippi and Ohio Rivers)
- Candidiasis - only systemic or extensive mucosal or cutaneous candidiasis
- Coccidioides immitis (endemic south-western US and Central and South America)
- Cryptococcus
- Cytomegalovirus
- Herpes simplex (disseminated)
- Herpes zoster (disseminated; ophthalmic; involvement of 2 or more dermatomes)
- Histoplasmosis (pulmonary or disseminated; most common tropical areas Tennessee-Ohio-Mississippi river basins)
- Listeriosis
- Mycobacterium TB
- Mycobacterium avium
- NonTB mycobacteria
- Pneumocystis pneumonia

This list is indicative and not exhaustive.

10.11 APPENDIX 11: ABBREVIATIONS

ACQ-6:	asthma control questionnaire 6-items
AD:	atopic dermatitis
ADA:	anti-drug antibody
ADR:	adverse drug reaction
AE:	adverse event
AESI:	adverse event of special interest
ALT:	alanine aminotransferase
CLC:	Charcot-Leyden crystal
COPD:	chronic obstructive pulmonary disease
COVID-19:	Coronavirus Disease-2019
CRS:	chronic rhinosinusitis
CRSsNP:	chronic rhinosinusitis without nasal polyposis
CRSwNP:	chronic rhinosinusitis with nasal polyposis
CSR:	clinical study report
CSU:	chronic spontaneous urticaria
CT:	computed tomography
ECG:	electrocardiogram
ECP:	eosinophilic cationic protein
eCRF:	electronic case report form
ELISA:	enzyme-linked immunosorbent assay
EoE:	eosinophilic esophagitis
EOS:	end of study
EOT:	end of treatment
EQ-5D:	EuroQol-5 dimensions
ESS:	endoscopic sinus surgery
EU:	European Union
FEF:	forced expiratory flow
FeNO:	Fractional exhaled nitric oxide
FEV_1:	Forced expiratory volume
FVC:	forced vital capacity
GA^2LEN:	Global Allergy and Asthma European Network
GCP:	Good Clinical Practice
GDPR:	General Data Protection Regulation
HBcAb:	hepatitis B core antibody
HBsAb:	hepatitis B surface antibody
HBsAg:	hepatitis B surface antigen
HBV:	hepatitis B virus
HCRU/P:	Health Care Resource Utilization/Productivity
HCV:	hepatitis C virus
HCVAb:	hepatitis C virus antibody
HIV:	human immunodeficiency virus
HRQoL:	health-related quality of life

IB:	Investigator’s Brochure
ICF:	informed consent form
IEC:	Independent Ethics Committee
IgE:	immunoglobulin E
IL:	interleukin
IL-4Rα:	interleukin 4 receptor alpha subunit
IMP:	investigational medicinal product
INCS:	intranasal corticosteroids
IRB:	Institutional Review Board
IRT:	interactive response technology
ITT:	intent-to-treat
IVIG:	intravenous immunoglobulin
LABA:	long-acting β2-adrenergic receptor agonists
LAMA:	long-acting muscarinic acetylcholine receptor antagonists
LMK:	Lund-Mackay
LTE4:	leukotriene E4
NAb:	neutralizing antibody, neutralizing antibody
NC:	nasal congestion
NES:	Normalized Enrichment Score
NMPA:	National Medical Products Administration
NPS:	nasal polyp score
OCS:	oral corticosteroids
PCSA:	potentially clinically significant abnormality
PD:	pharmacodynamic
PGDM:	prostaglandin D2 metabolite
PGIC:	Patient Global Impression of Change
PGIS:	Patient Global Impression of Severity
PK:	pharmacokinetics
PN:	prurigo nodularis
PRO:	Patient-Reported Outcome
PT:	preferred term
q2w:	every 2 weeks
QTcF:	QT interval corrected using Fridericia's formula
SAE:	serious adverse event
SAP:	statistical analysis plan
SC:	subcutaneous
SCS:	systemic corticosteroids
SD:	standard deviation
SNOT-22:	Sino-Nasal Outcome Test 22-item
SoA:	Schedule of Activities
SOC:	system organ class
SUSAR:	suspected unexpected serious adverse reaction
TARC:	thymus-and activation-regulated chemokine
TB:	tuberculosis
TEAE:	treatment-emergent adverse event
TESAE:	treatment-emergent serious adverse event

TNF:	tumor necrosis factor
TSS:	total symptom score
ULN:	upper limit of normal
UPSIT:	University of Pennsylvania smell identification test
US:	United States
VAS:	Visual Analog Scale
WOCBP:	women of childbearing potential
WOCF:	worst observation carried forward

10.12 APPENDIX 12: PROTOCOL AMENDMENT HISTORY

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

10.12.1 Amended protocol 01 (08 July 2021)

This amended protocol 01 (amendment 01) is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

10.12.1.1 OVERALL RATIONALE FOR THE AMENDMENT

The primary purpose of this amendment is to change the primary analysis population to the intent-to-treat (ITT) population in Part A and to remove comorbid asthma as inclusion criterion as per a Health Authority request. The Sponsor changed the handling of sinonasal surgery from composite strategy to hypothetical strategy in the primary estimand to better reflect the clinical scenario. Additional changes are described in the table below.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Cover page	To add the Sponsor's name and address that were missing To add the NCT number	To provide missing information.
Section 1.1 Synopsis	Acronym 'Liberty CRSsNP ORION' added	To provide missing information.
Sections 1.2 Schema and 1.3 Schedule of Activities (SoA)	Following text added: Note that Part B will not start until after primary analysis of Part A.	Clarification
Section 1.3 SoA	Nasal endoscopy: Addition of local reading for excluding purulent discharge	To allow for improved visual assessment of discharge by local investigator as difficult to evaluate in video by central readers
	Urinalysis (urine dipstick): Note added that China will use the urine sample analysis	To clarify that for participants enrolled in China, the urine

Section # and Name	Description of Change	Brief Rationale
		analysis will be performed at laboratory (not dipstick) as per local medical practice
	Footnote k: V6 was corrected to V5 as follows: A CT scan was performed at V5 (Week 24 for Parts A and B).	Correction
	Footnote r was changed to: Clinical laboratory testing at V1 includes hepatitis screen covering hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (HBsAb), hepatitis B core antibody (HBcAb) including total HBcAb, hepatitis C virus antibodies (HCVAb), HIV screen (anti-HIV-1 and HIV-2 antibodies). In case of results showing HBsAg (negative) and HBcAb (positive), an HBV DNA testing will be performed and should be confirmed negative prior to randomization. In case of results showing HCVAb (positive), HCV RNA testing will be performed and should be confirmed negative prior to randomization	HBcAb IgM and IgG were removed as only HBcAb total test is performed at Central Laboratory. Adjusted language to allow for clarity on when to do reflex testing for HBV or HCV.
	Footnote t was added: Urine biomarkers (LTE4, PGDM, creatinine) collection time and date to be collected.	Clarification
	Footnotes v and w: Not applicable in China was added.	Correction
Section 2.3.1 Risk assessment	Addition of a reference to the current Investigator's Brochure (IB) for the number of participants exposed to dupilumab in clinical studies.	Clarification
Section 3 Objectives and endpoints and 1.1 Synopsis	Addition of a secondary objective and related endpoints in Part A (at Weeks 24 and 52) as follows: Objective: To evaluate the effect of dupilumab in the subgroup of participants with screening blood eosinophil count ≥300 cells/mm^3 compared to placebo Endpoints: -Change from baseline to Weeks 24 and 52 (Part A) in opacification of sinuses assessed by CT scan using LMK score in the screening blood eosinophil count ≥300 cells/mm^3 population. -Change from baseline to Weeks 24 and 52 (Part A) in sinus total symptom score (sTSS) using the screening blood eosinophil count ≥300 cells/mm^3 population. -Evaluation of other secondary endpoints listed above in the screening blood eosinophil count ≥300 cells/mm^3 population.	To evaluate the effect of dupilumab in a subgroup of interest as the primary analysis population was changed to the ITT population regardless of eosinophil levels in Part A, per Health Authority request.

Section # and Name	Description of Change	Brief Rationale
Section 3.1 Appropriateness of measurements	The text was simplified.	Edited for clarity.
Section 4.1 Overall design and 1.1 Synopsis	Correction of the alert for IRT modified from 50% to no more than 70% as follows: Alert built to limit the number of participants without comorbid asthma to no more than 70% of the randomized population.	To allow flexibility in recruitment of comorbid asthma population
Section 5.1 Inclusion criteria	I 06. was modified to remove b) comorbid asthma as follows: Participants must have at least one of the 2 following features: a) Prior sinonasal surgery (see note at end of section 5.2 for definitions of sinonasal surgery) for CRS b) Treatment with SCS therapy for CRS as defined by any dose and duration within the prior 2 years before screening (Visit 1) or intolerance/contraindication to SCS.	Per Health Authority request
	Inclusion criterion I 09. was corrected to remove 'men' as follows: Contraception use by women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.	Correction
Section 5.2 Exclusion criteria	Exclusion criterion E 01. was corrected to add 'observed during nasal' as follows: a) Participants with nasal polyposis observed during nasal endoscopy at Visit 1.	Correction
	Exclusion criterion E 02. was corrected to replace blood boil example by hemangioma example.	Correction
	Exclusion criterion E 16. was corrected to add 'within 12 months or who discontinued dupilumab use due to adverse event' as follows: Participation in prior dupilumab clinical study or have been treated with commercially available dupilumab within 12 months or who discontinued dupilumab use due to an adverse event	Correction
Section 5.4 Screen failures	Removal of the last sentence of the paragraph: There is no need to screen fail such participants if the test finally meets the eligibility criteria.	Correction
Section 6.3 Measures to minimize bias: randomization and blinding	Reference to specific regions (Asia, East Europe or Western Countries) was removed from the sentence: randomization will be stratified by region.	Removed due to being too specific and will be described in further detail in the statistical analysis plans (SAPs).
	Code breaking: Investigator could decide at his/her discretion to contact the Sponsor to	To clarify that the responsibility to unblind treatment assignment in emergency situations resides

Section # and Name	Description of Change	Brief Rationale
	discuss the situation in case of unblinding participant's intervention assignment.	solely with the investigator as per the EMA GCP Inspectors Working Group (GCP IWG) and the Clinical Trial Facilitation Group (CTFG). Consequently, the Sponsor cannot require or insist on being involved in the decision to unblind, stall or delay in any way the unblinding of trial participant treatment in emergency situations.
Section 6.5.2 Prohibited medications	Removal of antifungals as prohibited medication and addition of "systemic" to antibiotics.	Correction
Section 8 Study assessments and procedures	Addition of the order of assessments/procedures to be conducted during study visits.	For clarity
	Correction of amount of blood collected for adults in Part A and B and addition of amount of blood collected in adolescents in Part B.	Correction
Section 8.1.8 EuroQol-5 dimensions questionnaire	Clarification that the adult version of the questionnaire that is adapted to participants age 16 and older "can be used for participants aged 12-15 as stated in the EQ-5D user guide".	For clarity
Section 8.6 Pharmacodynamics	Addition of analysis of periostin and total protein in nasal secretions. Addition of analysis of urine creatinine. Nasal brushing biomarkers: addition of nasal brushing RNA analysis. Addition of whole blood deoxyribonucleic acid for pharmacogenetic analysis.	To add analyses that are intended to be performed on samples being collected in the protocol that were inadvertently omitted
Section 8.7 Genetics	Clarification that pharmacogenomic testing from whole blood samples was optional while transcriptomics on nasal brushings was mandatory.	For clarity
Section 9.3 Populations for analyses Section 9.4.2 Primary endpoint(s) and 1.1 Synopsis	The primary efficacy analysis population was changed from ITT population with screening blood eosinophil count ≥300 cells/mm^3 to ITT population for Part A. Intercurrent event handling strategy for prohibited medications added in Table 7.	Per Health Authority request for Part A
Section 9.2 Sample size determination Section 9.4.2 Primary endpoint(s) Section 9.4.3 Secondary endpoint(s)	Power calculations updated for Part A. Screening blood eosinophil count added as covariate in model-based analyses for Part A.	To reflect change in the primary efficacy analysis population
Section 9.4.1 General considerations	Multiplicity considerations updated	
Section 9.4.2 Primary endpoint(s) and 1.1 Synopsis	Intercurrent event handling strategy for undergoing sinonasal surgery for CRSsNP prior to	To change handling of sinonasal surgery in the primary estimand to

Section # and Name	Description of Change	Brief Rationale
	Week 24 was changed from “data after surgery will be assigned to the worst possible score (composite strategy)” to “Data collected after surgery will be set to missing and the worst post-baseline value on or before the time of surgery will be used to impute missing Week 24 value (WOCF). For participants with no post-baseline values, the baseline value will be used (hypothetical strategy).” Sensitivity/supplementary analyses updated	an approach more appropriate for this clinical setting and to update supplementary analyses accordingly
Section 10.1.7 Data quality assurance	“printed or electronic CRF" was replaced by “eCRF”	Clarification
Section 10.2 Appendix 2: Clinical Laboratory tests	Table 8: routine urinalysis was replaced by urine dipstick. Addition of footnote b: For participants enrolled in China, the urine analysis will be performed at laboratory (not dipstick).	Correction
	HIV viral load test was removed	Correction
	Only total HBcAb will be performed. Revision of HBV DNA testing in case of HBsAg (negative) and HBcAb (positive). Revision of HCV RNA testing in case of HCVAb (positive).	Adjusted language to allow for clarity on when to do reflex testing for HBV or HCV
Section 10.4 Appendix 4: Contraceptive guidance and collection of pregnancy information	For male participants with partners who become pregnant, the following sentence was removed: ‘This applies only to male participants who receive dupilumab’.	Correction
Section 10.11 Appendix 11: Abbreviations	List of abbreviations updated	Correction
Section 10.12 Appendix 12: Protocol amendment history	Section updated to state that the Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents	Aligned with Sanofi procedures.
Global	Minor editorial updates and formatting changes were made.	To correct minor errors

11 REFERENCES

1. Pleis JR, Lucas JW, Ward BW. Summary health statistics for U.S. adults: National Health Interview Survey, 2008. Vital Health Stat 10. 2009;(242):1-157.

2. Jarvis D, Newson R, Lotvall J, Hastan D, Tomassen P, Keil T, et al. Asthma in adults and its association with chronic rhinosinusitis: the GA2LEN survey in Europe. Allergy. 2012;67(1):91-8.

3. Hamilos DL, Holbrook EH. Chronic rhinosinusitis: Clinical manifestations, pathophysiology, and diagnosis. Waltham: UpToDate Inc. 2017.

4. Benjamin MR, Stevens WW, Li N, Bose S, Grammer LC, Kern RC, et al. Clinical characteristics of patients with chronic rhinosinusitis without nasal polyps in an academic setting. J Allergy Clin Immunol Pract. 2019;7(3):1010-6.

5. Stevens WW, Peters AT, Tan BK, Klingler AI, Poposki JA, Hulse KE, et al. Associations Between Inflammatory Endotypes and Clinical Presentations in Chronic Rhinosinusitis. J Allergy Clin Immunol Pract. 2019;7:2812-20.

6. Stevens WW, Ocampo CJ, Berdnikovs S, Sakashita M, Mahdavinia M, Suh L, et al. Cytokines in chronic rhinosinusitis: role in eosinophilia and aspirin-exacerbated respiratory disease. Am J Respir Crit Care Med. 2015;192(6):682-94.

7. Tomassen P, Vandeplas G, Van Zele T, Cardell LO, Arebro J, Olze H, et al. Inflammatory endotypes of chronic rhinosinusitis based on cluster analysis of biomarkers. J Allergy Clin Immunol. 2016;137(5):1449-56.e4.

8. Kato A. Immunopathology of chronic rhinosinusitis. Allergol Int. 2015;64(2):121-30.

9. Tan BK, Klingler AI, Poposki JA, Stevens WW, Peters AT, Suh LA, et al. Heterogeneous inflammatory patterns in chronic rhinosinusitis without nasal polyps in Chicago, Illinois. J Allergy Clin Immunol. 2017;139(2):699-703.e7.

10. Wang X, Zhang N, Bo M, Holtappels G, Zheng M, Lou H, et al. Diversity of TH cytokine profiles in patients with chronic rhinosinusitis: a multicenter study in Europe, Asia, and Oceania. J Allergy Clin Immunol. 2016;138(5):1344-53.

11. Bachert C. GA2LEN Sinusitis Cohort: Main Findings (data on file). 2020.

12. Matsuwaki Y, Ookushi T, Asaka D, Mori E, Nakajima T, Yoshida T, et al. Chronic rhinosinusitis: risk factors for the recurrence of chronic rhinosinusitis based on 5-year follow-up after endoscopic sinus surgery. Int Arch Allergy Immunol. 2008;146(suppl1):77-81.

13. Sella GC, Tamashiro E, Sella JA, Aragon DC, de Mendonça TN, de Paula Arruda LK, et al. Asthma is the dominant factor for recurrence in chronic rhinosinusitis. J Allergy Clin Immunol Pract. 2020;08(1):302-9.

14. Lal D, Scianna JM, Stankiewicz JA. Efficacy of targeted medical therapy in chronic rhinosinusitis, and predictors of failure. Am J Rhinol Allergy. 2009;23(4):396-400.

15. Rosenfeld RM, Piccirillo JF, Chandrasekhar SS, Brook I, Ashok Kumar K, Kramper M, et al. Clinical practice guideline (update): adult sinusitis. Otolaryngol Head Neck Surg. 2015;152(2 Suppl):S1-S39.

16. Simpson EL, Bieber T, Guttman-Yassky E, Beck LA, Blauvelt A, Cork MJ, et al. Two Phase 3 Trials of Dupilumab vs Placebo in Atopic Dermatitis. N Engl J Med. 2016;375(24):2335-48.

17. Castro M, Corren J, Pavord ID, Maspero J, Wenzel s, Rabe KF, et al. Dupilumab Efficacy and Safety in Moderate-to-Severe Uncontrolled Asthma. N Engl J Med. 2018;378(26):2486-96.

18. Kevin Kunzmann. Dupilumab hits Phase 3 endpoints for eosinophilic esophagitis. HCP Live, 2020 May 27 [Cited: 2020 Jun 05]. Available from: https://www.mdmag.com/medical-news/dupilumab-phase-3-endpoints-eosinophilic-esophagitis

19. Bachert C, Han JK, Desrosiers M, Hellings PW, Amin N, Lee SE, et al. Efficacy and safety of dupilumab in patients with severe chronic rhinosinusitis with nasal polyps (LIBERTY NP SINUS-24 and LIBERTY NP SINUS-52): results from two multicenter, randomized, double-blind, placebo-controlled, parallel-group phase 3 trials. Lancet. 2019;394(10209):1638–50.

20. Maspero JF, Katelaris CH, Busse WW, Castro M, Corren J, Chipps BE, et al. Dupilumab Efficacy in Uncontrolled, Moderate-to-Severe Asthma with Self-Reported Chronic Rhinosinusitis. J Allergy Clin Immunol Pract. 2020;8(2):527-39.

21. Bhattacharyya N, Gilani S. Prevalence of Potential Adult Chronic Rhinosinusitis Symptoms in the United States. Otolaryngol Head Neck Surg. 2018;159(3):522-5.

22. Han DH, Kim SW, Cho SH, Kim DY, Lee CH, Kim SS, et al. Predictors of bronchial hyperresponsiveness in chronic rhinosinusitis with nasal polyps. Allergy. 2009:64(1):118-22.

23. Tokunaga T, Sakashita M, Haurna T, Asaka D, Takeno S, Ikeda H, et al. Novel scoring system and algorithm for classifying chronic rhinosinusitis: the JESREC study. Allergy. 2015;70(8):995-1003.

24. Ho J, Hamizan A, Alvarado R, Rimmer J, Sewell W, Harvey RJ. Systemic predictors of eosinophilic chronic rhinosinusitis. Am J Rhinol Allergy. 2018;32(4):252-7.

25. Hu Y, Cao PP, Liang GT, Cu YH, Liu Z. Diagnostic significance of blood eosinophil count in eosinophilic chronic rhinosinusitis with nasal polyps in Chinese adults. Laryngoscope. 2012;122(3):498-503.

26. Delemarre T, Holtappels G, De Ruyck N, Zhang N, Nauwynck H, Bachert C, et al. Type 2 inflammation in chronic rhinosinusitis without nasal polyps: Another relevant endotype. JACI 2020 (in press): https://doi.org/10.1016/j.jaci.2020.04.040) last accessed 17-Jul-2020.

27. Kambara R, Minami T, Akazawa H, Tsuji F, Sasaki T, Inohara H, et al. Lower airway inflammation in eosinophilic chronic rhinosinusitis as determined by exhaled nitric oxide. Int Arch Allergy Immunol. 2017;173(4):225-32.

28. Ho J, Earls P, Harvey RJ. Systemic biomarkers of eosinophilic chronic rhinosinusitis. Curr Opin Allergy Clin Immunol. 2020;20:23-29.

29. Ding GQ, Zheng CQ. The expression of MUC5AC and MUC5B mucin genes in the mucosa of chronic rhinosinusitis and nasal polyposis. Am J Rhinol. 2007;21(3):359-66.

30. Cao PP, Li HB, Wang BF, Wang SB, You XJ, Cui YH, et al. Distinct immunopathologic characteristics of various types of chronic rhinosinusitis in adult Chinese. J Allergy Clin Immunol 2009;124(3):478-84,484.e1-2.

31. Martinez-Anton A, Debolos C, Garrido M, Roca-Ferrer J, Barranco C, Alobid I, et al. Mucin genes have different expression patterns in healthy and diseased upper airway mucosa. Clin Exp Allergy. 2006;36(4):448-57.

32. Bolger WE, Butzin CA, Parsons DS. Paranasal sinus bony anatomic variations and mucosal abnormalities: CT analysis for endoscopic sinus surgery. Laryngoscope. 1991;101(1Pt1):56-64.

33. Malekzadeh S, McGuire JF. The new histologic classification of chronic rhinosinusitis. Curr Allergy Asthma Rep. 2003;3(3):221-6.

34. Kanoh S, Tanabe T, Rubin BK. IL-13-induced MUC5AC production and goblet cell differentiation is steroid resistant in human airway cells. Clin Exp Allergy. 2011;41(12):1747-56.

35. Bautista MV, Chen Y, Ivanova VS, Rahimi MK, Watson AM, Rose MC. IL-8 regulates mucin gene expression at the posttranscriptional level in lung epithelial cells. J Immunol. 2009;183(3):2159-66.

36. Shimizu S, Kouzaki H, Ogawa T, Takezawa K, Tojima I, Shimizu T. Eosin-ophil-epithelial cell interactions stimulate the production of MUC5AC mucin and profibrotic cytokines involved in airway tissue remodeling. Am J Rhinol Allergy. 2014;28(2):103-9.

37. Lund VJ, Mackay, IS. Staging in rhinosinusitus. Rhinology. 1993;31:183-4.

38. Metson R, Gliklich RE, Stankiewicz JA, Kennedy DW, Duncavage JA, Hoffman SR, et al. Comparison of sinus computed tomography staging systems. Otolaryngol Head Neck Surg. 1997;117(4):372-9.

39. Oluwole M, Russell N, Tan L, Gardiner Q, White P. A comparison of computerized tomographic staging systems in chronic sinusitis. Clin Otolaryngol Allied Sci. 1996;21(1):91-5.

40. Scadding G, Hellings P, Alobid I, Bachert C, Fokkens W, Van Wijk RG, et al. Diagnostic tools in Rhinology EAACI position paper. Clin Transl Allergy. 2011;1(1):1-39.

41. Hopkins C, Gillett S, Slack R, Lund VJ and Browne JP. Psychometric validity of the 22-item sinonasal outcome test. Clin Otolaryngol. 2009;34(5):447-54.

42. Deeb R, Malani PN, Gil B, Jafari-Khouzani K, Soltanian-Zadeh H, Patel S, et al. Three-dimensional volumetric measurments and analysis of the maxillary sinus. American journal of rhinology and allergy. 2011;25(3);152-56.

43. Fokkens W, Lund VJ, Mullol J, Bachert C, Alobid I, Baroody F, et al. EPOS 2012: European position paper on rhinosinusitis and nasal polyps 2012. A summary for otorhinolaryngologists. Rhinology. 2012;50(1):1-12.

44. Juniper EF, Svensson K, Mork AC, Stahl E. Measurement properties and interpretation of three shortened versions of the Asthma Control Questionnaire. Respir Med. 2005;99(5):553-8.

45. EuroQol Group. EuroQol-A new facility for the measurement of health-related quality of life. Health Policy. 1990;16(3):199-208.

46. [redacted]

47. [redacted].

48. Sampson HA, Munoz-Furlong A, Campbell RL, Adkinson NF, Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: Summary report - Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol. 2006;117:391-7.

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