AMENDED CLINICAL TRIAL PROTOCOL 03

Protocol title:	**A randomized double-blind placebo-controlled parallel group study assessing the efficacy and safety of dupilumab in patients with Allergic Fungal Rhinosinusitis (AFRS)**
Protocol number:	**EFC16724**
Amendment number:	**03**
Compound number (INN/Trademark):	**SAR231893** **Dupilumab/Dupixent®**
Study phase:	**Phase 3**
Short title:	**Dupilumab in AFRS** **LIBERTY-AFRS-AIMS**
Sponsor name:	**Sanofi-Aventis Recherche & Développement**
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Regulatory agency identifier number(s):

IND:	IND105379
EudraCT:	2020-002999-12
NCT:	NCT04684524
WHO:	U1111-1246-7549
EUDAMED	Not applicable
Other:	Not applicable

Date:	01-Mar-2023	Total number of pages: 129

PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY

Document	Country/countries impacted by amendment	Date, version
Amended Clinical Trial Protocol 03	All	01 March 2023, version 1 (electronic 3.0)
Amended Clinical Trial Protocol 02	All	23 November 2021, version 1 (electronic 2.0)
Amended Clinical Trial Protocol 01	All	30 March 2021, version 1 (electronic 1.0)
Original Protocol		31 August 2020, version 1 (electronic 2.0)

Amended protocol 03 (01 March 2023)

This Amended Protocol 03 (Amendment 03) 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

Given the changing dynamics during the COVID-19 pandemic period, the Sponsor has decided to update the primary endpoint from the proportion of subjects who undergo or plan to receive rescue therapy (SCS and/or surgery) to an objective endpoint that is not impacted by the pandemic dynamics and is clinically relevant, namely change from baseline in sinus opacifications assessed by computerized tomography (CT) scans using the Lund Mackay (LMK) score at Week 52. Consequently, the sample size is updated from 120 subjects to 62 subjects. Sinus CT scan opacification reflects both nasal polyps burden in the sinuses as well as the sinus mucosal thickening and accumulation of inflammatory secretions, including allergic fungal mucin, a hallmark of AFRS (1). Therefore, objective evaluation of sinus opacification (LMK) is widely used to evaluate disease progression and management in the sinuses and is considered a clinically relevant measure for the evaluation of efficacy of dupilumab in clinical signs of AFRS, a rare disease with a limited geographical distribution to warm and humid climates. The proportion of participants who undergo or plan to receive rescue therapy (SCS and/or surgery) will be assessed as a secondary endpoint.

Minor changes and clarifications and typographical errors are not mentioned in the table below.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis, 3 Objectives and Endpoints	The primary objective updated from • To evaluate the ability of dupilumab to reduce the need for rescue therapy with systemic corticosteroids (SCS) or surgery for AFRS in patients with AFRS who previously have had sino-nasal surgery To • To evaluate the efficacy of treatment with dupilumab to reduce sinus opacification in a population with allergic fungal rhinosinusitis (AFRS)	The LMK score is a clinically relevant measure of efficacy in a rare disease with limited geographic distribution.
	The key secondary endpoint switched to primary endpoint as below: • Change from baseline in sinus opacifications assessed by computerized tomography (CT) scans using the Lund Mackay (LMK) score at Week 52	To align primary endpoint with change in primary objective.
	The primary endpoint switched to secondary endpoint as below: • Proportion of participants who receive SCS and/or undergo/plan to undergo surgery for AFRS during the planned study treatment period	Since the new primary endpoint is change from baseline in LMK score at Week 52, the previous primary endpoint is now a secondary endpoint.
1.1 Synopsis, 3 Objectives and Endpoints, 9.4.3 Secondary endpoint(s)	[redacted]	
1.1 Synopsis, 4.1 Overall Design	Added text for stratification by time from last surgery to include 'surgery naïve participants' for those in '≤2 years' group	To align with the removal of inclusion criterion I04.
1.1 Synopsis, 4.1 Overall Design, 3.1 Appropriateness of Measurements, 9.2 Sample size determination	The sample size changed from 120 (60 per arm) to 62 (31 per arm). The updated study power is >99% for the primary endpoint and 80% for the secondary endpoint using an alpha=0.05.	A sample size of 62 participants would provide ample power for the new primary endpoint based on change from baseline in LMK at Week 52, which is a clinically relevant measure of efficacy. The new sample size would allow for sufficient power for the original primary endpoint of rescue therapy utilization as a secondary endpoint.
	Updated text to reflect switching of primary to secondary endpoint and vice-versa.	
1.1 Synopsis, 9.4.2 Primary endpoint(s), 9.4.3 Secondary endpoint(s)	In statistical considerations, 1) primary and secondary endpoint switched, 2) stratification factor of disease pattern removed from the statistical model, and 3) intercurrent event of taking SCS for any reason changed from treatment policy to composite strategy (WOCF).	The primary and secondary endpoints were switched, and the sample size was optimized based on this change. The stratification factor for disease pattern was removed from the statistical model due to only rare unilateral participants identified. The treatment policy was changed to composite strategy, an approach more appropriate for this clinical setting.

Section # and Name	Description of Change	Brief Rationale
1.2 Schema	Schema updated with updated number of participants in each study arm	To reflect the change in sample size
1.3 Schedule of Activities (SoA)	Updated Footnote 'c' to add more clarity in study completion definition.	Clarification of study completion date to align with Section 4.4.
	Added below text to Footnote 'j' Questionnaires in paper form are not permitted; only electronic form is allowed.	Clarification that paper documentation is not permitted.
	Added below text to Footnote 'm' 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 for UPSIT assessment due to variable availability of testing materials at sites.
1.3 Schedule of Activities (SoA), 8.2.2 Vital signs	Added below text to footnote 'o' for vital signs and added to the vital signs sub-section Height must be collected at each visit only for pediatric participants; collect height for adult participants at screening visit (V1) only.	Clarification that height documentation for adults is only required at Visit 1.
5.1 Inclusion Criteria	Deleted the following inclusion criteria: I 04. History of sino-nasal surgery(ies). Note: Examples of sino-nasal surgery but not limited to include endoscopic sinus surgery (ESS) and may involve removal of inflamed/dysfunctional mucosa and may include procedures such as anterior and posterior ethmoidectomy, maxillary antrostomy, sphenoidotomy, frontal sinusotomy, and/or polypectomy.	To accommodate variations in treatment paradigm per local practice.
	Updated the heading for I06 from 'Sex' to 'Sex, contraceptive/barrier method and pregnancy testing requirements/breastfeeding' and updated the WOCBP definition.	Administrative/SOP updates
5.4 Screen Failures	Added below sentence at the end of section: All other screening procedures must be repeated for rescreening.	Clarification that screen failed participants who are rescreened need repeat assessments for visit 1.
8.1 Efficacy Assessments	Moved the below sub-section after the sub-section for Three-dimensional volumetric measurement of the sinuses: 8.1.2 Proportion of participants who receive SCS and/or undergo/plan to undergo surgery for AFRS during the planned study treatment period	In order to reflect the change in primary endpoints.
[redacted]		
8.6 Pharmacodynamics	Removed measurement of secreted P-glycoprotein	Test is unable to be performed by the Sponsor due to assay limitations.

Section # and Name	Description of Change	Brief Rationale
9.4.1 General considerations	Alpha level of 0.01 was changed to 0.05 and study is considered positive when the primary endpoint achieves statistical significant with 2-sided significance level 0.05.	The alpha level was adjusted to support an optimized sample size for this rare condition.
10.1.5 Dissemination of clinical study data	Replaced clinicalstudydatarequest.com by vivli.org	Administrative change.
10.2 Appendix 2: Clinical Laboratory Tests, 10.6 Appendix 6: Liver and Other Safety: Actions and Follow-Up Assessments	Added below footnote in Table 9 - Protocol-required laboratory assessments, for clinical chemistry: 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. Added this same text as note in Section 10.6 Appendix 6	Clarification on preference for local lab to perform urgent tests associated with DILI.
10.3.2 Definition of SAE	Deleted following text from list of medically important events: Cancers diagnosed during the study or aggravated during the study	Correction, as cancers are already separately considered SAEs.
10.7 Appendix 7: Clinician-Reported Outcomes And Patient-Reported Outcomes	Added new appendices for following questionnaires: 10.7.5 Morning Diary, [redacted] Added watermark “For Review Only” to all the questionnaires	Addition of screenshots of patient reported outcome tools to allow clarification to sites.
Throughout	Updated patient to participant wherever applicable	Formatting and typographical

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1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Protocol title: A randomized double-blind placebo-controlled parallel group study assessing the efficacy and safety of dupilumab in patients with Allergic Fungal Rhinosinusitis (AFRS)

Short title: Dupilumab in AFRS
LIBERTY-AFRS-AIMS

Rationale:

Allergic Fungal Rhinosinusitis (AFRS) is a chronic disease characterized by a robust type 2 inflammatory response directed against colonizing fungi in the sinuses with accumulation of eosinophilic mucin containing fungal hyphae, which results in persistent sinus opacification and nasal polyp formation. This disease accounts for a small (<10%) portion of patients with chronic rhinosinusitis (CRS). The disease predominantly occurs in regions with warm, humid climates. Although all patients present with nasal polyps and there are shared type 2 driven inflammatory pathways underlying the 2 conditions, AFRS is distinct from chronic rhinosinusitis with nasal polyposis (CRSwNP) in its diagnosis, presentation, clinical course, pathophysiology, and management (2, 3). Unlike CRSwNP, diagnosis of AFRS requires evidence of immunoglobulin (Ig)E mediated inflammatory response to fungal hyphae (specific IgE serology or skin test), nasal polyps, characteristic computed tomography (CT) findings, eosinophilic mucin without fungal invasion into sinus tissue, and a positive fungal stain of sinus contents (4). Patients with AFRS have an indolent disease course, with slow growing opacification of sinuses due to mucin production. However, the disease can be severe and unlike CRSwNP, it often leads to bony erosion of the sinuses and even facial deformities. The disease occurs in a younger population with a mean age in the 20s to 30s (2, 5). Patients with AFRS are more likely to have concomitant asthma than the general population, but the overall incidence is lower at approximately 25% (6). The disease itself is driven by an interplay between the presence of fungal spores and a type 2 inflammatory reaction. This response shares many features with CRSwNP and type 2 mediators including interleukin-4 (IL-4), IL-5, and IL-13 have been found to be upregulated in tissue from both diseases. However, molecular endotyping has also identified pathways that are distinct to AFRS, which differentiate AFRS from CRSwNP as a subtype of CRS demonstrating an extreme of type 2 inflammations, such as the ICOS, CD28, and PKCΘ pathways, which play pivotal roles in type 2 inflammatory effector function (7). Although there are rare cases of AFRS in children ≥6 to <12 years of age, in these children the disease commonly leads to facial dysmorphism. The growing facial skeleton of younger children may account for the higher degree of dysmorphism seen as compared to adults. Asymmetric disease and unilateral sinus disease are more frequent in children (above 6 years of age) compared with adults while incidence of bony erosion is comparable with adults (8, 9).

Current treatment paradigms require surgical debridement via endoscopic sinus surgery (ESS) to remove thick mucus as well as any coexisting nasal polyps, followed by adjuvant oral corticosteroid taper. Patients require chronic suppression with topical corticosteroids and may need frequent oral steroid bursts. There is a high early recurrence rate after surgery even with

systemic and topical nasal corticosteroids requiring frequent systemic steroid use and repeated surgeries. Delayed surgery can lead to increased risk for complications as bony erosions thin the sinus walls. The role of antifungals remains unclear and they are currently not recommended (10). There remains great unmet need in identifying novel therapies that address inflammatory underpinnings of the disease processes, minimize the need for systemic corticosteroids (SCS) and their associated side effects, prevent recurrence, prevent complications and bony erosion, and achieve long-lasting disease control.

Dupilumab is a fully human monoclonal antibody (mAb) directed against the interleukin 4 receptor alpha subunit (IL-4Rα), which is a component of IL-4 receptors Type I and Type II, as well as the IL-13 type II 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. Type 2 inflammation is responsible for several pathophysiological mechanisms including inhibition of mast cell and basophil degranulation, reduction in serum IgE levels, and potentially eosinophil trafficking into tissues. Dupilumab has demonstrated efficacy across a broad range of diseases driven by type 2 inflammation, including atopic dermatitis (AD), asthma, and CRSwNP.

In the CRSwNP development program, dupilumab demonstrated a positive benefit-risk and clinically significant efficacy across radiological, endoscopic, and clinical symptoms of disease, resulting in significant reduction in sinus opacification, the need for SCS, and surgery. AFRS patients were not included in the previous dupilumab CRSwNP program. Both AFRS and CRSwNP are a subtype of CRS and share common disease characteristics, including type 2 inflammatory pattern as well as some elements of disease presentation, eg, sinus inflammation, nasal polyps, and symptoms like nasal congestion and rhinorrhea.

Dupilumab, therefore, offers promise of significant benefit above and beyond current standard of care in AFRS and may provide an alternative for those patients who relapse after surgery and may obviate the need for repeated SCS and/or surgeries.

Objectives and endpoints

Objectives	Endpoints
Primary	
• To evaluate the efficacy of treatment with dupilumab to reduce sinus opacification in a population with allergic fungal rhinosinusitis (AFRS)	• Change from baseline in sinus opacifications assessed by computerized tomography (CT) scans using the Lund Mackay (LMK) score at Week 52
Secondary	
• To evaluate the efficacy of treatment with dupilumab to reduce sinus opacification in a population with allergic fungal rhinosinusitis (AFRS) at Week 24	• Change from baseline in sinus opacifications assessed by CT scans using the LMK score at Week 24
• To assess the efficacy of dupilumab to reduce the need for rescue treatments	• Proportion of participants who receive SCS and/or undergo/plan to undergo surgery for AFRS during the planned study treatment period

Objectives	Endpoints
• To evaluate the efficacy of treatment with dupilumab in improving symptoms in AFRS	• Change from baseline in monthly average nasal congestion/obstruction score from the Nasal Symptom Diary at Week 24 and Week 52 • Change from Baseline in the monthly average anterior/posterior rhinorrhea score from the Nasal Symptom Diary at Week 24 and Week 52
• To evaluate the efficacy of dupilumab to reduce nasal polyp formation in participants with AFRS	• Change from baseline in endoscopic nasal polyp score (NPS) compared with placebo at Week 24 and Week 52
• To evaluate the efficacy of dupilumab in improving overall symptom severity and quality of life in AFRS	• Change from baseline in 22-item sino-nasal outcome test (SNOT-22) total score at Week 24 and Week 52 • Change from baseline in monthly average total symptom score (TSS) derived from the Nasal Symptom Diary at Week 24 and Week 52 • Change from baseline in visual analog scale (VAS) rhinosinusitis at Week 24 and Week 52
• To evaluate the efficacy of dupilumab in improving sense of smell in participants with AFRS	• Change from baseline in University of Pennsylvania smell identification test (UPSIT) at Week 24 and Week 52 • Change from baseline in the score of decreased/loss of smell using the Nasal Symptom Diary at Week 24 and Week 52
• To explore the effect of dupilumab as assessed by three-Dimensional CT volumetric measurement of the paranasal sinuses	• Change from baseline to Week 52 in three-Dimensional CT volumetric measurement of the paranasal sinuses
• To evaluate the safety and tolerability of dupilumab when administered to participants with AFRS	• Incidence of treatment-emergent adverse events (TEAEs) or serious adverse events (SAEs) through Week 52
• To evaluate the pharmacokinetics (PK) of dupilumab in participants with AFRS	• Dupilumab concentration in serum over time
• To characterize the effect of dupilumab on total IgE and specific IgE	• Percent change from baseline in total IgE in serum compared with placebo over the 52-week treatment period • Percent change from baseline in fungal-specific IgE in serum compared with placebo over the 52-week treatment period
• To assess immunogenicity to dupilumab in participants with AFRS	• Assessment of incidence of treatment-emergent anti-drug antibodies (ADA) to dupilumab over time

Overall design:

This is a Phase 3, multicenter, 52-week treatment, parallel-group, double-blind, randomized, placebo-controlled study to investigate the efficacy of dupilumab 300 mg every 2 weeks (q2w) for adults and adolescents/children (≥6 to <12 years) ≥60 kg, or dupilumab 200 mg q2w for adolescents/children ≥30 kg and <60 kg, and dupilumab 300 mg every 4 weeks (q4w) for adolescents/children ≥15 kg and <30 kg with signs and symptoms of AFRS. The study will primarily investigate the efficacy of dupilumab to reduce disease burden in the sinuses (sinus opacification) by radiographic imaging. In addition, the study will also evaluate efficacy of dupilumab to reduce the need for repeated SCS and/or surgery, nasal polyps burden, clinical symptoms, and explore other measures of disease activity.

Disclosure Statement:

This is an interventional study with 2 arms that are blinded to both participants and Investigators.

Number of participants:

Approximately 62 participants (31 per arm) with AFRS with prior history of surgery will be randomized in a 1:1 ratio to receive either dupilumab or matching placebo. Randomization will be stratified first by age (adults versus adolescents/children). In adults, randomization will be stratified further by time from last surgery (≤2 years [including surgery naive participants], >2 years), disease pattern (unilateral/bilateral in the endoscopy at screening), and country. In adolescents/children, randomization will not be stratified further.

Intervention groups and duration:

Study intervention(s)

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

- Dupilumab 300 mg q2w for all adults, 300 mg q2w for adolescents/children ≥60 kg at screening, 200 mg q2w for adolescents/children ≥30 kg and <60 kg at screening, or 300 mg q4w for adolescents/children ≥15 kg and <30 kg at screening.
- Matching placebo.

Duration of study period (per participant):

- Screening period (2 to 4 weeks).
- Randomized investigational medicinal product (IMP) intervention period (52 weeks ±3 days).
- Follow-up period (12 weeks ±5 days).

Investigational medicinal products:

- Dupilumab 300 mg and placebo matching dupilumab 300 mg supplied in visually indistinguishable pre-filled syringes.
- Dupilumab 200 mg and placebo matching dupilumab 200 mg supplied in visually indistinguishable pre-filled syringes.

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.
- Dupilumab 200 mg: a 175 mg/mL dupilumab solution in a pre-filled syringe to deliver 200 mg in a 1.14 mL injection.

Route of administration: subcutaneous (SC) injection

Dose regimen:

- One injection of 300 mg q2w for all adults and for adolescents/children weighing ≥60 kg at screening.
- One injection of 200 mg q2w for adolescents/children ≥30 kg and <60 kg at screening.
- One injection of 300 mg q4w for adolescents/children ≥15 kg and <30 kg at screening.

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.
- Placebo matching dupilumab 200 mg: identical formulation to the active 200 mg formulation without dupilumab, in a pre-filled syringe to deliver placebo in a 1.14 mL injection.

Route of administration: SC injection

Dose regimen:

- One injection of placebo matching 300 mg q2w for all adults and for adolescents/children weighing ≥60 kg at screening.
- One injection of placebo matching 200 mg q2w for adolescents/children ≥30 kg and <60 kg at screening.
- One injection of placebo matching 300 mg q4w for adolescents/children ≥15 kg and <30 kg at screening.

Post-trial access to study medication

Posttrial access to study medication will not be provided.

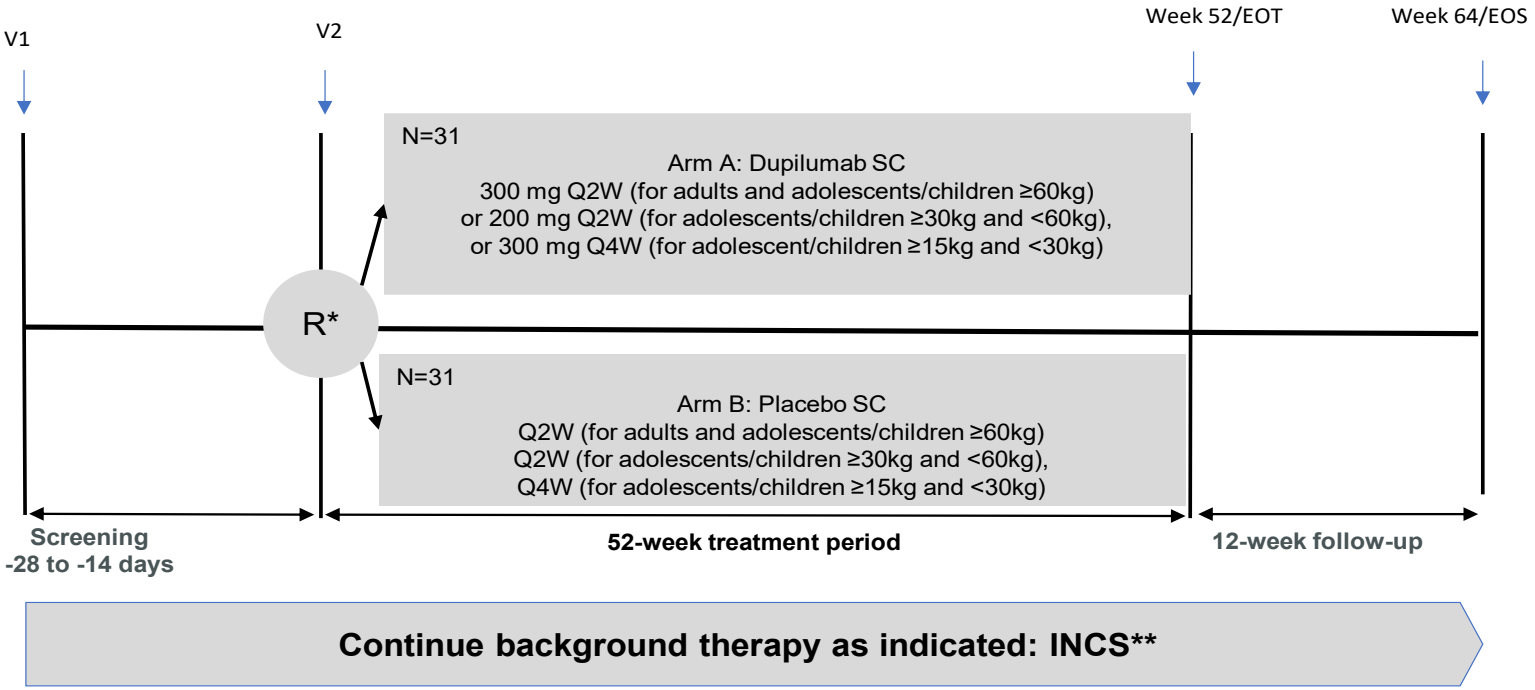
Statistical considerations:

- **Primary endpoint:**
  - The primary endpoint of change from baseline in LMK score at Week 52 will be analyzed using an analysis of covariance (ANCOVA) model with the baseline LMK score, intervention group, time from last surgery (≤2 years, >2 years) and region (combined countries) as covariates, with intercurrent events and missing data being handled by a hybrid method of the worst-observation carried forward (WOCF) and multiple imputation. For participants who undergo/plan to undergo surgery for AFRS, take SCS for any reason or start prohibited biologics, data collected after these intercurrent events (IEs) will be excluded from analysis and the worst post-baseline

value on or before the IE will be assigned to the Week 52 value (ie, WOCF approach). For participants with no post-baseline values, the baseline value will be used (composite strategy). Participants who discontinue the study intervention prematurely are encouraged to follow the planned clinical visits and, in these participants (if without or before the IEs that need to be handled with composite strategy), all data collected after study intervention discontinuation will be included in the analysis (treatment policy strategy). In case there are missing data, a multiple imputation approach will be used to impute missing Week 52 values, and this multiple imputation will use all data from participants but will exclude data from participants who undergo/plan to undergo surgery for AFRS, take SCS for any reason or start prohibited biologics on or before Week 52. Each of the imputed complete data will be analyzed by fitting an analysis of covariance (ANCOVA) model with the baseline covariate and factors for intervention group, time from last surgery (≤2 years, >2 years), and region (combined countries). Statistical inference obtained from all imputed data will be combined using Rubin's rule. Descriptive statistics including number of participants mean, standard error, and least squares (LS) means will be provided. In addition, difference in LS means and the corresponding 95% confidence intervals (CI) will be provided along with the p-values.

- **Secondary endpoints:**
  - The change from baseline to Week 24 and Week 52 in the continuous secondary endpoints will be analyzed using the same analysis approach as for the primary endpoint of change from baseline in LMK score at Week 52.
  - The secondary endpoint of proportion of participants who receive SCS and/or undergo/plan to undergo surgery for AFRS during the 52-week treatment period will be analyzed using a Cochran-Mantel-Haenszel (CMH) test stratified by time from last surgery (≤2 years, >2 years) and region (combined countries). All data collected after study intervention discontinuation and before starting prohibited biologics will be included in the analysis. Participants who discontinue the study follow-up without an event will be considered as no event. The estimate of the odds ratio between dupilumab and placebo will be derived with the corresponding 95% CI and p-value.

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



Q2W: every 2 weeks, Q4W: every 4 weeks, SC: subcutaneous, EOT: end of treatment, EOS: end of study, INCS: intranasal corticosteroids,
R*: randomization;
**For patients already on INCS prior to screening

1.3 SCHEDULE OF ACTIVITIES (SOA)

Procedure	Screening 2-4 wks D-28 to D-14	Intervention period weeks						Follow-up (Wk 64, 12 weeks after EOT)/EOS[c]	Notes
		Wk 0 D1[a]	Wk 2 D15[x]	Wk 12 D85	Wk 24 D169	Wk 36 D252	Wk 52 D364 EOT[b]		
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	Visit window: +3 days for Visit 2, ±3 days for Visits 3 to 7, ±5 days for Visit 8
Screening and baseline									
Informed consent/assent[d]	X								
Inclusion and exclusion criteria	X	X							Recheck clinical status before randomization.
Participant demography	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]	←----------							----------→	
Prior/Concomitant medications	X	X	X	X	X	X	X	X	Check INCS as prior medication at screening and background medication during study period. Record rescue therapy, if applicable.
Randomization		X							
Log-in to IRT	X	X	X	X	X	X	X	X	

Procedure	Screening 2-4 wks D-28 to D-14	Intervention period weeks						Follow-up (Wk 64, 12 weeks after EOT)/EOS[c]	Notes
		Wk 0 D1[a]	Wk 2 D15[x]	Wk 12 D85	Wk 24 D169	Wk 36 D252	Wk 52 D364 EOT[b]		
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	Visit window: +3 days for Visit 2, ±3 days for Visits 3 to 7, ±5 days for Visit 8
Study intervention[g]									
IMP administration[h]		←----------	----------	----------	----------	----------	----------→		IMP will be administered every 14 ±3 days (q2w) for participant weighing ≥30 kg (measured at screening) or 28±3 days (q4w) for participant weighing <30 kg (measured at screening). Between visits at site, home administration is allowed after appropriate training of the participant (or parent/legally authorized representative, or caregiver). The planned last dose is at Week 50 for q2w injections and Week 48 for q4w injections.
Efficacy assessments[j]									
Nasal Endoscopy[i]	X	X		X	X	X	X	X	For participant aged ≥6 to <12 years old, nasal endoscopy will only be mandatory at screening, Week 0, Week 24, and Week 52.
CT scan[k]	X				X		X		Initial CT scan to be done during screening period results should be available prior to randomization (Visit 2). Week 24 CT scan is not required for adolescents/children.

Procedure	Screening 2-4 wks D-28 to D-14	Intervention period weeks						Follow-up (Wk 64, 12 weeks after EOT)/EOS[c]	Notes
		Wk 0 D1[a]	Wk 2 D15[x]	Wk 12 D85	Wk 24 D169	Wk 36 D252	Wk 52 D364 EOT[b]		
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	Visit window: +3 days for Visit 2, ±3 days for Visits 3 to 7, ±5 days for Visit 8
Dispense or download daily diary for symptoms	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. Not required for children aged ≥6 to <12 years.
Nasal Symptom Diary (includes nasal congestion, loss of smell, anterior and posterior rhinorrhea; TSS derived from these 4 items)[l]	<----------Daily diary---------->								Morning assessments captured daily. Not required for children aged ≥6 to <12 years.
22 item Sino-Nasal Outcome Test (SNOT-22)[m]		X		X	X	X	X	X	Not required for children aged ≥6 to <12 years.
Smell test (UPSIT)[m]		X	X	X	X		X	X	Not required for children aged ≥6 to <12 years.
Visual analog scale (VAS) for rhinosinusitis[m]		X	X	X	X	X	X	X	Not required for children aged ≥6 to <12 years.
[redacted]									

Procedure	Screening 2-4 wks D-28 to D-14	Intervention period weeks						Follow-up (Wk 64, 12 weeks after EOT)/EOS[c]	Notes
		Wk 0 D1[a]	Wk 2 D15[x]	Wk 12 D85	Wk 24 D169	Wk 36 D252	Wk 52 D364 EOT[b]		
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	Visit window: +3 days for Visit 2, ±3 days for Visits 3 to 7, ±5 days for Visit 8
[redacted]									
Safety assessments[j]									
Vital signs[o]	X	X		X	X	X	X	X	
12-lead ECG	X								Local reading
AE review	←----------							----------→	
SAE review	←----------							----------→	
Laboratory assessment									
Laboratory assessments (including hematology and biochemistry)[p]	X	X		X	X		X	X	
Urinalysis (urine dipstick)[p]	X	X		X	X		X	X	
HBV, HCV, HIV, TB testing[q]	X								TB test (performed locally if required and results noted in the eCRF).

Procedure	Screening 2-4 wks D-28 to D-14	Intervention period weeks						Follow-up (Wk 64, 12 weeks after EOT)/EOS[c]	Notes
		Wk 0 D1[a]	Wk 2 D15[x]	Wk 12 D85	Wk 24 D169	Wk 36 D252	Wk 52 D364 EOT[b]		
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	Visit window: +3 days for Visit 2, ±3 days for Visits 3 to 7, ±5 days for Visit 8
Pregnancy test (WOCBP only)[r]	X	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)[s]		X		X	X		X	X	
Antidrug antibody sampling (ADA)[s]		X		X	X		X	X	
Serum total IgE and fungal specific IgE[t]	X			X	X		X		Only positive Allergen Specific IgE at screening would be retested at the following visits. If restrictions for exportation of samples, quantification will be done in country central lab as per local regulation.
[redacted]									

Procedure	Screening 2-4 wks D-28 to D-14	Intervention period weeks						Follow-up (Wk 64, 12 weeks after EOT)/EOS[c]	Notes
		Wk 0 D1[a]	Wk 2 D15[x]	Wk 12 D85	Wk 24 D169	Wk 36 D252	Wk 52 D364 EOT[b]		
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	Visit window: +3 days for Visit 2, ±3 days for Visits 3 to 7, ±5 days for Visit 8
[redacted]									

[redacted] ADA: anti-drug antibody; AE: adverse event; CT: computerized tomography; D: day; [redacted] ECG: electrocardiogram; eCRF: electronic case report form; EOS: end of study; EOT: end of treatment; FEF: forced expiratory flow; FEV1: forced expiratory volume; FVC: forced vital capacity; HBcAb: hepatitis B core antibody; HBsAg: hepatitis B surface antigen; HBV: hepatitis B virus; HCV: hepatitis C virus; HCVAb: hepatitis C virus antibody; HIV: human immunodeficiency virus; IEC: Independent Ethics Committee; Ig: immunoglobulin; IMP: investigational medicinal product; IRB: Institutional Review Board; INCS: intranasal corticosteroids; IRT: Interactive response technology; NPS: Nasal Polyp Score; PK: pharmacokinetics; [redacted]; PRO: Patient-Reported outcome; [redacted]; SAE: serious adverse event; SC: subcutaneous; SNOT-22: 22-item sino-nasal outcome; TB: tuberculosis; TSS: total symptom score; UPSIT: University of Pennsylvania smell identification test; VAS: visual analog scale; V: Visit; Wk: Week; WOCBP: women of childbearing potential.

a All assessments at Visit 2, (Day 1) are to be conducted pre-IMP dose with the exception of the assessment of local tolerability of SC injections. Note: Under particular circumstances, that might require additional time, such as eosinophilic mucin collection or skin testing performed during the screening, the screening period can be extended to a maximum of additional 14 days (maximum of 42 ±3 days).

b Participants who discontinue the study treatment prematurely (prior to completing the 52-week treatment period) will perform the 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.

c If a participant discontinues treatment period prematurely before Week 40 but completes follow-up to Week 52, he/she will be considered to have completed the study.

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

e Past medical history including allergic comorbidities (asthma, aspirin sensitivity, allergic rhinitis etc). Surgeries will be assessed including type and dates of sino-nasal 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 eCRF. Fungal stain assessment (positive/negative/not done).

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 AE or 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 In case of emergency (eg, natural disaster, pandemic) remote visit (except for Baseline, Week 24 and Week 52) could be considered (eg, Home nursing, Telehealth) 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 lab tests and clinical assessment procedures can be considered to be conducted locally per local regulation requirement.

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

i Nasal endoscopy (including use of decongestants before the procedure): The participant will be considered eligible based on a V1 central reading followed by a V2 local reading of NPS score of 2 out of 4 for unilateral polyps or 3 out of 8 for bilateral polyps.

j Assessments/procedures should be conducted in the following order: Patient-Reported outcome (PRO), Investigator assessments, safety and laboratory assessments (including sample collection for ADA, PK, biomarker, and optional archival serum/plasma, DNA and RNA), and administration of IMP. Questionnaires in paper form are not permitted; only electronic form is allowed.

k CT scan should be performed during screening period before first administration of IMP, at V5 (Week 24 if accepted per local EC requirement) and at V7 (Week 52), and central reading will be used for comparison baseline (BL) to Week 52 for the primary analysis and at EOT. 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. If participant need to have CT scan around the time of surgery the next scheduled CT scans per protocol do not need to occur after a surgery for AFRS. In any case participants may not have more than 3 CT scans during the study.

l Electronic diary is used for daily recording of nasal symptoms: 1) nasal congestion/obstruction 2) anterior rhinorrhea (runny nose), 3) posterior rhinorrhea (post nasal drip), and 4) loss of sense of smell, scored using a 0-3 categorical scale where 0 = no symptoms, 1 = mild symptoms, 2 = moderate symptoms and 3 = severe symptoms). This device is dispensed at V1 and information is downloaded from this device on the other indicated days.

[redacted]

o Vital signs, including blood pressure (mm Hg), pulse (beats per minute), respiratory rate (breaths per minute), body temperature (degrees Celsius), body weight (kg), and height (cm) will be measured at the screening and randomization visits (V1 and V2) and subsequent visit pre-specified in the flow-chart. Vital signs will be measured prior to receiving IMP at the clinic visits in the semi-supine or sitting position using preferably the same arm at each visit. Height must be collected at each visit only for pediatric participants; collect height for adult participants at screening visit (V1) only.

p Refer to Section 10.2 and central laboratory manual for collection details. China will use the urine sample analysis (not dipstick).

q Clinical laboratory testing at V1 includes hepatitis screen covering HBsAg, HBcAb total, HCVAb and HIV screen (anti-HIV-1 and HIV-2 antibodies). In case of results showing HBsAg (negative), and HBcAb total (positive), an HBV DNA testing will be performed and confirmed negative prior to randomization. In case of results showing HCV Ab (positive), an HCV RNA will be performed and should be confirmed negative prior to randomization.

r Only for women of childbearing potential: Serum pregnancy test at V1 and urine pregnancy tests at V2 and every 4 weeks thereafter. A negative result must be obtained between V1 and V2 prior to randomization visits. Urinary test could be performed at home with or without the assistance of a home care provider after appropriate training. In case of positive urine test, the study treatment will be withheld and a serum pregnancy test to confirm the pregnancy should be performed as soon as possible. Pregnancy will lead to definitive treatment discontinuation in all cases.

s At indicated time points serum dupilumab concentration and ADA samples will be collected and archived prior to administration of investigational product. Blood samples for PK and ADA assessment may be collected in case a suspected SAE. In response to AEs of special interest like anaphylaxis or hypersensitivity additional ADA samples may be collected at or near the event based on the medical judgment of the Investigator and/or Sponsor representative. Pharmacokinetic and ADA samples will be collected unless restricted due to local regulation. However, the PK and ADA samples will be collected for safety assessment in the event of an SAE. Samples for ADA will only be collected for analysis in the event of any SAE for participants from China sites.

t For sites that cannot send fungal specific IgE to central lab to test timely, additional local [redacted] tests or skin test may be needed to meet participant's eligibility.

[redacted]

x For participants ≥15 kg to <30 kg at screening and injection every 4 weeks, Visit 3 will be at Week 4. Parent/legally authorized representative, or caregiver injection training will be performed at this visit.

2 INTRODUCTION

Allergic fungal rhinosinusitis is a type 2 mediated disease characterized by thick mucus, opacification of the sinuses, and nasal polyps. Dupilumab is a fully human monoclonal antibody directed against the IL-4Rα, which is a component of IL-4 receptors Type I and Type II, as well as the IL-13 type II 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 inflammations 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 CRS and by blocking the activity of these cytokines, dupilumab has been shown to be an effective treatment for CRSwNP including improved sinus opacification, reduction in nasal polyp burden and improved symptom scores.

2.1 STUDY RATIONALE

Allergic fungal rhinosinusitis is a chronic disease of the sinuses characterized by a type 2 inflammatory response to the presence of fungal hyphae. There is a great unmet need to identify a therapy that can suppress disease progression and potentially limit the need for recurrent surgery or oral corticosteroid exposure. This indolent disease is chronic and is associated with a gradual progression, thick mucus and nasal polyps. Current treatment paradigms require endoscopic nasal sinus surgery including debridement of mucus and polypectomy, followed by a tapering schedule of adjuvant oral corticosteroids. The disease is chronic in nature, and can recur despite surgery, particularly with continued exposure to fungal spores in endemic areas. Patients with recurrence will need rescue therapy, including a short course of oral corticosteroids and even repeat surgery.

Allergic fungal rhinosinusitis is driven by a type 2 inflammatory response in the presence of fungal spores, and therefore is highly likely to respond to dupilumab treatment. The presence of type 2 inflammation is evidenced by polyp formation as well as responsiveness to corticosteroids. Molecular profiling has demonstrated elevations in type 2 inflammatory markers including IL-4, IL-5 (promoter of eosinophil survival, differentiation and taxis), and IL-13, eosinophil cationic protein (eosinophil activation product), eotaxins (eosinophil chemoattractants), P-glycoprotein (marker of eosinophilia, that correlates with Lund Mackay [LMK] score) and immunoglobulin E (IgE) from the nasal mucosa and local secretions (11, 12) as well as overexpression of eosinophilia-related genes (13). Whole gene microarray analysis from ethmoid mucosa has demonstrated an overexpression of type 2 inflammatory genes among patients with AFRS.

Dupilumab is a fully human monoclonal antibody directed against the IL-4Rα, which is a component of IL-4 receptors type I and type II, as well as the IL-13 type II 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 inflammations 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 CRS, asthma and other atopic diseases and by blocking the activity of these cytokines, dupilumab has been shown to be an effective treatment for CRSwNP, a type 2 inflammatory process. This includes 2 successful Phase 3 studies of 24- and 52-weeks duration, in which 300 mg q2w of dupilumab used on top of topical corticosteroids (mometasone furoate nasal spray) in patients with CRSwNP demonstrated a positive benefit-risk and clinically significant efficacy across radiological, endoscopic, and clinical symptoms of disease, resulting in significant reduction in need for SCS and surgery (14). Therefore, given the high degree of overlap between the immunologic drivers for mucus production and nasal polyp formation, considering both AFRS and CRSwNP are a subtype of CRS and share common disease characteristics, including type 2 inflammatory pattern, as well as some elements of disease presentation, eg, sinus inflammation, nasal polyps, and symptoms like nasal congestion and rhinorrhea it is anticipated that dupilumab will have a similar impact on disease burden in patients with AFRS.

Dupilumab, therefore, offers promise of significant benefit above and beyond current standard of care in AFRS and may provide an alternative for those patients who relapse after surgery and may obviate the need for repeated SCS and/or surgeries.

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

2.2 BACKGROUND

Disease Background and Unmet Medical Need

Allergic fungal rhinosinusitis is a disease driven by a type 2 inflammatory response to fungal spores that presents with a chronic and indolent course, mucous and nasal polyp formation in the sinuses and nasal cavity (2).

Allergic fungal rhinosinusitis is present worldwide, predominantly identified in regions with warm and humid climates such as the Southeastern United States (US) (15), and has also been described globally including Japan (16), Turkey (17), Saudi Arabia (18), and India (19). Although the disease is characterized by CRS, and all patients must have nasal polyps as part of the diagnostic criteria, AFRS represents a distinct disease that is driven by dynamic interplay between fungal spores and host defenses. The disease occurs in a younger population with a mean age in the 20s to 30s (2, 5). There may be a greater predominance of African Americans and some reports suggest a greater predominance among individuals with lower socioeconomic status (20). Patients with AFRS are more likely to have concomitant asthma than the general population, but the overall incidence is lower at approximately 25% (6). AFRS typically presents in young adults in their late teens and twenties, however there are rare case reports of AFRS in children between 6 to 12 years of age (9).

More often the presentation of AFRS is subtle and indolent. Patients typically complain of nasal airway obstruction developed gradually (1). Nasal discharge typically has a thick mucoid peanut-butter like appearance. Without timely intervention, possible complications in patients with AFRS can include visual disturbances, proptosis, facial deformity, and intracranial sequelae. The incidence of bony erosion in AFRS has been reported to be between 20% to 90% (21).

The CT findings can be distinctive and may include the presence of unilateral disease, hyperdensities, bony demineralization of the sinuses, and bone erosion of the sinuses. CT scans of the sinuses in AFRS patients typically show near-complete opacification with heterogeneous radiodensity (hyperdensities) of the soft tissue of the sinuses (21). Although there are rare cases of AFRS in children ≥6 to <12 years of age, in these children the disease commonly leads to facial dysmorphism in children. The growing facial skeleton of younger children may account for the higher degree of dysmorphism seen as compared to adults. Asymmetric disease and unilateral sinus disease are more frequent in children (above 6 years of age) compared with adults while incidence of bony erosion is comparable with adults (8, 9).

Allergic fungal rhinosinusitis is a disease marked by type 2 inflammation driven by dynamic interaction of fungal hyphae locked within thick sinus mucus and type 2 inflammatory responses. Patients have elevated serum IgE antifungal antibodies and eosinophils, and the inflammatory mucus is characterized by the presence of eosinophils (21). Patients with AFRS have notably higher levels of serum IgE antifungal antibodies than CRSwNP (3, 21). Molecular phenotyping has demonstrated that the epithelium of patients with AFRS shares many common overexpressed genes with CRSwNP (13). This includes type 2 inflammatory genes, including those involved with IgE and eosinophil chemotaxis and activation, such as eotaxin-3 (22). Large scale gene expression profiling including tissue from patients with CRSwNP and AFRS has demonstrated shared overexpression of type 2 inflammatory pathways including those involved with IL-4, IL-5, and IL-13 (13). However, molecular endotyping has also identified pathways that are distinct to AFRS, which differentiate AFRS from CRSwNP as a subtype of CRS demonstrating an extreme of type 2 inflammation such as the iCOS, CD28 and PKCϴ signaling pathways, which play pivotal roles in type 2 inflammatory effector function (7).

Allergic fungal rhinosinusitis is identified by distinct diagnostic criteria that were developed by Bent and Kuhn (4). This includes the presence of nasal polyps and characteristic CT opacification, as well as the presence of IgE mediated inflammatory response to fungal hyphae as characterized by specific IgE positivity or skin prick testing, as well as sheets of eosinophils presence in sinus mucus. Aspergillus species are the most commonly identified fungi. Other funguses include Bipolaris and Curvularia (3). In 1999, Ponikou showed that treating mucus with a reducing agent, dithiothreitol (DTT), could release fungi trapped within the mucin. Using this technique, his group showed positive fungal cultures from nasal secretions collected from 96% of chronic rhinosinusitis (CRS) patients and 100% of patients without CRS. Fungal staining has high variability (10-100% false positive rate) and low specificity. In practice this means that a negative fungal stain does not rule out the diagnosis of AFRS, while saprophytic fungal growth is not necessarily diagnostic of AFRS. This uncertainty is reflected in the fact that fungal culture is only considered supportive evidence in the Bent and Kuhn diagnostic criteria in contrast to the other four criteria which are key for the diagnosis (CT, polyps, elevated specific IgE, and eosinophilic mucin). Therefore, fungal culture is used as supportive evidence. However, the remainder of the Bent and Kuhn criteria is necessary for making the diagnosis of AFRS (23).

Except for the mildest cases, AFRS usually requires surgical intervention, followed by a prolonged course of adjuvant medical therapy (21). Medical therapy alone is regularly ineffective in alleviating symptoms and surgical intervention, alone or in combination with medical therapy is required (3). The large majority of patients will undergo surgical ESS with mucus debridement followed by adjuvant therapy including oral corticosteroid taper over 2 weeks

to 6 months with or without chronic topical (intranasal) corticosteroids (3, 21, 24). Recurrence can occur, and risk factors may include inadequate full debridement at the time of surgery or noncompliance with/inability to tolerate topical and oral corticosteroids (25). Overall recurrence rates after surgery are reported to range from 10% to 100% (3). The median interval for revision surgery in AFRS was much shorter than CRSwNP (2 versus 7 years) (26). Postoperative oral corticosteroids help decrease disease recurrence (21). However, even in AFRS patients treated with postoperative systemic steroids and with topical steroid, approximately 10% to 30% of patients experience disease recurrence within 6 months to 1 year after surgery (27, 28, 29). Despite the widespread acceptance of these treatment modalities, the optimal dose, duration, and tapering regimen of postoperative oral corticosteroids have not been addressed. A short-term oral corticosteroid rescue therapy can be considered for acute exacerbation. In the pediatric population, early efforts should be made to transition from a systemic regimen of corticosteroids to intranasal topical steroid therapy to avoid the side effects of systemic steroids (9). Multiple repeated oral corticosteroid rescue or long-term use of oral corticosteroids can cause significant side effects, including psychosis, insomnia, weight gain, poor control of glucose level, high blood pressure, Cushing's syndrome, adrenal insufficiency, osteoporosis, glaucoma, etc (24). Patients who continue to have progressive disease have increased risk for erosion of the bony sinuses, which can lead to facial deformities as well as increase the complexity and risk at the time of endoscopic surgery. The role of antifungals remains unclear and they are currently not recommended (10). There are currently no therapies that are approved specifically for the treatment of AFRS. There remains great unmet need in identifying novel therapies that address inflammatory underpinnings of the disease processes, minimizes the need for SCS and surgery and their associated side effects, prevents recurrence, prevents complications and bony erosion, and achieve a long-lasting disease control.

2.3 BENEFIT/RISK ASSESSMENT

The Sponsor also recognizes that the "Coronavirus Disease 2019" (COVID-19) pandemic may have an impact on the conduct of clinical studies. The Sponsor will monitor the situation closely and ensure the integrity of the study conduct and data (see Section 8).

More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AE) of dupilumab are available in the IB.

2.3.1 Benefit assessment

Dupixent (dupilumab) is authorized for marketing in over 50 countries worldwide including the US, European Union (EU) (Centralized Procedure), Japan, China, Canada, and Australia for adult atopic dermatitis (AD) indication. Dupilumab is also authorized in the US, EU, and other jurisdictions for the adolescent AD indication, and in the US, EU, Japan and other jurisdictions for the adult and adolescent asthma indication. Dupilumab also has approval for its chronic rhinosinusitis with nasal polyposis (CRSwNP) indication in the US, EU, and Japan. For the latest information, please refer to the current IB.

Allergic fungal rhinosinusitis usually requires surgical intervention, followed by a prolonged course of adjuvant medical therapy. Recurrence rates are high after surgery. There are currently no therapies

that are approved specifically for the treatment of AFRS. There remains great unmet need in the treatment of AFRS. Considering this unmet medical need and the known mechanism of dupilumab, the Sponsor is proposing to develop dupilumab for AFRS for the following reasons:

- AFRS is a type 2 inflammatory disease. Dupilumab has demonstrated efficacy across a broad range of diseases driven by type 2 inflammation, including AD, asthma, and CRSwNP.
- Dupilumab demonstrated significant efficacy in reducing sinus opacification, symptoms, and nasal polyp burden in CRSwNP, a disease that shares clinical and molecular features with AFRS.
- Dupilumab demonstrated reduction in proportion of patients requiring rescue with SCS and/or surgery in the CRSwNP development program. Given that surgery and SCS use are common with AFRS and are accompanied by well-established risks, there is a potential for benefit in reducing their use in AFRS.
- Patients with AFRS were excluded from the dupilumab CRSwNP registrational studies.

Dupilumab, therefore, offers promise of significant benefit above and beyond current standard of care in AFRS and may provide an alternative for those patients who relapse after surgery and may obviate the need for repeated SCS and/or surgeries.

2.3.2 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, a total of 10 191 participants were enrolled into the development program for dupilumab and are included in the safety population: 382 as healthy volunteers, 4405 from AD studies, 3614 from asthma studies, 782 from CRSwNP studies, 232 from eosinophilic esophagitis (EoE) studies, 103 from the grass allergy study, 145 from peanut allergy studies, 511 from the chronic obstructive pulmonary disease (COPD) study, 5 from PN studies, and 12 from the 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 sales figures 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 to 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 (ADRs) 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 further details). More significant serious allergic reactions were very rare.

Importantly, no increased overall infection risk was observed in participants 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 SCS 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 participants, 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.

To date, the safety profile has been similar among adult, adolescent and child ≥6 to <12 years old participants in asthma and AD populations and adult participants with CRSwNP. 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 AFRS will have a favorable safety profile as observed across other type 2-driven immunological disorders.

2.3.3 COVID-19 Benefit-risk assessment

Dupilumab has shown clinical benefit in several type-2 driven immunological disorders, such as AD, asthma, and chronic rhinosinusitis with nasal polyposis. In asthma and AD, clinical benefit has also been established in certain pediatric patients (asthma in adolescents and AD in 6 to 18 years old) and a similar benefit-risk profile to adults has been observed.

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

Currently, as sufficient data in patients with COVID-19 who are being treated with dupilumab is not available. 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 with dupilumab.

The target population of EFC16724 is patients with uncontrolled AFRS 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 EFC16724 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, CRSwNP), where type 2 inflammation is the underlying driver of the disease process.

Based on the aforementioned potential benefits to patients participating in EFC16724, the Sponsor's assessment is that the benefit-risk remains favorable for patients to participate in this trial.

2.3.4 Overall benefit: risk conclusion

Based on the evidence to support the potential therapeutic benefit in AFRS, a patient population with an unmet medical need, considering the favorable benefit/risk profile across multiple indications, and the extensive available safety database, the Sponsor is proposing to conduct a Phase 3 program with dupilumab for the treatment of patients with AFRS.

3 OBJECTIVES AND ENDPOINTS

Table 1 - Objectives and endpoints

Objectives	Endpoints
Primary	
• To evaluate the efficacy of treatment with dupilumab to reduce sinus opacification in a population with allergic fungal rhinosinusitis (AFRS)	• Change from baseline in sinus opacifications assessed by computerized tomography (CT) scans using the Lund Mackay (LMK) score at Week 52
Secondary	
• To evaluate the efficacy of treatment with dupilumab to reduce sinus opacification in a population with allergic fungal rhinosinusitis (AFRS) at Week 24	• Change from baseline in sinus opacifications assessed by CT scans using the LMK score at Week 24
• To assess the efficacy of dupilumab to reduce the need for rescue treatments	• Proportion of participants who receive SCS and/or undergo/plan to undergo surgery for AFRS during the planned study treatment period
• To evaluate the efficacy of treatment with dupilumab in improving symptoms in AFRS	• Change from baseline in monthly average nasal congestion/obstruction score from the Nasal Symptom Diary at Week 24 and Week 52
	• Change from baseline in the monthly average anterior/posterior rhinorrhea score from the Nasal Symptom Diary at Week 24 and Week 52
• To evaluate the efficacy of dupilumab to reduce nasal polyp formation in participants with AFRS	• Change from baseline in endoscopic nasal polyp score (NPS) compared with placebo at Week 24 and Week 52
• To evaluate the efficacy of dupilumab in improving overall symptom severity and quality of life in AFRS	• Change from baseline in 22-item sino-nasal outcome test (SNOT-22) total score at Week 24 and Week 52
	• Change from baseline in monthly average total symptom score (TSS) derived from the Nasal Symptom Diary at Week 24 and Week 52
	• Change from baseline in visual analog scale (VAS) rhinosinusitis at Week 24 and Week 52
• To evaluate the efficacy of dupilumab in improving sense of smell in participants with AFRS	• Change from baseline in University of Pennsylvania smell identification test (UPSIT) at Week 24 and Week 52
	• Change from baseline in the score of decreased/loss of smell using the Nasal Symptom Diary at Week 24 and Week 52
• To explore the effect of dupilumab as assessed by three-Dimensional CT volumetric measurement of the paranasal sinuses	• Change from baseline to Week 52 in three-Dimensional CT volumetric measurement of the paranasal sinuses
• To evaluate the safety and tolerability of dupilumab when administered to participants with AFRS	• Incidence of treatment-emergent adverse events (TEAEs) or serious adverse events (SAEs) through Week 52
• To evaluate the PK of dupilumab in participants with AFRS	• Dupilumab concentration in serum over time

Objectives	Endpoints
• To characterize the effect of dupilumab on total IgE and specific IgE	• Percent change from baseline in total IgE in serum compared with placebo over the 52-week treatment period • Percent change from baseline in fungal-specific IgE in serum compared with placebo over the 52-week treatment period
• To assess immunogenicity to dupilumab in participants with AFRS	• Assessment of incidence of treatment-emergent anti-drug antibodies (ADA) to dupilumab over time
[redacted]	

3.1 APPROPRIATENESS OF MEASUREMENTS

The primary objective of this study is to evaluate the efficacy of dupilumab through reduction in sinus opacification. This study will evaluate the efficacy of dupilumab in a patient population who have significant disease burden in the sinuses and nasal cavity (LMK ≥9 out of 12 for unilateral or ≥12 out of 24 for bilateral and NPS ≥2 out of 4 for unilateral or ≥3 out of 8 for bilateral). AFRS is identified by distinct diagnostic criteria that were developed by Bent and Kuhn (4). This includes the presence of nasal polyps and characteristic CT opacification. For AFRS, CT scans are used clinically to evaluate the disease severity and progression. The CT findings in this disease can be distinct and may include the presence of hyperdensities, bony demineralization of the sinuses, and bone erosion of the sinuses. Computed tomography scans of the sinuses in AFRS patients typically show near-complete opacification with heterogeneous radiodensity (hyperdensities) of the soft tissue of the sinuses (21). Both mucus accumulation and mucosal thickening contribute significantly to sinus opacification (30). Therefore, sinus opacification is considered as one of the key disease signs to be observed in this study. Computed tomography imaging quantified based on the degree of sinus opacification provides visualization of mucin involvement in the sinuses, which may not be detectable through other measurements. Lund Mackay score will be used to quantify the degree of opacification of each sinus on CT scan. The change from baseline in sinus opacifications assessed by CT scans using the LMK score at Week 52 is selected as the primary endpoint for the study. The LMK scoring system has been validated in previous studies (31, 32, 33). In the CRSwNP development program for dupilumab, sinus CT scan was a key secondary endpoint used to assess sinus disease burden, in which significant improvement in the CT LMK score of sinus opacification was observed. Importantly, in dupilumab CRSwNP studies, improvement in LMK was accompanied by improvement in measures of symptoms including nasal congestion (NC), loss of smell and total symptom score. Computed tomography imaging will be read by control blinded reviewers.

The need for SCS or surgery at Week 52 is a secondary endpoint. Patients with AFRS typically have a high relapse rate after surgery requiring several SCS bursts as rescue to control the disease and many patients require repeat surgery. The need for frequent SCS and/or sino-nasal surgery is an important part of disease burden. Reducing the need for SCS and repeat surgery will decrease the risk of SCS associated side effect and surgery complications. In the CRSwNP program, dupilumab dramatically reduced the proportion of participants requiring SCS use and the proportion of participants who required surgery. To date there is no other alternative treatment for these patients other than another course of SCS or another surgery. Therefore, reducing occurrence of systemic steroids use and/or surgery will also reflect the disease status improvement.

Clinically, AFRS can present long-term subjective symptoms of nasal obstruction and congestion, reduction in or loss of the sense of smell, and anterior and posterior rhinorrhea. The presence or absence of polyps is confirmed by performing endoscopy. These symptoms can greatly impact patient's QoL. Thus, the secondary endpoints of this study include changes from baseline at Week 24 and Week 52 assessed by the patient Nasal Symptom Diary in which key subjective symptoms will be recorded as the monthly average of nasal congestion/obstruction score, anterior/posterior rhinorrhea score, and decreased/loss of smell (UPSIT) and in addition a monthly average of total symptom score (TSS) derived from these 4 items; other secondary endpoints are the endoscopic nasal polyp score (NPS) used to evaluate the efficacy of dupilumab to reduced

nasal polyp burden. The visual analog scale (VAS) will be completed by each participant to assess specifically rhinosinusitis severity at Week 24 and Week 52. Three-dimensional CT volumetric measurement of the sinuses will also be used to explore the disease (volume of air, thickness of mucosa, and lateral wall) across all individual sinuses as an exploratory secondary endpoint. In addition, [redacted]

[redacted] Reduction in serum IgE level may be a biomarker for the control of type 2 inflammation. Based on previous research, increase in total serum IgE level of 10% or more in patients with AFRS after surgery might be helpful to detect recurrence of sinus disease and predict the need for recurrent sinus surgery (34). Therefore, change in total IgE and fungal-specific IgE will be measured as secondary endpoints.

The proposed study design and endpoints will answer important clinical questions regarding the ability of dupilumab to reduce the need of SCS rescue therapy and surgery, objective signs of the disease, and symptoms reported by patients, which are the most relevant clinical practice assessments and reflect current standard of care. Forced expiratory volume (FEV1) and asthma control questionnaire 6-item version (ACQ-6) questionnaire will be used in AFRS patients with asthma for lung function and symptom improvement.

Other efficacy assessments based in Patient-Reported Outcomes (PRO) including health-related quality of life (HRQoL) using the specific HRQoL 22-item sino-nasal outcome test (SNOT-22) instrument will also be measured to evaluate the potential real life benefit.

4 STUDY DESIGN

4.1 OVERALL DESIGN

This is a Phase 3, multicenter, 52-week treatment, parallel-group, double-blind, randomized, placebo-controlled study to investigate the efficacy of dupilumab 300 mg q2w for adults and adolescents/children (≥6 to <12 years) ≥60 kg, or dupilumab 200 mg q2w for adolescents/children ≥30 kg and <60 kg, dupilumab 300 mg q4w for adolescents/children ≥15 kg and <30 kg with signs and symptoms of AFRS. The study will primarily investigate the efficacy of dupilumab to reduce disease burden in the sinuses (sinus opacification) by radiographic imaging. In addition, the study will also evaluate efficacy of dupilumab to reduce the need for repeated SCS and/or surgery, nasal polyps burden, clinical symptoms, and explore other measures of disease activity.

Approximately 62 participants (31 per arm) with AFRS who satisfy the inclusion and exclusion criteria will be randomized in a 1:1 ratio to receive either dupilumab or matching placebo:

- Dupilumab 300 mg q2w for all adults, 300 mg q2w for adolescents/children ≥60 kg at screening, or 200 mg q2w for adolescents/children ≥30 kg and <60 kg at screening, or 300 mg q4w for adolescents/children ≥15 kg and <30 kg at screening.
- Matched placebo.

Randomization will be stratified first by age (adults versus adolescents/children [≥6 years old]). In adults, randomization will be stratified further by time from last surgery (≤2 years [including surgery naive participants], >2 years), disease pattern (unilateral/bilateral in the endoscopy at screening), and country. In adolescents/children, randomization will not be stratified further.

Duration of study period (per participant):

- Screening period (2 to 4 weeks): to determine a participant's eligibility and continue with his/her own background intranasal corticosteroids (INCS) prior to randomization.
- Randomized IMP intervention period (52 weeks ±3 days): to randomize the participants into a treatment arm and treat with dupilumab or placebo dose regimen.
- Follow-up period (12 weeks ±5 days): to continue to collect data for PK, immunogenicity, safety, and efficacy after the participant has completed the randomized IMP intervention period.

The total duration of study participation for participants that complete the randomized treatment period and posttreatment follow-up is approximately 68 weeks. The schedule of the visits is described in the specific flow-chart in Section 1.3.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

The study is designed as a randomized, double-blind, placebo-controlled and parallel-group study to evaluate the efficacy and safety of dupilumab on top of current standard of care background therapy in the treatment of AFRS, utilizing multiple objective and subjective outcome measures.

To be eligible, participants need to have a confirmed diagnosis of AFRS based on well-accepted Bent and Kuhn criteria (4). The proposed inclusion criteria will identify participants with AFRS demonstrated to have high disease burden and significant symptoms by high CT LMK score (≥9 out of 12 for unilateral polyps or ≥12 out of 24 for bilateral polyps), and NPS score (≥2 out of 4 for unilateral polyps or 3 out of 8 for bilateral polyps). Adolescents can be treated much like an adult with similar disease processes (35). AFRS in children is similar to adults with 50% of them presenting unilateral nasal polyposis versus about 30% in adults. Thus, the current entry criteria are suitable to include the population (age ≥6 years) in the study (36).

As currently there is no approved medication specifically for AFRS, a placebo-controlled design is appropriate and provides for the most robust assessment of the efficacy and safety of dupilumab in the target participant population. Dupilumab or matched placebo will be added on top of background standard treatment as applicable, based on clinical consensus (3, 10). Participants will continue to take their background therapy as they do prior to the study. Rescue medications and/or surgery for AFRS deemed necessary by Investigators will be allowed, which mirrors the expected future therapeutic paradigm of dupilumab in this population in clinical practice.

The 52-week treatment duration is considered sufficient for efficacy evaluation based on the efficacy results from pivotal dupilumab studies in CRSwNP. Dupilumab 300 mg q2w demonstrated statistically significant and clinically meaningful improvement across all primary and multiplicity-adjusted secondary outcome measures at Week 24 and at Week 52. Early beneficial effect was seen from Week 2 to Week 4, followed by a progressive improvement through 52 weeks. The 52-week duration is also appropriate to evaluate safety considering the extensive safety experience with the related condition of CRSwNP. The posttreatment 12-week follow-up period is based on the expected PK of dupilumab after the last dose, ie, the time for systemic concentrations to decline to non-detectable levels in most 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 PK, safety and efficacy of dupilumab, the selected dosing regimens for this study are dupilumab 300 mg q2w for adults and for adolescents/children ≥60 kg, 200 mg q2w for adolescents/children ≥30 kg and <60 kg, and 300 mg q4w for adolescents/children ≥15 kg and <30 kg.

These dose regimens are expected to achieve concentrations in serum that saturate the target-mediated clearance pathway and have demonstrated similar efficacy in adult and adolescent participants with asthma and AD, and in adults with CRSwNP. The PK of dupilumab has been

found to be consistent across populations of participants with AD, asthma, and CRSwNP, as well as healthy volunteers. In prior studies with dupilumab, body weight has been the only covariate identified with a meaningful impact on dupilumab PK. 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 and have an acceptable safety profile in adult and adolescent participants with moderate-to-severe AD, moderate-to-severe asthma, and adult participants with CRSwNP. Consistent with the observed PK and pharmacodynamics (PD) profile of nasal polyps response (gradual development of response during the treatment period as well as slow offset of response during off-treatment period) in participants with CRSwNP, PK/PD simulation of co-primary endpoints of NPS and nasal congestion showed minimal difference in the development of treatment effect and steady-state response of NPS and nasal congestion in the presence and absence of the loading dose of 600 mg on Day 1 in participants with CRSwNP. Therefore, as in the pivotal CRSwNP program, no loading dose is included in the present study for AFRS participants.

Three hundred (300) mg q2w with a loading dose of 600 mg for adolescents/children ≥60 kg, 200 mg q2w with a loading dose of 400 mg for adolescents/children ≥30 kg to <60 kg OR 300 mg q4w with a loading dose of 600 mg for adolescents/children ≥15 kg to <30 kg are the approved dosing regimens for AD. These dosing regimens in adolescents/children achieved steady-state trough concentration similar to 300 mg q2w in adult participants with AD. Given the lack of significant sustained difference at the steady state PK and PD profiles observed between CRSwNP participants who had loading dose and participants who did not have loading dose, in this study, 2-tiered weight-based dosing regimens without a loading dose are included for AFRS adolescent/child participants, to achieve comparable PK exposure to 300 mg q2w AFRS adult participants in both adolescent weight groups.

The collective PK/PD, clinical efficacy, and safety data of dupilumab across diverse disease populations suggest that the selected dose regimens for this study will be efficacious and safe for the treatment of adult and adolescent/child (≥6 to <12 years) AFRS 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 at Week 64.

If a participant discontinues treatment period prematurely before Week 40 but completes follow-up to Week 52, 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 6 years of age at the time of signing the informed consent. Note: For those countries where local regulations do not permit enrollment of children aged ≥6 to <12 years, the recruitment will be restricted to those who are ≥12 years of age (or the minimum legal age for adolescents in the country of the investigational site). For those countries where local regulations do not permit enrollment of children aged ≥6 to <12 years of age and adolescents, the recruitment will be restricted to those who are ≥18 years of age.

Type of participant and disease characteristics

I 02. Participants with the diagnosis of AFRS adapted from criteria by Bent and Kuhn (meeting all):

a) IgE mediated inflammatory response to fungal hyphae (specific IgE serology or skin test)

Evidence of sensitization to fungus by skin testing (at screening or documented historical positive skin test in the previous 12 months), or positive fungal-specific IgE in serum at screening.

b) Nasal polyposis confirmed by nasal endoscopy at screening.

c) Characteristic CT signs to be performed during screening period and can include any of the below signs as assessed by central reader:

- hyperdensities
- bony demineralization
- bone erosion of sinus

d) Eosinophilic mucin/mucus identified within 5 years prior to screening or at screening with or without positive fungal stain.

e) Criterion deleted as per Amended Protocol 01.

I 03. AFRS patients with the following:

a) An endoscopic NPS of at least 2 out of 4 for unilateral polyps or 3 out of 8 for bilateral polyps at Visit 1 (central reading) and Visit 2 (local reading) and,

b) Sinus opacification in CT scan with an LMK score of 9 for patients with unilateral polyps or 12 for patients with bilateral polyps during screening period and,

I 04. Criterion deleted in Amended Protocol 03.

Weight

I 05. Body weight ≥15 kg at screening.

Sex, contraceptive/barrier method and pregnancy testing requirements/breastfeeding

I 06. Male and/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 an acceptable contraceptive method as described in Appendix 4 (Section 10.4) of the protocol during the study (up to 12 weeks after the last dose of study intervention).
  - 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 on Day 1 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 07. Capable of giving signed informed consent as described in Appendix 1 (Section 10.1) of the protocol which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol. In countries where legal age of majority is above 18 years, a specific ICF must also be signed by the participant's legally authorized representative. For adolescents (≥12 to <18 years) and for children (≥6 to <12 years), both the adolescent/child and the parent/legally authorized representative must sign the specific ICF/assent form.

5.2 EXCLUSION CRITERIA

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

Medical conditions

E 01. Patients with conditions/concomitant diseases making them non-evaluable at Visit 1 or for the primary efficacy endpoint such as:
- Antrochoanal polyps.
- Nasal septal deviation that would occlude at least one nostril.
- Acute sinusitis, nasal infection or upper respiratory infection within 2 weeks prior to Visit 1 (patient can be rescreened after resolution of symptoms).
- Ongoing rhinitis medicamentosa.
- Eosinophilic granulomatous polyangiitis (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. Patients with nasal cavity malignant tumor and benign tumors (eg, papilloma, hemangioma, etc).

E 03. Known of fungal invasion into sinus tissue.

E 04. 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 05. Histories 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 06. Severe concomitant illness(es) that, in the Investigator's judgment, would adversely affect the patient's 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, etc), 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 07. Known or suspected history of 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 08. Patients with active TB or 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 patient 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 ethic boards.

E 09. 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 10. History of malignancy within 5 years before Visit 1, except completely treated in situ carcinoma of the cervix, completely treated and resolved nonmetastatic squamous or basal cell carcinoma of the skin.

E 11. Known or suspected alcohol and/or drug abuse.

E 12. History of systemic hypersensitivity or anaphylaxis to dupilumab or any of its excipients.

E 13. Planned major surgical procedure during the patient's participation in this study.

E 14. Patient 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 15. Treatment with commercially available dupilumab within 12 months, participation in prior dupilumab clinical trial, or discontinued dupilumab use due to adverse event.

E 16. Patients who are treated with intranasal corticosteroid drops; intranasal steroid emitting devices/stents; nasal spray using exhalation delivery system, such as Xhance™, during screening period.

E 17. Patients who are on INCS spray unless they have received stable dose for at least 4 weeks prior to Visit 1.

E 18. Patients who have undergone sinus intranasal surgery (including polypectomy) within 6 months prior to Visit 1.

E 19. For patients receiving systemic antifungals for AFRS treatment at screening: unwilling to stop antifungal therapy at screening.

E 20. Patients who have taken:

- Biologic therapy/systemic immunosuppressant to treat inflammatory disease or autoimmune disease (eg, rheumatoid arthritis, inflammatory bowel disease, primary biliary cirrhosis, systemic lupus erythematosus, multiple sclerosis, etc) within 4 weeks before Visit 1 or 5 half-lives, whichever is longer.
- Any investigational mAb within 5 half-lives or within 6 months before Visit 1 if the half-life is unknown.
- Anti-IgE therapy (omalizumab) within 4 months prior to Visit 1.

E 21. 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:

- Patient for whom administration of live (attenuated) vaccine can be safely postponed will be eligible to enroll into the study.
- Patients who have their vaccination preponed can enroll in the study only after a gap of 4 weeks following administration of the vaccine.

E 22. Leukotriene antagonists/modifiers unless patient is on a continuous treatment for at least 30 days prior to Visit 1.

E 23. Initiation of allergen immunotherapy within 3 months prior to Visit 1 or a plan to begin therapy or change its dose during the screening or treatment period.

E 24. Patients received SCS during screening period.

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

Noncompliance to completion of the e-diary

E 26. Participants who do not demonstrate at least the following for acceptable compliance: Completing the e-diary for any 4 mornings in the 7 days immediately preceding Baseline Visit (Visit 2).

Diagnostic assessments

E 27. Patients with any of the following result at the Screening Visit (Visit 1):

- Positive (or indeterminate) hepatitis B surface antigen (HBsAg) or,
- Positive total hepatitis B core antibody (HBcAb) and a negative hepatitis B surface antigen (HBsAg) with a positive hepatitis B virus (HBV) DNA or,

- Positive hepatitis C virus antibody (HCVAb) with a positive hepatitis C virus (HCV) RNA.

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 trial 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 the International Council for Harmonisation [ICH] Good Clinical Practice [GCP] Ordinance E6).

E 32. Any specific situation during study implementation/course that may raise ethical concerns.

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.

5.3 LIFESTYLE CONSIDERATIONS

No restrictions are required.

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently randomly assigned to study intervention. 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's 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 screening period, these laboratory assessments may be repeated, at the discretion of the Investigator, if it is judged to be likely to return to 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 90 days old. If the rescreening is performed outside of the 90 days window, the CT scan must be repeated. All other screening procedures must be repeated for rescreening.

6 STUDY INTERVENTION AND CONCOMITANT THERAPY

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study 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 200 mg or Dupilumab 300 mg	Placebo
Type	Biological	Other
Dose formulation	Dupilumab 200 mg: A 175 mg/mL dupilumab solution in a pre-filled syringe to deliver 200 mg in 1.14 mL. or Dupilumab 300 mg: A 150 mg/mL dupilumab solution in a pre-filled syringe to deliver 300 mg in 2 mL.	Placebo matching dupilumab 200 mg will be supplied as an identical formulation to the active 200 mg formulation without dupilumab, in a pre-filled syringe to deliver placebo in 1.14 mL. or 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)	200 mg or 300 mg	0 mg
Dosage level(s)	One injection of 200 mg q2w for adolescents/children ≥30 kg and <60 kg at screening or One injection of 300 mg q2w for all adults and for adolescents/children weighing ≥60 kg at screening or One injection of 300 mg q4w for adolescents/children ≥15 kg and <30 kg at screening	One injection of placebo matching 200 mg q2w for adolescents/children ≥30 kg and <60 kg at screening or One injection of placebo matching 300 mg q2w for all adult participants and for adolescents/children weighing ≥60 kg at screening or One injection of placebo matching 300 mg q4w for adolescents/children ≥15 kg and <30 kg at screening
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

The IMP will be administered every 14 ±3 days (q2w) or 28 ±3 days (q4w) during the 52-week treatment period (with the last IMP administration at Week 50 for q2w administrations and at Week 48 for q4w administrations).

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 parent/legally authorized representative, or caregiver). The Investigator or delegate will prepare and inject the first dose of IMP at Visit 2, in front of the participant (or parent/legally authorized participant representative/caregiver). The participant (or parent/legally authorized representative/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) different training ways (eg, training remotely with instruction provided by phone) can be performed (and will be documented in the participant's study file). If the participant (or parent/legally authorized representative/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.

Between the protocol-scheduled on-site visits, interim visits may be required for IMP dispensing. As an alternative to these visits 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. The monitoring period may be extended as per country-specific or local site-specific requirements.

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 their healthcare provider or emergency services.

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 or q4w injections. Injections in the upper arms could be done only by a trained person (parent/legally authorized representative/caregiver trained by Investigator or delegate) or health care professional but not the participants themselves.

For doses not given at the study site, diaries will be provided to record information related to the injections. The 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 interventions 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 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 to Patient 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 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 an 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 telephone number and call-in directions for the interactive voice response system and/or the log in information and directions for the interactive web response system will be provided to each site.

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

The randomization will be stratified by age (adults versus adolescents/children) first. In adults, randomization will be further stratified by time from last surgery (≤2 years, >2 years), disease pattern (unilateral/bilateral in the endoscopy at screening), and country. In adolescents/children, randomization will not be further stratified.

At screening (Visit 1), the Investigator or designee will contact the IRT system to receive the participant number. If a participant who had previously failed screening is approached for rescreening, a new ICF/assent form 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 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 Schedule of Activities (SOA) (see Section 1.3). Returned study intervention should not be re-dispensed to the participants.

Methods of blinding

Dupilumab 300 mg/200 mg and matching placebo matching dupilumab 300 mg/200 mg will be provided in identically matched 2 mL/1.14 mL pre-filled syringes that are visually indistinguishable for each dose. Syringes and box will be labeled with a treatment kit number. While these are double-blind with regard to the treatment with either dupilumab or placebo, they are not blinded to weight-based dose levels, due to the different volume size (2 mL versus 1.14 mL) of the dose level of dupilumab (300 mg/matching placebo or 200 mg/matching placebo) that will be used for the different weight categories for adolescents/children. In addition, in children, the study is not blinded to dose regimen due to the different frequency of IMP administration (q4w versus q2w).

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 case report form, as applicable.

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

6.4 STUDY INTERVENTION COMPLIANCE

- 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 to Patient 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 electronic case report form (eCRF).
- The monitor in charge of the study then checks the eCRF data by comparing them with the IMP which he/she has retrieved and 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 e-diary and used/unused kits/pre-filled syringes during the site visits and documented in the source documents and eCRF. Changes 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. Intervention start and stop dates, including dates for intervention delays and/or dose reductions will also 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 screening 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/Sponsor representative should be contacted if there are any questions regarding concomitant or prior therapy.

6.5.1 Background treatments

Participants that are using background INCS must have a stable dose regimen for at least 1 month at the time of V1. From the time of screening throughout the study treatment period, they should not change their background medications.

Intranasal corticosteroids other than nasal spray such as, drops, stents, or devices are not allowed as background treatment.

6.5.2 Prohibited medications

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

- Intravenous immunoglobulin (IVIG) therapy.
- 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 systemic steroids are prohibited during screening and study treatment period except that a short term (<2 weeks) oral corticosteroids are allowed only in study treatment period as rescue medication (see rescue medication in Section 6.5.3).
- Live, attenuated vaccines.
- Other monoclonal antibodies (biological immunomodulators), including but not limited to anti-IgE, anti-IL-5 and anti-TNF, etc.
- Systemic antifungals and antibiotics are prohibited during screening and study treatment period except for rescue use (see rescue medication in Section 6.5.3).

Permitted concomitant medication

The following treatments are allowed:

- Intranasal normal saline.
- 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, aminophyllines).
- Inhaled corticosteroids.
- Systemic antihistamines.
- Leukotriene antagonists/modifiers are permitted during the study, only for participants who were on a continuous treatment for ≥30 days prior to Visit 1.
- Allergen immunotherapy in place for ≥3 months prior to Visit 1 is permitted and the dose should be kept stable during screening and study treatment period.

- 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 for example lidocaine are allowed before nasal brushing or before endoscopy.
- Other concomitant medication may be considered on a case-by-case basis by the Investigator in consultation with the Sponsor/Sponsor representative if required.

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 requiring medical intervention, the Investigator may consider rescue treatment with:

- Systemic antibiotics (up to 2 weeks) in case of acute infection.
- Short term courses (prednisone or prednisolone up to 2 weeks) of oral corticosteroids for AFRS or short courses of oral corticosteroids to treat other serious coexisting diseases (such as asthma exacerbation).
- Short term (≤4 weeks) systemic antifungal treatment based on participant's tolerability.
- Intranasal corticosteroids spray (initiation of INCS spray or change in dosing of a background INCS spray during the study period).
- Sino-nasal surgery for AFRS (8 weeks of IMP treatment is recommended prior to surgery to allow onset of treatment effect). For participants who undergo or are planned for surgery for AFRS, the Investigator may decide to continue IMP up to the time of surgery or end of treatment whichever date comes first. At the time of surgery, the participants will be permanently discontinued from study treatment.

Note: It is recommended if a participant must use SCS as per the Investigator's decision, the site should make every effort to perform clinical assessments (including an endoscopy, if it is needed) before starting treatment with SCS. If a participant needs to have CT scan around the time of surgery the next scheduled CT scan per protocol does not need to occur after surgery for AFRS. In any case, participants may not have more than 3 CT scans during the study. All this information collected will be recorded in dedicated eCRF pages.

6.6 DOSE MODIFICATION

No IMP dose modification is allowed. This is also applicable for adolescent participants who become adult during the study or participants who change weight band during the study.

6.7 INTERVENTION AFTER THE END OF THE STUDY

Sponsor will not be responsible for intervention after the EOS Visit. Intervention after the EOS Visit will be at the discretion of the 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 (definitive discontinuation) study intervention. If study intervention is definitively 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 they decide to do so, at any time and irrespective of the reason, or this may be the Investigator's decision. All efforts should be made to document the reasons for treatment discontinuation, and this should be documented in the eCRF.

Participants must be withdrawn from the study treatment (ie, from any further IMP) 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 the participant's involvement 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 they are treated with the specific prohibited medications mentioned in Section 6.5.2.
- Sino-nasal surgery.
- If they miss 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 request 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 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).

Any abnormal laboratory value 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 52-week treatment period) will perform, as soon as possible, the early termination visit with all assessments normally planned for the end of treatment (EOT) Visit (Visit 7) (refer Section 8.1.1) including a pharmacokinetics sample, if appropriate, to assure a complete clinical assessment in close temporal proximity to the premature termination of study treatment is available.

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 day 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 status of AFRS 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 treatment should be reinitiated at the next scheduled administration, maintaining the planned dose.

If 2 consecutive IMP doses have been missed, the study treatment 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 will have considered 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 parent(s)/caregiver(s)/legally authorized representative(s) decide to do so, 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). See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- The participant will be permanently discontinued both from the study intervention and from the study at that time.
- If the participant withdraws consent for 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 and 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.
- Should the participant continue 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, 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/assent form 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.
- Assessments/procedures should be conducted in the following order: daily symptoms of nasal congestion; loss of smell and rhinorrhea; SNOT-22; VAS rhinosinusitis; [redacted] and administration of IMP. Note:
- PRO questionnaires should be completed by the participants (not applicable for children aged ≥6 and <12 years) 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.
- Participants under 18 years of age will have a caregiver or a tutor.
- Adolescents completing the PRO questionnaires may be helped by their parents/caregivers for the reading and the understanding of the instructions, a word or a question of the questionnaires if they encounter difficulties to answer. However, adolescents (not applicable for those aged ≥6 and <12 years) should answer the question themselves; parents/caregivers should not influence nor interpret their child's answer. Parents/caregivers should not select any of the response choices on behalf of their child; only help on transcribing accurately the answers will be allowed.
- 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 230 mL for adults, 195 mL for adolescents, and 87 mL for children with weight ≥20 to <30 kg or 71 mL for children with weight ≥15 to <20 kg. 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 pandemic requiring public health emergency), the continuity of clinical study conduct and oversight may require implementation of temporary or alternative mechanisms, eg, 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 in response to COVID-19 are to be documented as being related to COVID-19 and will remain in effect only for the duration of the public health emergency.

8.1 EFFICACY ASSESSMENTS

8.1.1 Computerized tomography scans

For both LMK scores, three-dimensional volumetric measurement of the sinuses [redacted] the same acquisitions (sequences) will be used for centralized imaging data assessments and scoring by an independent physician reviewer for the imaging data

8.1.1.1 Lund Mackay score

Computerized tomography scans using the LMK scores allows the assessment of sinus opacification.

The CT scan LMK staging system represents the most widely established method of sinus CT scoring in clinical trials. Lund Mackay 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 (31, 32, 33).

Computed tomography scans should be performed anytime during the screening period before first administration of IMP at Visit 2 (baseline CT data), at Visit 5 (Week 24), and Visit 7 (Week 52). 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 Independent Ethics Committee (IEC)/Institutional Review Board (IRB), these countries will be exempted from all the planned study CT scans until approval from these committees is received. A 3-month window is required between 2 CT scans in screening period if a participant needs to be rescreened. 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 (Visit 7). Week 24 CT scan is not required for adolescents/children. In any case, participants may not have more than 3 CT scans during the study. If a participant needs to have CT scan around the time of surgery the next scheduled CT scan per protocol does not need to occur after surgery for AFRS.

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

8.1.1.2 Three-dimensional volumetric measurement of the sinuses

This method is used to calculate: (37)

- 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.

8.1.2 Proportion of participants who receive SCS and/or undergo/plan to undergo surgery for AFRS during the planned study treatment period

Systemic corticosteroids use

Use of systemic steroids for rescue treatment of AFRS or for another reason will be captured by the Investigator (or designee) on the appropriate page(s) of the eCRF page and the date and dosing information (daily dose, duration, INN). The reason for SCS use will be also captured.

Surgery (actual or planned) for AFRS

For participants who undergo or plan to have surgery for AFRS, the reason (worsening signs and/or symptoms during the study), the expected and real surgery date, the type and outcome of surgery will be recorded in a specific eCRF page. If surgery:

- Is performed during the study treatment period, participant and Investigator may decide to continue IMP up to the time of surgery or 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 and will be instructed to return to the study site as described in Section 1.3.
- Is performed during the follow-up the participants will be assessed according to the procedures normally planned for the EOS Visit and will be instructed to return to the study site as described in Section 1.3.
- Date is scheduled after the planned end of study; a follow-up contact(s) will be scheduled around the time of planned surgery to document the surgery date and outcome.

8.1.3 Nasal symptom diary, including nasal congestion/obstruction, loss of smell, and anterior and posterior rhinorrhea

The Nasal Symptom Diary is designed to assess the severity of CRS nasal symptoms on daily basis. These symptoms include nasal congestion/obstruction, loss of smell, anterior rhinorrhea and posterior rhinorrhea (38). 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. (Table 3).

Table 3 - Nasal congestion/obstruction symptom severity

Scale	Symptoms
0	No symptoms
1	Mild symptoms (symptoms clearly present, but minimal awareness and easily tolerated)
2	Moderate symptoms (definite awareness of symptoms that is bothersome but tolerable)
3	Severe symptoms (symptoms that are hard to tolerate, cause interference with activities or daily living)

The TSS is a composite score (ranging between 0 and 9) consisting of the sum of the following symptoms assessed daily in the morning: nasal congestion/obstruction, decreased/loss of sense of smell, rhinorrhea (average of anterior/posterior nasal discharge). Higher scores on the TSS indicate greater symptom severity.

The psychometric properties of nasal congestion as an individual item, including validity, reliability and ability to detect changes have been demonstrated in adult patients with CRSwNP. Within-person (responder definition) meaningful threshold has been determined in the CRSwNP population as follows: -0.48 to -1.14 for NC, -0.88 to -1.00 for loss of smell, and -1.15 to -3.60 for TSS.

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 reviewing as well as compliance to background/rescue therapy and overall e-diary compliance. The site should follow-up with the participant as appropriate.

The Nasal Symptom Diary will be administered electronically.

Participants will complete the Nasal Symptom Diary as described in the SoA (Section 1.3).

8.1.4 Nasal polyps score

The bilateral endoscopy NPS allows the assessment of nasal polyp formation. Polyps on each side of the nose will be graded based on polyp size scores: 0 = no polyps; 1 = small polyps in the middle meatus not reaching below the inferior border of the middle turbinate; 2 = polyps reaching below the lower border of the middle turbinate; 3 = large polyps reaching the lower border of the inferior turbinate or polyps medial to the middle turbinate, 4 = large polyps causing complete obstruction. The total score is the sum of the right and left nostrils, ranging from 0 to 8.

The NPS grading score is a recognized tool that is widely used to assess nasal polyps in clinical development programs (14, 39, 40, 41).

Clinicians will perform the measure as described in the SoA (Section 1.3).

8.1.5 22-item sino-nasal outcome test

The SNOT-22 is a PRO questionnaire designed to assess the impact of CRS on participants HRQoL (42). 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 (42). 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 (42).

The SNOT-22 is provided in Appendix 7 (Section 10.7.2).

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

8.1.6 Rhinosinusitis severity visual analog scale

The rhinosinusitis VAS is used to evaluate the overall severity of the rhinosinusitis (38). 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

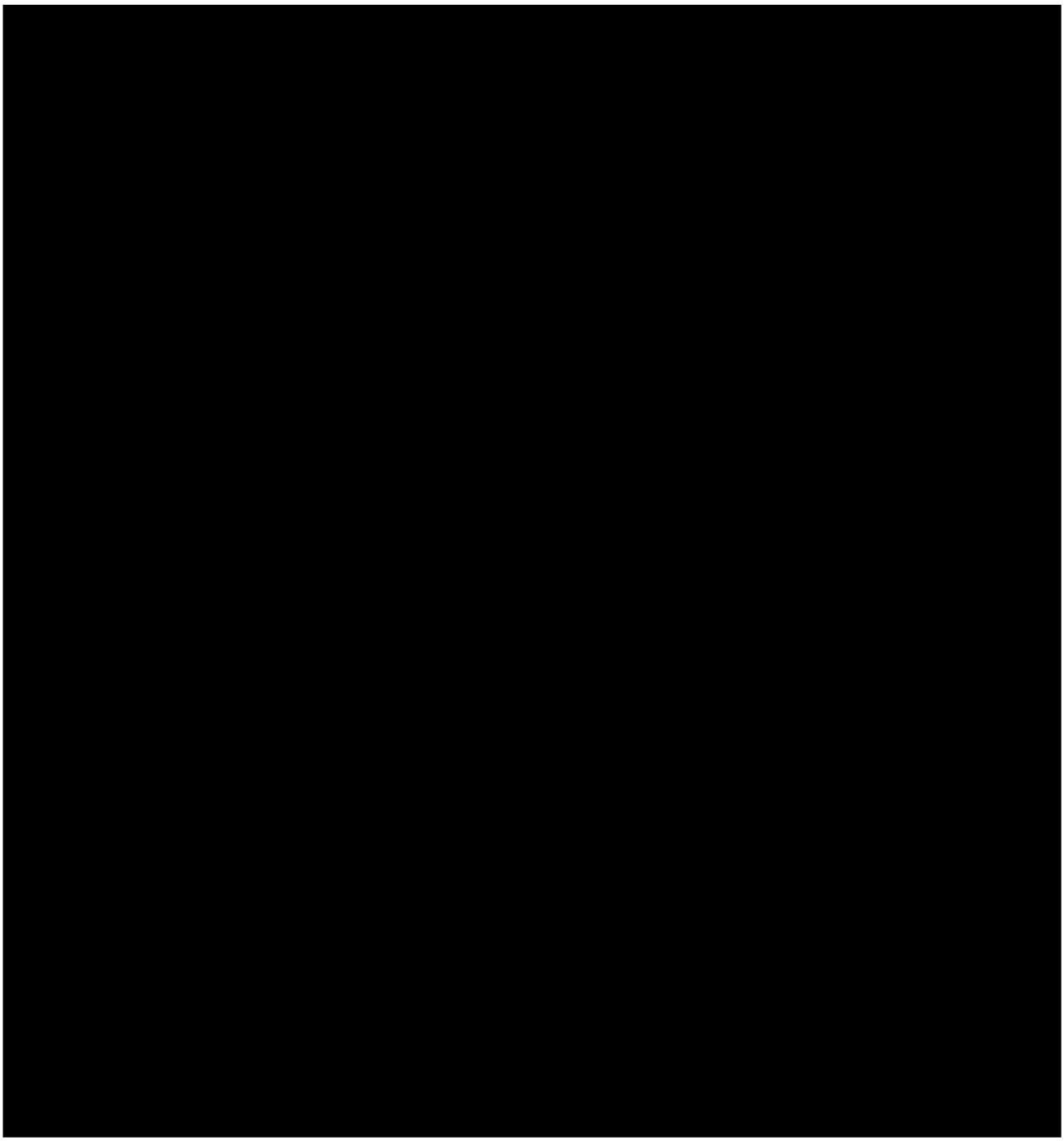
The rhinosinusitis VAS is provided in Appendix 7 (Section 10.7.3).

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

8.1.7 University of Pennsylvania smell identification test

The University of Pennsylvania smell identification test (UPSIT) (UPSIT 40 odorant test) 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 1 odorant per page. Above each odorant strip is a multiple-choice question with 4 alternative words to describe the odor and 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. Participants can be classified based on their score (43). UPSIT will be translated and culturally adapted according to industry practice in order to account for the different cultural contexts of participants and thus easing identification of the odorant depending on degree of smell loss.

Clinician will administer and score the UPSIT that will be completed by the participant as described in the SoA (Section 1.3). If UPSIT is planned on the same day as nasal endoscopy and the endoscopy is conducted under local anesthetic, the assessments with UPSIT must be performed before anesthetics use to ensure that the effect of anesthetics will not interfere with UPSIT interpretation.



[redacted]

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 exam), 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 AE.

8.2.2 Vital signs

- Vital signs will be measured in a semi-supine or sitting position after 5 minutes rest and will include body 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), randomization (Visit 2), and all following visits as specified in SoA (Section 1.3). Height must be collected at each visit only for pediatric participants; collect height for adult participants at screening visit (V1) only.

8.2.3 Electrocardiograms

A simple 12-lead electrocardiogram (ECG) will be obtained for screening purpose only as defined in SoA (Section 1.3).

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 which 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/Sponsor representative.
  - 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 or AE or dose modification), then the results must be recorded in the eCRF.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

Adverse events 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 ICF/assent form until the EOS visit at the time points specified in the SoA (Section 1.3).

All SAEs and adverse events of special interest (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 AE or SAE 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 AE and SAE 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 pre-specified 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 a SAE is essential so that legal obligations and ethical responsibilities toward 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 a 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 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 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 screens in the eCRF.

AESIs 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 a 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. It 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
  - 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 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). 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/Sponsor representative 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/Sponsor representative (determined on a case-by-case basis).
5. Document appropriately in the eCRF.

Decisions regarding dose interruptions will be made by the Investigator in consultation with the Sponsor/Sponsor representative based on the clinical evaluation of the participant.

8.5 PHARMACOKINETICS AND IMMUNOGENICITY ASSESSMENTS

8.5.1 Systemic drug concentration and antidrug antibodies

8.5.1.1 Sampling time

Blood samples will be collected for the assessment of functional dupilumab and anti-dupilumab antibodies in serum as specified in the SoA (Section 1.3). Special procedures for the 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 antibodies (ADA) is provided in Table 4.

Table 4 - Summary of handling procedures

Sample type	Functional dupilumab	Anti-dupilumab antibody
Matrix	Serum	Serum
Blood sample volume	2 mL	2 mL
Anticoagulant	None	None
Blood handling procedures	See Operational Manual	See Operational Manual
Serum aliquot split	2 aliquots	2 aliquots
Storage conditions	<6 months: below -20°C <24 months: below -80°C (preferred)	<6 months: below -20°C <24 months: below -80°C (preferred)
Serum shipment condition	In dry ice	In dry ice

8.5.1.3 Bioanalytic method

Serum PK and ADA samples will be assayed using validated methods as described in Table 5.

Table 5 - Summary of bioanalytical methods for functional dupilumab and anti-dupilumab antibodies

Analyte	Functional dupilumab	Anti-dupilumab antibody
Matrix	Serum	Serum
Analytical technique	ELISA	Electro-chemiluminescence
Site of bioanalysis	Regeneron	Regeneron

ELISA: enzyme-linked immunosorbent assay.

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 or hypersensitivity, PK and ADA samples may be collected at or near the onset of the event based on the medical judgment of the Investigator and/or Sponsor representative. 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/assent form.

8.6 PHARMACODYNAMICS

Several types of samples will be collected to quantify the following PD biomarkers:

[redacted]

For timing of PD sample collection refer to SoA (Section 1.3).

More detailed information on the collection, handling, transport, and preservation of samples (eg, minimum volumes required for blood collection and for aliquots for each biomarker assay) will be provided in a separate laboratory manual.

Assay methodologies are briefly summarized below:

- Plasma/serum biomarkers:
  [redacted] Total and fungal-specific IgE will be measured with a quantitative method (eg, Phadia ImmunoCAP) approved for diagnostic testing.

[redacted]

Some procedures for PD assessments specific to sites in China are described in the laboratory manual.

[redacted]

8.8 BIOMARKERS

Pharmacodynamic and pharmacogenetics biomarkers are described in Section 8.6 and Section 8.7.

An optional collection of serum/plasma samples that will be archived for other biomarker research is also part of this study:

- The archived samples may be used for research purposes related to respiratory diseases such as AFRS or inflammatory diseases (eg, exploratory biomarkers of disease or drug effect), pathway biology, additional drug safety assessments or development and validation of bioassay methods beyond those defined in the present protocol.
- Samples (including unused samples or leftover samples after testing) may also be used for research to develop methods, assays, prognostics and/or companion diagnostics related to dupilumab, disease process, pathways associated with disease state, and/or mechanism of action of the study intervention.
- Samples may be stored for a maximum of 15 years (or according to local regulations) following the last participant's last visit for the study at a facility selected by the Sponsor to enable further analysis.

[redacted]

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/parent(s)/legally authorized representative (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 either to the drug, the mechanism of action, and the disease or its associated conditions. [redacted] 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

The following null and alternative hypotheses will be tested for dupilumab versus placebo:

- H0: No treatment difference between dupilumab and placebo.
- H1: There is a treatment difference between dupilumab and placebo.

9.3 POPULATIONS FOR ANALYSES

The following populations are defined (Table 6):

Table 6 - Populations for analyses

Population	Description
Screened	All participants who sign the ICF/assent form
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.
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 treatment 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 first dose of the study treatment. 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 treatment. Participants will be analyzed according to the intervention actually received.

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

Endpoints not required for children aged ≥6 to <12 years will be analyzed using the ITT population in adults and adolescents (≥12 to <18 years).

9.4 STATISTICAL ANALYSES

The statistical analysis plan (SAP) will be developed and finalized prior to database lock and will describe the participant populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the most important endpoints including the primary and secondary endpoints.

9.4.1 General considerations

All comparisons will be of dupilumab (300 mg q2w and 300 mg q4w and 200 mg q2w) versus placebo.

The baseline value is defined generally as the last available value before randomization. For endpoints collected on the daily Nasal Symptom Diary, baseline is defined as the average of the scores in the 7 days prior to randomization.

For efficacy analyses, a multiplicity-controlled hierarchical testing is proposed to control the overall type-I error rate for testing the primary and select secondary efficacy endpoints at an alpha of 0.05. The detailed hierarchical testing procedure will be defined in the study SAP. The study is considered positive when the primary endpoint achieves statistical significance with 2-sided significance level 0.05.

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 pandemics pandemic requiring public health emergency on the efficacy (eg, missing data due to COVID-19) and safety will be detailed in the SAP.

9.4.2 Primary endpoint(s)

The primary estimand for the primary endpoint of change from baseline in LMK score at Week 52 is the composite/treatment policy strategy, as described in Table 7.

Table 7 - Summary of primary estimand for the primary endpoint

Endpoint Category	Estimands			
	Endpoints	Population	Intercurrent event(s) handling strategy and missing data handling	Population-level summary
Objective: To evaluate the efficacy of treatment with dupilumab to reduce sinus opacification in a population with allergic fungal rhinosinusitis (AFRS)				
Primary endpoint	Change from baseline in LMK score at Week 52	ITT	The following intercurrent events will be handled with a composite strategy; data after the IE will be excluded and the worst post-baseline value on or before the start of the IE will be assigned to the Week 52 value (WOCF); for participants with no post-baseline values, the baseline value will be used. • Undergo/plan to undergo surgery for AFRS prior to Week 52 • Taking SCS for any reason prior to Week 52 • Starting prohibited biologics prior to Week 52 The following IEs will be handled with the treatment policy strategy (without IEs that need to be handled with composite strategy). All assessments after starting such IE will be included. • Discontinuing the study intervention • Taking antifungals or other prohibited/rescue medications In addition, the missing data imputation rules are as follows: • For missing data, a multiple imputation approach will be used to impute missing Week 52 values, and this multiple imputation will use all data from participants excluding participants who undergo/plan to undergo surgery for AFRS on or before Week 52.	ANCOVA model with intervention group, time from last surgery (≤2 years, >2 years), region (countries combined), and relevant baseline measurement as covariates is used. Statistical inference obtained from all imputed data by ANCOVA model will be combined using Rubin's rule.

The primary endpoint of change from baseline in LMK score at Week 52, will be analyzed using an analysis of covariance (ANCOVA) model with the baseline LMK score, intervention group, time from last surgery (≤2 years, >2 years) and region (combined countries) as covariates, with intercurrent events and missing data being handled by a hybrid method of the worst-observation carried forward (WOCF) and multiple imputation. For participants who undergo/plan to undergo surgery for AFRS, take SCS for any reason or start prohibited biologics, data collected after these IEs will be excluded from analysis and the worst post-baseline value on or before the IE will be assigned to the Week 52 value (ie, WOCF approach). For participants with no post-baseline values, the baseline value will be used (composite strategy). Participants who discontinue the

study intervention prematurely are encouraged to follow the planned clinical visits and, in these participants (if without or before the IEs that need to be handled with composite strategy), all data collected after study intervention discontinuation will be included in the analysis (treatment policy strategy). In case there is missing data, a multiple imputation approach will be used to impute missing Week 52 values, and this multiple imputation will use all participants excluding participants who undergo/plan to undergo surgery for AFRS, take SCS for any reason or start prohibited biologics on or before Week 52. Each of the imputed complete data will be analyzed by fitting an ANCOVA model with the baseline covariate and factors for intervention group, time from last surgery (≤2 years, >2 years), and region (combined countries). Statistical inference obtained from all imputed data will be combined using Rubin's rule. Descriptive statistics including number of participants mean, standard error, and LS means will be provided.
In addition, difference in LS means and the corresponding 95% CI will be provided along with the p-values.

[redacted]

Subgroup analyses

To assess the consistency in treatment effects across different subgroup levels, subgroup analyses will be performed for the primary efficacy endpoint with respect to age group, gender, region, and other factors that will be specified in the SAP.

9.4.3 Secondary endpoint(s)

Statistical analysis methods for the secondary efficacy endpoints listed in Table 1 are presented below.

The primary estimand for the secondary endpoint of proportion of participants who receive SCS and/or undergo/plan to undergo surgery for AFRS during the 52-week treatment period is the treatment policy/while before rescue strategy, as described in Table 8.

Table 8 - Summary of primary estimand for the proportion secondary endpoint

Endpoint Category	Estimands			
	Endpoints	**Population**	**Intercurrent event(s) handling strategy and missing data handling**	**Population-level summary**
Secondary objective: To assess the efficacy of dupilumab to reduce the need for rescue treatments				
Secondary endpoint	Proportion of participants who receive SCS and/or undergo/plan to undergo surgery for AFRS during the 52-week treatment period.	ITT	The following IEs will be handled with a treatment policy strategy (if without/before taking prohibited biologics): • Discontinuation of study intervention • Taking antifungals or other prohibited/rescue medications The following IE will be handled with a while before rescue strategy, All data before starting prohibited biologics will be included in the analysis. • Starting prohibited biologics In addition, the missing data imputation rules are as follows: • Discontinuing the study follow-up without an event prior to discontinuation: Participant will be considered as no event.	Cochran-Mantel-Haenszel (CMH) test stratifying by time from last surgery (≤2 years, >2 years), and region (combined countries). The estimate of the odds ratio between dupilumab and placebo will be derived.

This secondary endpoint will be analyzed using a CMH test stratifying by time from last surgery (≤2 years, >2 years) and region (combined countries). All data collected after study intervention discontinuation and before starting prohibited biologics will be included in the analysis. Participants who discontinue the study follow-up without an event will be considered as no event. The estimate of the odds ratio between dupilumab and placebo will be derived with the corresponding 95% CI and p-value.

The change from baseline to Week 24 and Week 52 in the continuous secondary endpoints will be analyzed using the same analysis approach as for the primary endpoint of change from baseline in LMK score at Week 52.

[redacted]

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. The baseline value is defined generally as the last available value before first dose of IMP.

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.

Proportion of participants with at least 1 treatment-emergent adverse event (TEAE), treatment-emergent SAE, TEAE leading to death, and TEAE leading to permanent treatment 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.

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 treatment-emergent SAE.
- Any AE leading to death.
- Any TEAE leading permanent treatment 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 deaths 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.

Results and change from baseline for the laboratory 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 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 for clinical laboratory tests.

- PCSA criteria will determine which participants had at least 1 PCSA during the on-treatment period, taking into account all evaluations performed during the on-treatment period, including unscheduled or repeated evaluations. The number of all such participants will be the numerator for the on-treatment PCSA percentage.

The proportion of participants who had at least 1 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 database lock. The population PK and PD analyses might be presented separately from the main clinical study report (CSR).

9.5 INTERIM ANALYSES

There is no interim analysis planned as part of this study.

A primary database lock will be performed when all randomized participants have completed their treatment phase. Final analyses in the CSR will be based on all data collected up to this database lock.

The database will be updated at the end of the study for all participants to include the posttreatment follow-up information and updates for the events previously ongoing at the time of the primary lock. Additional data between this database lock and last participant completing last visit will be summarized in a CSR addendum.

9.6 DATA MONITORING COMMITTEE

Due to extensive clinical development and post-marketing safety profile for the 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 GCP Guidelines.
  - Applicable laws and regulations (eg, data protection law as General Data Protection Regulation [GDPR]).
- The protocol, protocol amendments, ICF/assent form, 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 trial 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/assent form 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/assent was obtained before the participant was enrolled in the study and the date the written consent/assent was obtained. The authorized person obtaining the informed consent/assent must also sign the ICF/assent form.
- In case of ICF/assent form amendment while the participants are still included in the study, they must be re-consented to the most current version of the ICF(s)/assent form. Where participants are not in the study anymore, teams in charge of the amendment must define if those participants must or not re-consent or be informed of the amendment (eg, if the processing of personal data is modified, if the Sponsor changes, etc).
- A copy of the ICF(s)/assent form must be provided to the participant or the participant's legally authorized representative.

Participants who are rescreened are required to sign a new ICF/assent form.

The ICF contains 2 separate sections that address 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/parent(s)/legally authorized representative will be told that they/their children 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/parent(s)/legally authorized representative's agreement to allow any remaining specimens to be used for exploratory research. Participants/parent(s)/legally authorized representatives 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. The study Sponsor, Sanofi is 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 ICF/assent form.

- 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 Dissemination of clinical study data

Study participants

Sanofi shares information about clinical trials and results on publically 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".

10.1.6 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/assent form, 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.

10.1.7 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.

10.1.8 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.

10.1.9 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 9 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 involvement in the study.

Table 9 - Protocol-required laboratory assessments

Laboratory assessments	Parameters
Hematology	
	Platelet count
	Red blood cell count
	Hemoglobin
	Hematocrit
	White blood cell count with differential:
	Neutrophils
	Lymphocytes
	Monocytes
	Eosinophils
	Basophils

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

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 China will use urine sample (not dipstick).

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

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

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

For children aged ≥6 to <12 years, laboratory assessments are based on the child's weight and are detailed in the laboratory manual.

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 fulfill 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); however, if local health authority requirements supersede this it will be reported per local health authority requirements.

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.
- Is a congenital anomaly/birth defect

e) **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. This list is illustrative and not derived from safety concerns specific to dupilumab:
        - 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
        - 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's representative 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 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 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 in adolescents or 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 1 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 hormone replacement therapy (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.

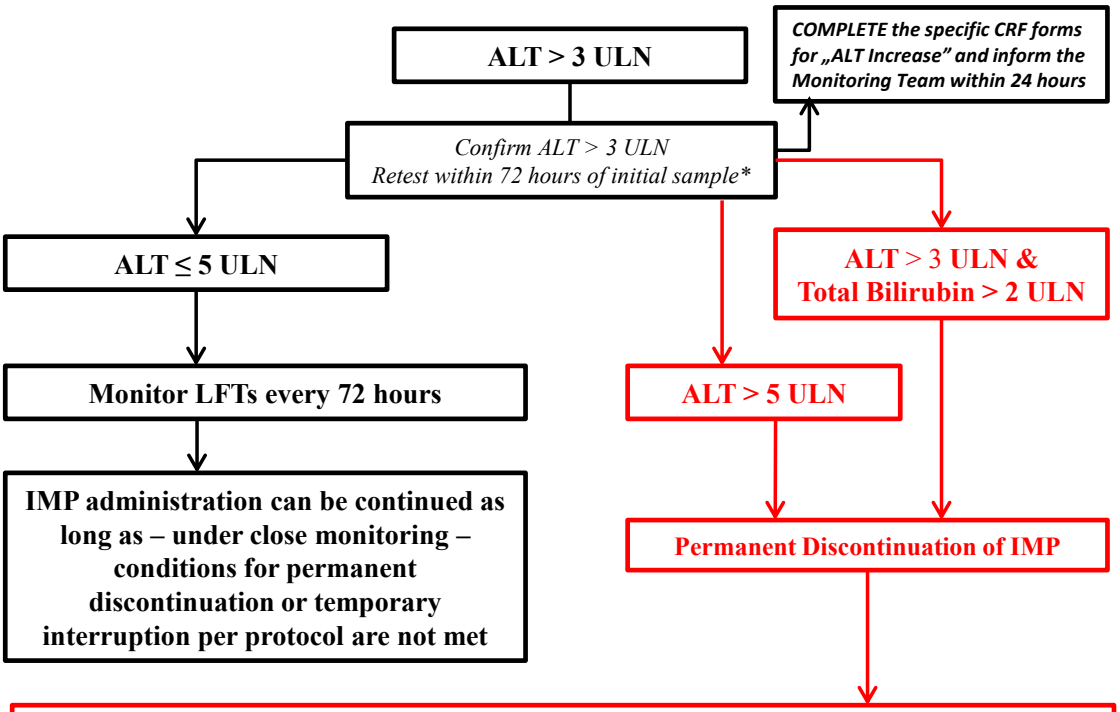
Female participants who become pregnant

- 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 8.3.5. 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

10.6 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

*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.

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

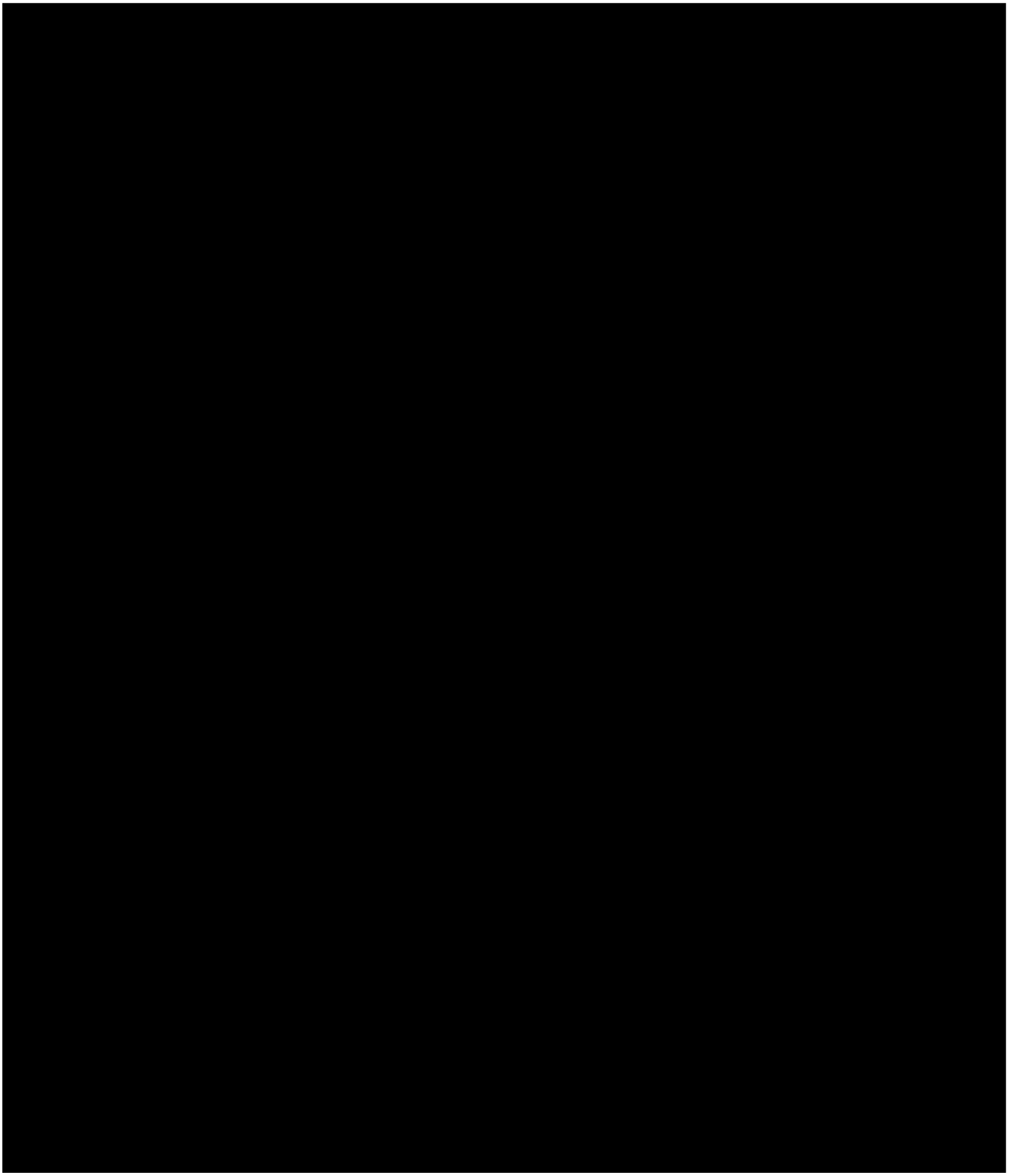
Note:

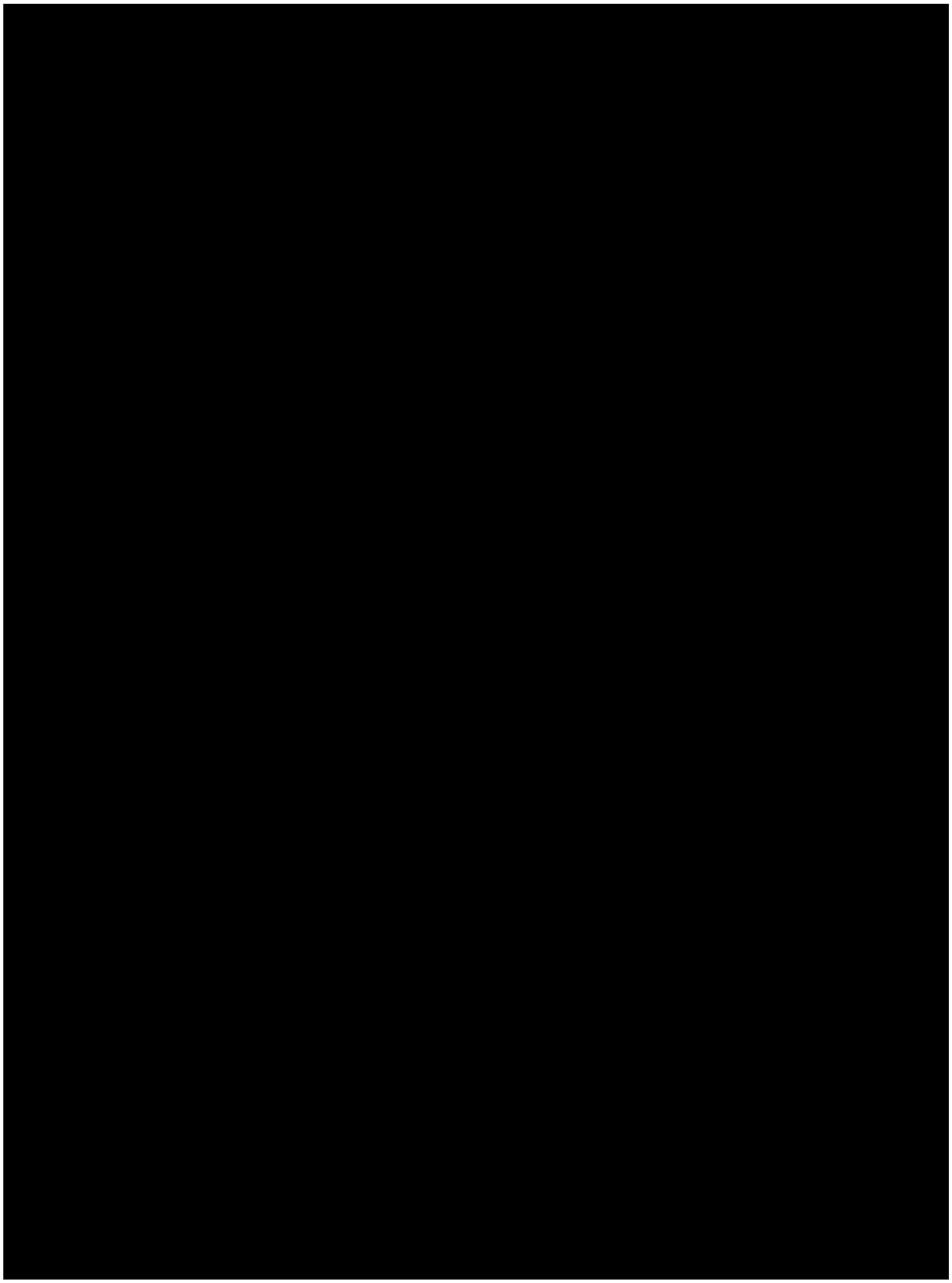
"Baseline" refers to ALT sampled at Baseline Visit; or if baseline value unavailable, to the latest ALT sampled before the Baseline Visit. The algorithm does not apply to the instances of increase in ALT during screening.

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: CLINICIAN-REPORTED OUTCOMES AND PATIENT-REPORTED OUTCOMES





10.7.2 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.

10.7.3 Rhinosinusitis visual analog scale

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

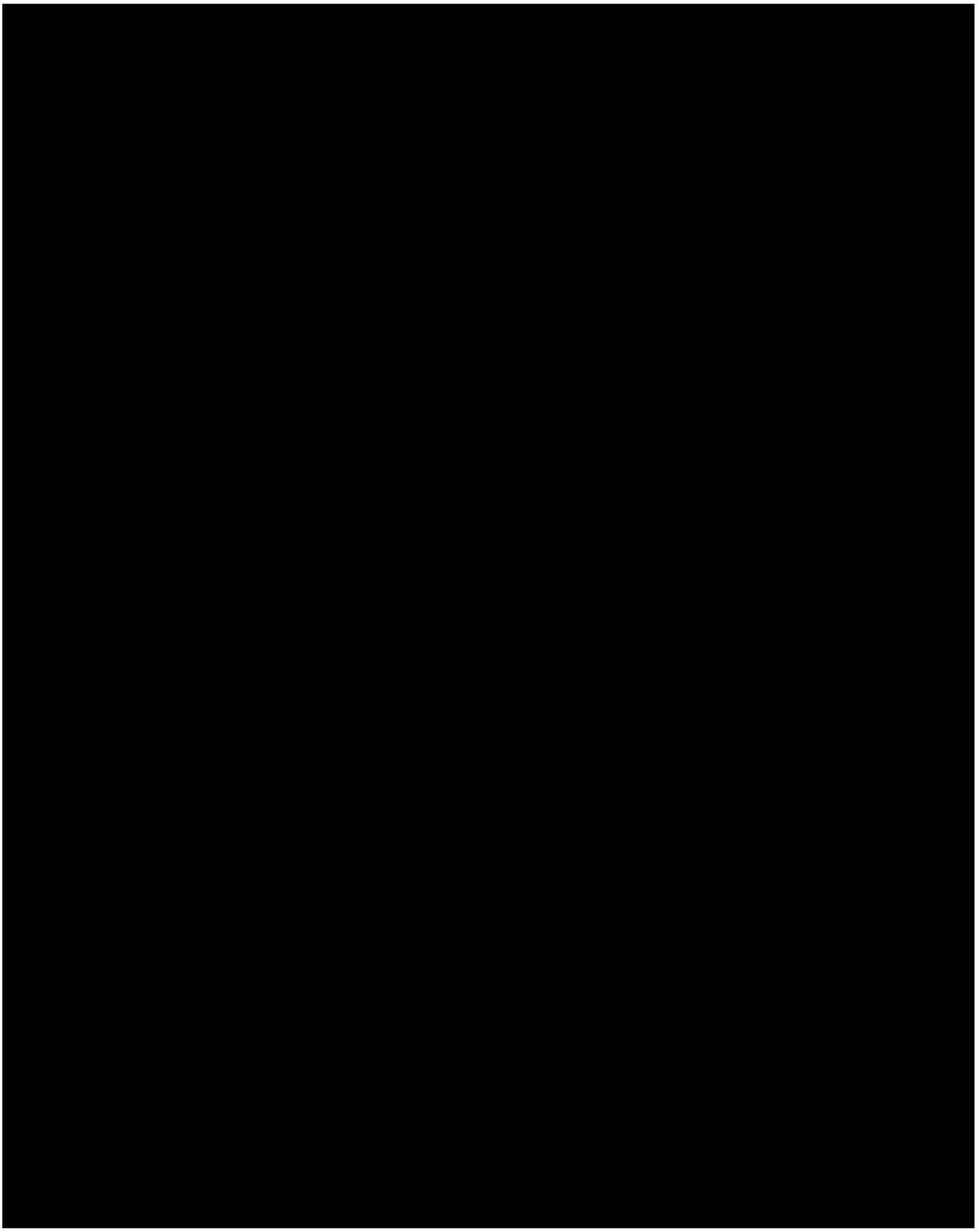
[redacted]

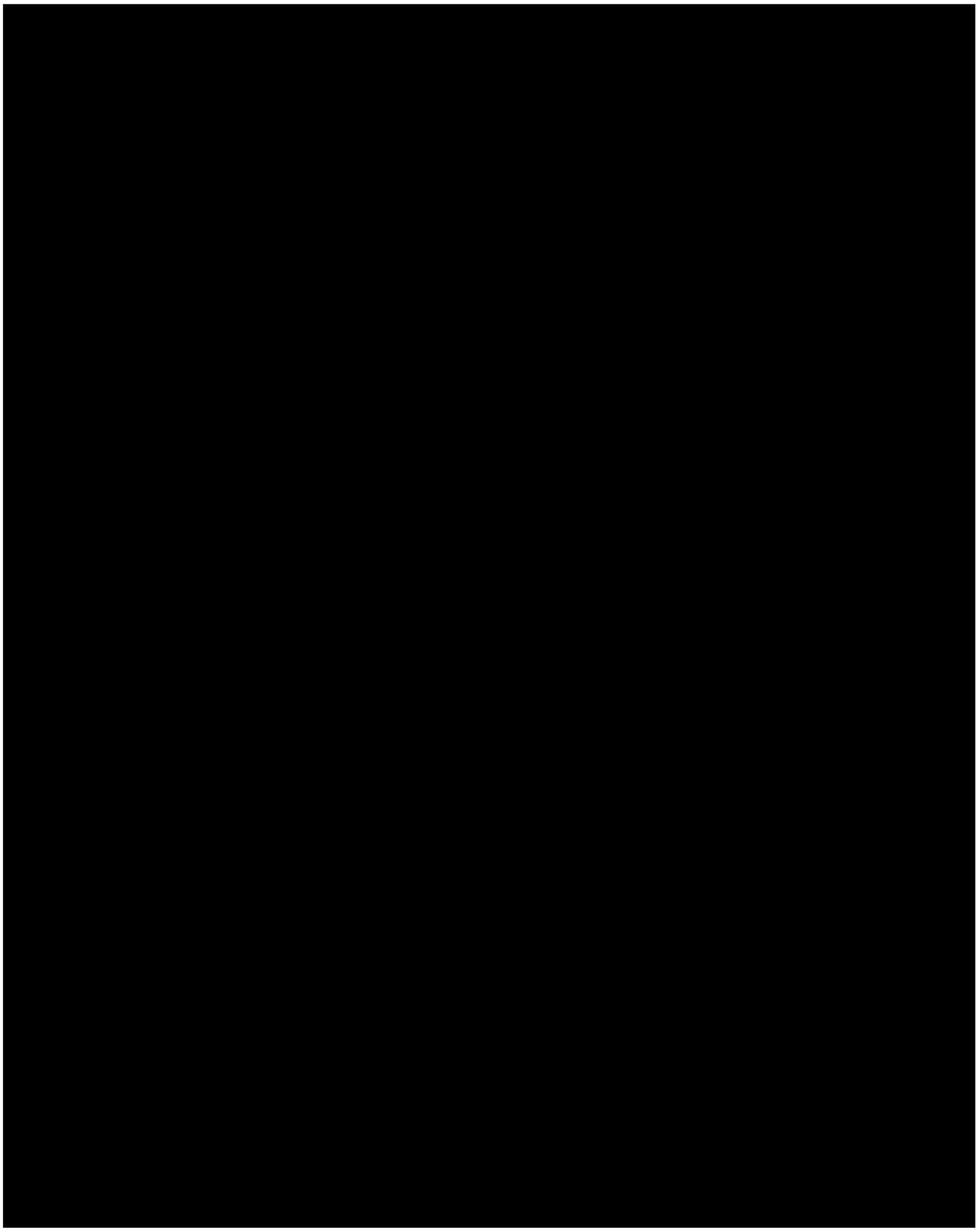
10.7.5 AFRS Morning Diary

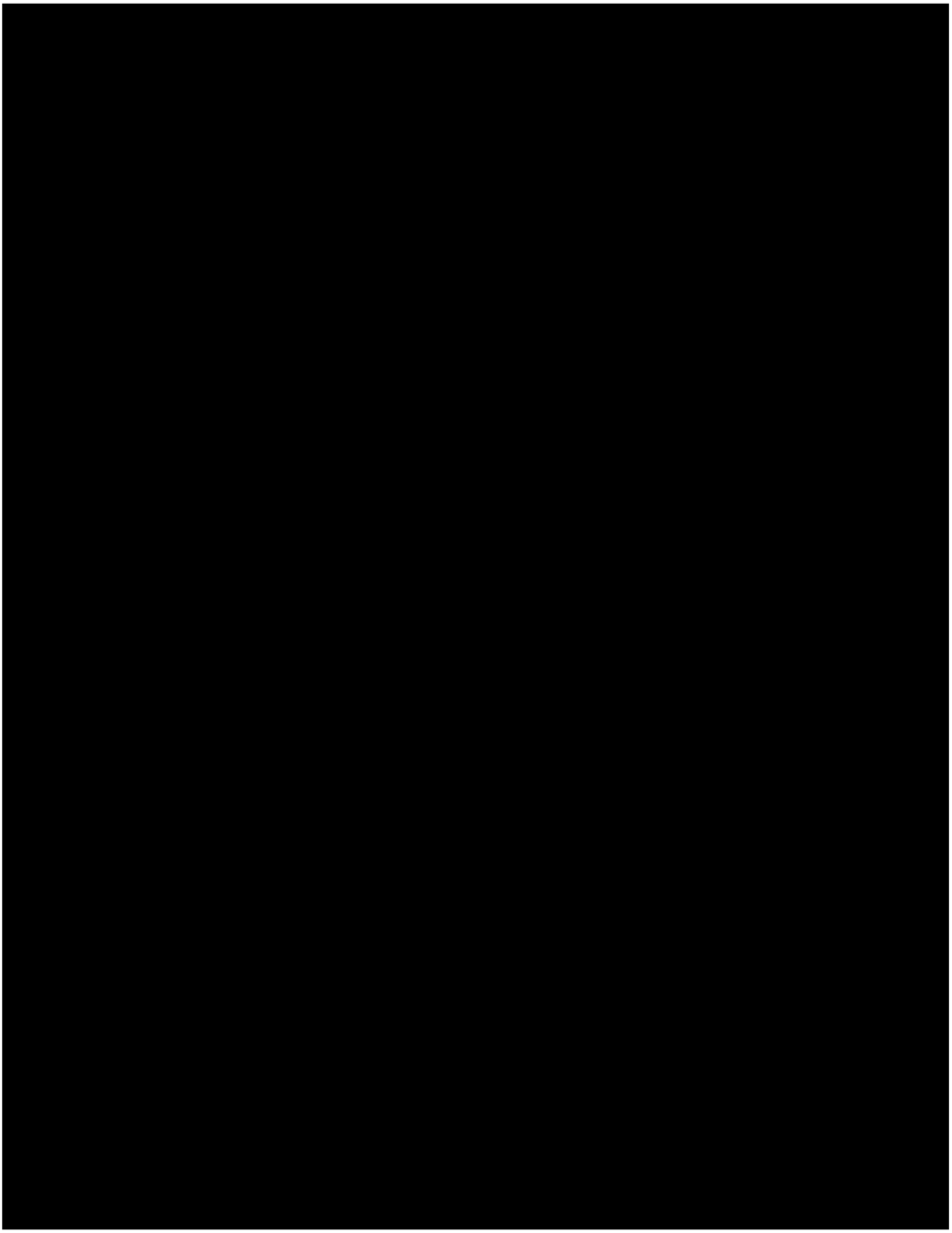
Sanofi_EFC16724 09JAN2023
English (US) v2.00

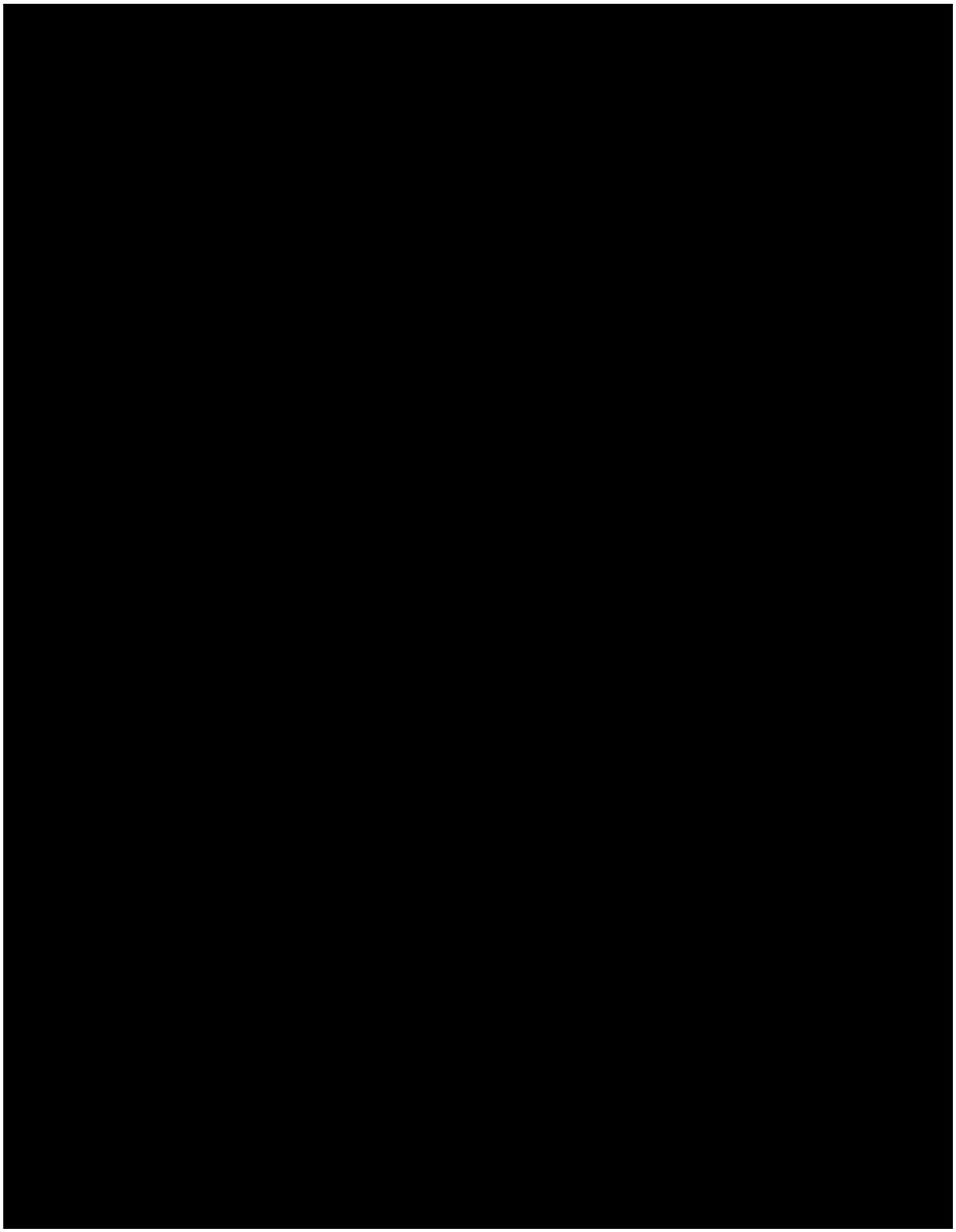
AFRS Morning Diary

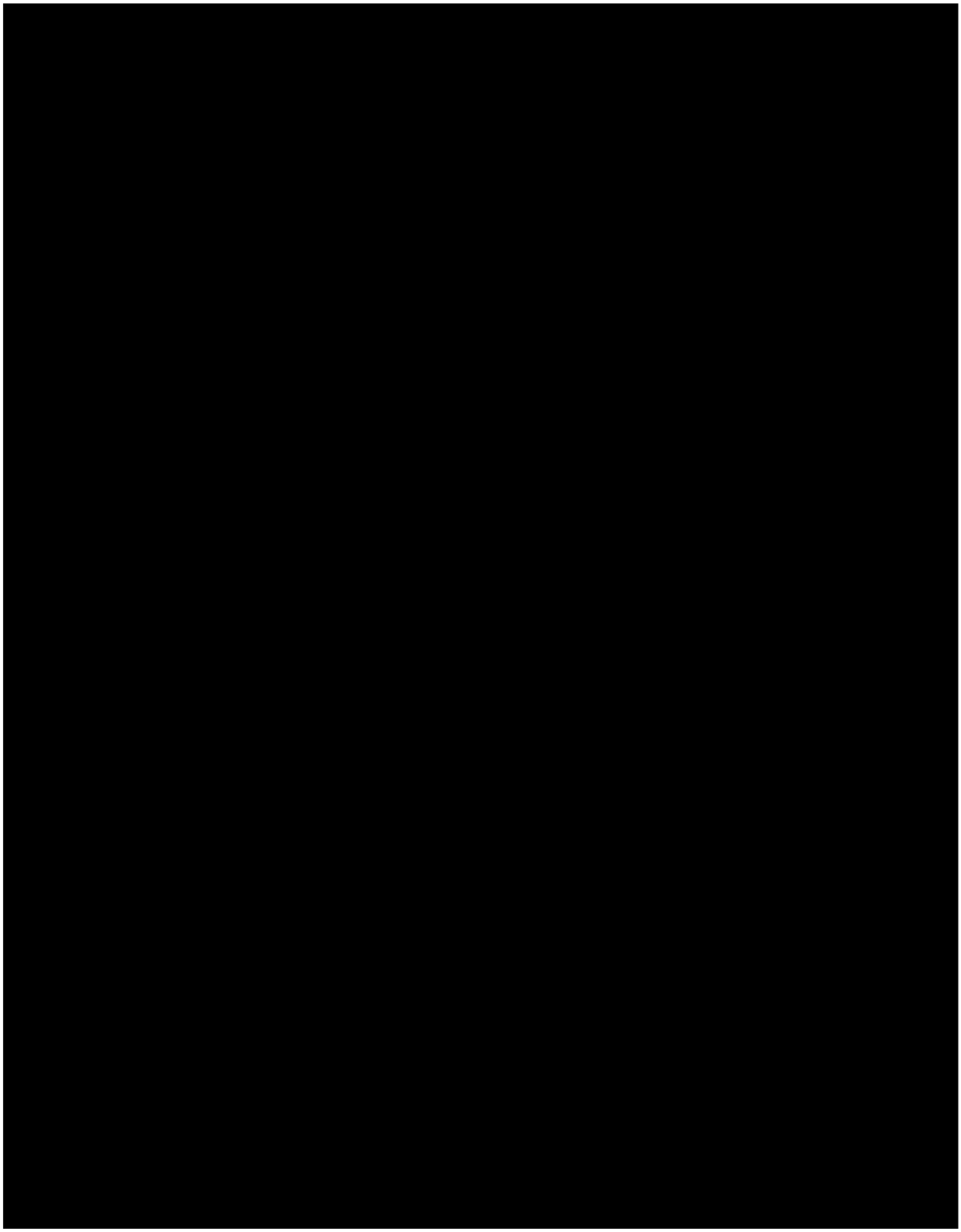
Question Text	Response Values
The following questions will ask you to rate your nasal disorder symptoms over the past 24 hours. Please make sure you assess your nasal symptoms shortly after getting up in the morning (before 12:00 noon).	–
The following questions will ask you to rate your nasal disorder 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
Since yesterday, did you decrease or increase your background rhinosinusitis nasal spray dose as prescribed below? {{{dt_INNmedicationNS070}}}: {{{dt_INNsprayNS070}}} 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.	–

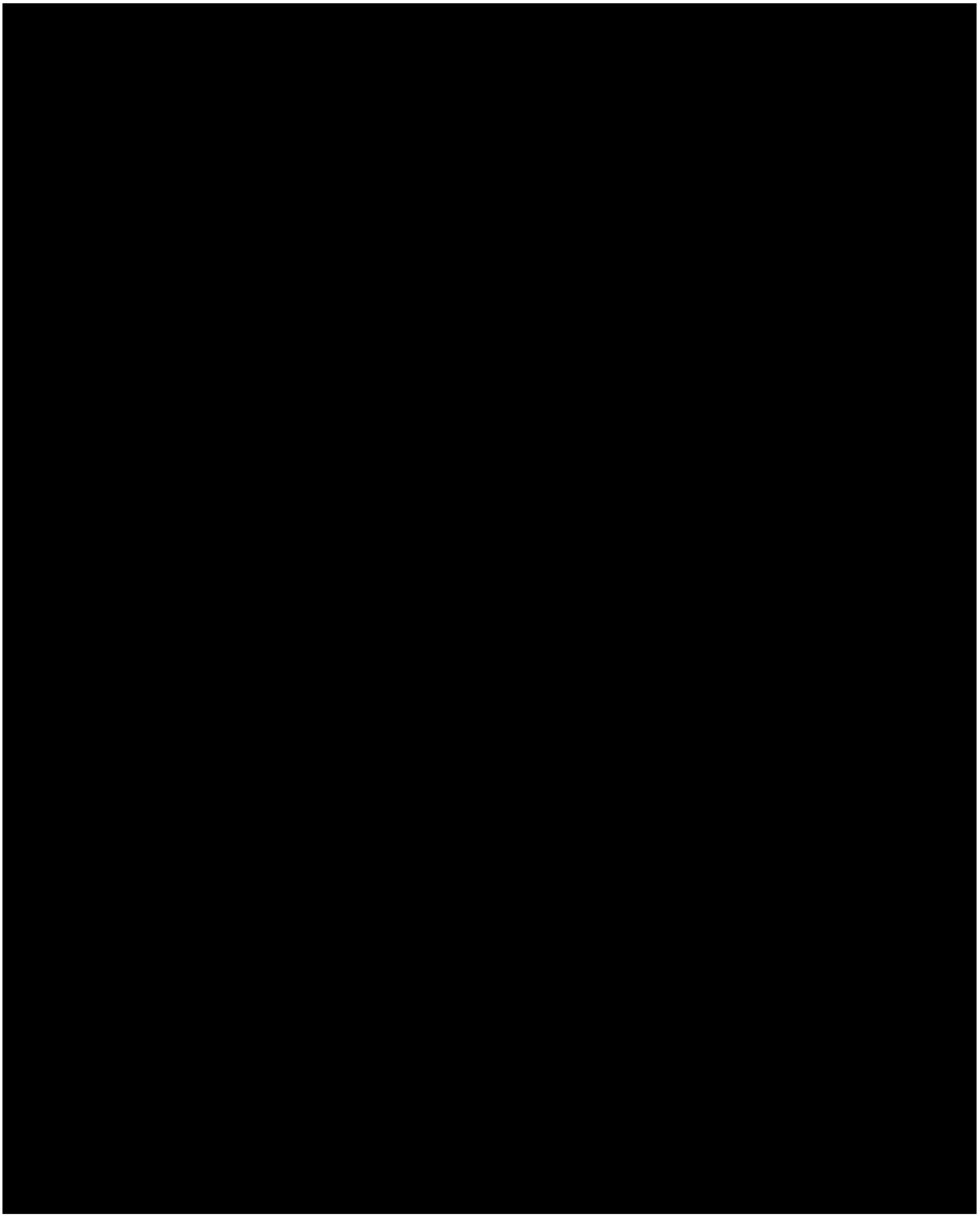


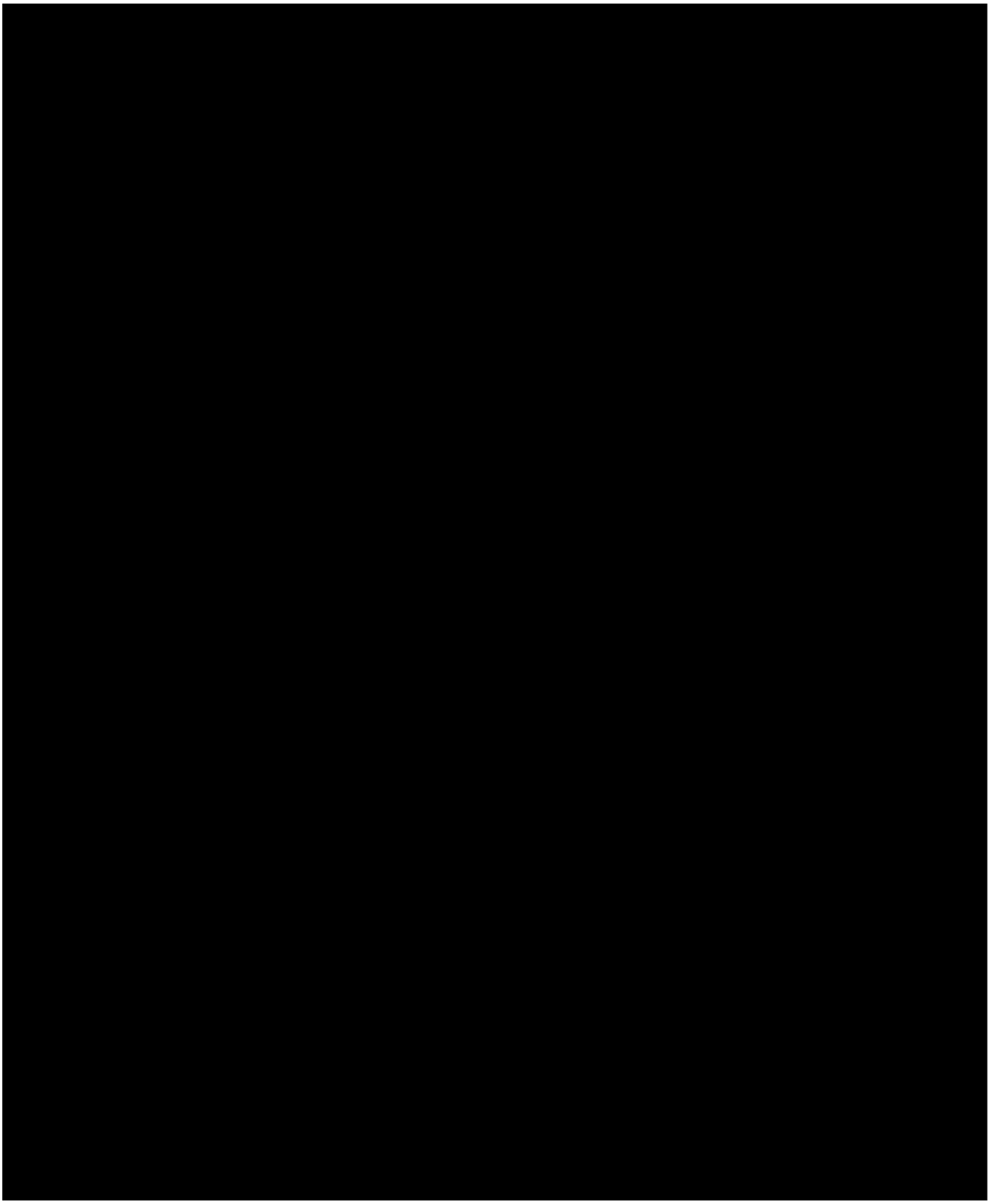


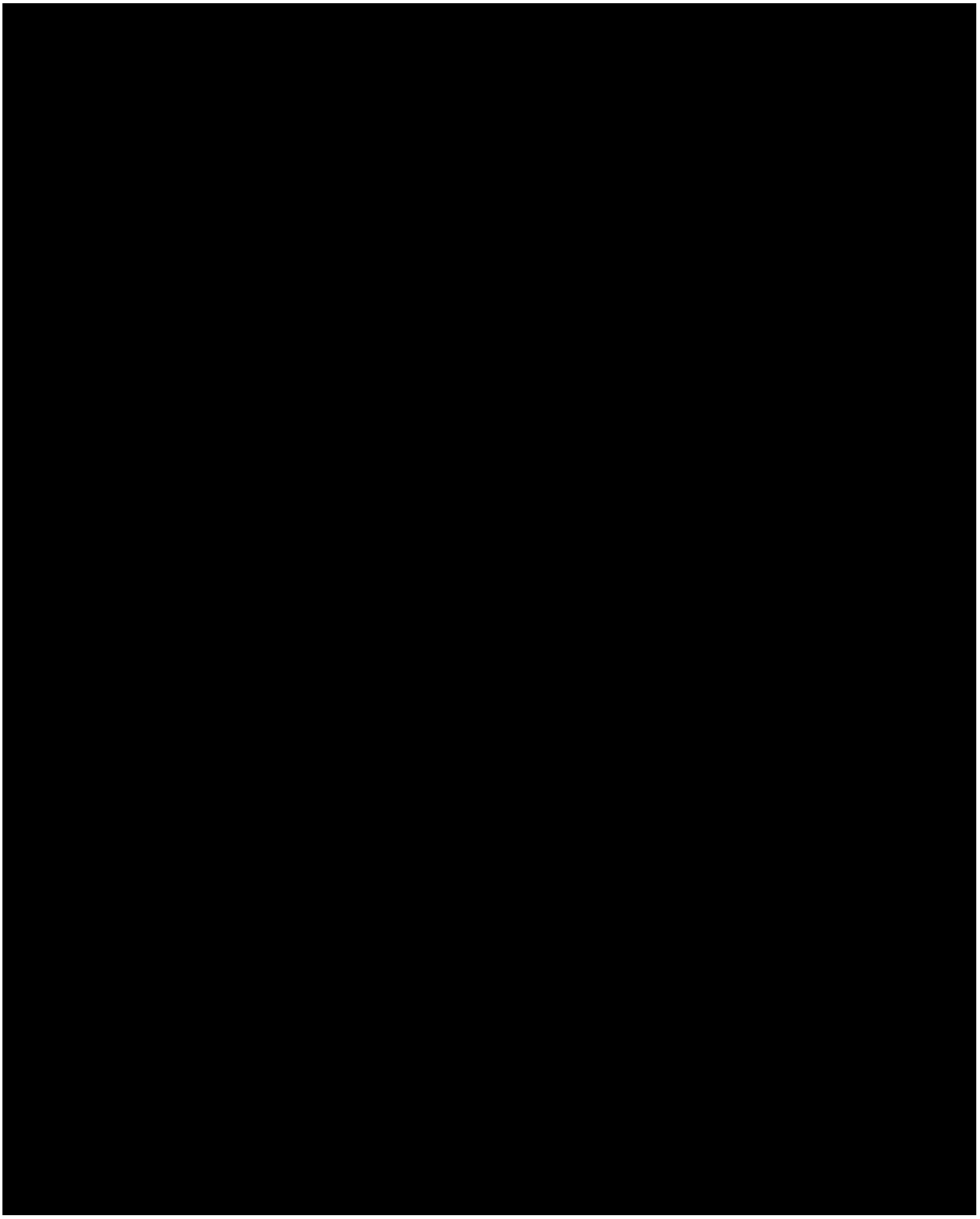












[redacted]

10.8 APPENDIX 8: COUNTRY-SPECIFIC REQUIREMENTS

Not applicable.

10.9 APPENDIX 9: DEFINITION OF ANAPHYLAXIS

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

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
- Non-TB mycobacteria
- Pneumocystis pneumonia

This list is indicative and not exhaustive.

10.11 APPENDIX 11: ABBREVIATIONS

[redacted]

ADA:	anti-drug antibodies
ADR:	adverse drug reaction
AE:	adverse event
AESI:	adverse event of special interest
AFRS:	allergic fungal rhinosinusitis
ALT:	alanine aminotransferase
ANCOVA:	analysis of covariance
CI:	confidence interval
CMH:	Cochran-Mantel-Haenszel
COPD:	chronic obstructive pulmonary disease
COVID-19:	Coronavirus Disease 2019
CRF:	case report form
CRS:	chronic rhinosinusitis
CRSwNP:	chronic rhinosinusitis with nasal polyposis
CSICF:	Core Study Informed Consent Form
CSR:	clinical study report
CT:	computed tomography
DILI:	drug-induced liver injury

[redacted]

eCRF:	electronic case report form
ELISA:	enzyme-linked immunosorbent assay
EoE:	eosinophilic esophagitis
EOS:	end of study
EOT:	end of treatment
ESS:	endoscopic sinus surgery
EU:	European Union

[redacted]

GDPR:	General Data Protection Regulation
HBcAb:	hepatitis B core antibody
HBsAg:	hepatitis B surface antigen
HBV:	hepatitis B virus
HCV:	hepatitis C virus
HCVAb:	hepatitis C virus antibody
HIV:	human immunodeficiency virus
HRQoL:	health-related quality of life
HRT:	hormone replacement therapy

IB:	investigator's brochure
ICF:	informed consent form
ICH:	International Council for Harmonisation
IEC:	Independent Ethics Committee
Ig:	immunoglobulin
IL:	interleukin
IMP:	investigational medicinal product
INCS:	intranasal corticosteroids
IRB:	Institutional Review Board
IRT:	interactive response technology
LMK:	Lund Mackay
LS:	least squares
mAb:	monoclonal antibody
NMPA:	National Medical Products Administration
NPS:	nasal polyp score
PCSA:	potentially clinically significant abnormality
PD:	pharmacodynamics
[redacted]	
PK:	pharmacokinetics
PRO:	patient-reported outcome
PT:	preferred term
q2w:	every 2 weeks
q4w:	every 4 weeks
[redacted]	
SAE:	serious adverse event
SAP:	statistical analysis plan
SC:	subcutaneous
SCS:	systemic corticosteroids
SNOT-22:	22-item sino-nasal outcome test
SOA:	Schedule of Activities
SOC:	system organ class
TB:	tuberculosis
TEAE:	treatment-emergent adverse event
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 (30 March 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.

OVERALL RATIONALE FOR THE AMENDMENT

This amendment institutes changes in response to Health Authorities feedback following review of the protocol and the overall pediatric development plan. The enrolment of study participants was extended to children aged ≥6 years old. The study assessments and the investigational medicinal products (IMP) were adapted to this population and are reflected in this amendment.

The inclusion criteria were modified to allow more suitable criteria for participant enrolment, while maintaining the necessary inclusion/exclusion criteria to achieve the scientific aims of the study and maintain patient safety.

Minor changes and typographical errors are not mentioned in the table below.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis	Rationale, overall design, number of participants and intervention groups and duration subsections were revised to include children aged ≥6 years old and an additional dose regimen for adolescents/children ≥15 kg and <30 kg of 300 mg q4w at screening.	Based on Health Authorities input regarding overall pediatric development plan and their recommendation to extend the inclusion to younger pediatrics, the age of participants was revised to be at least 6 years old and the dosage of IMP was selected to be 300 mg q4w for adolescents/children ≥15 kg and <30 kg.
	Statistical considerations: The redundant listing of the primary endpoint of the proportion of patients who received systemic corticoids (SCS) and/or undergo/plan to undergo surgery for AFRS during the planned study period was removed.	This redundant listing of the primary endpoint was removed as the repetition of the primary endpoint was unnecessary.
	Statistical considerations: an intercurrent event handling strategy for prohibited biologics and other prohibited medications was added.	As per Health Authorities request to propose intercurrent event handling strategies for prohibited biologic use and other prohibited medications.
	Statistical considerations: Added disease pattern (unilateral/bilateral in endoscopy at screening) as a factor in the statistical analysis model.	To account for this new randomization stratification factor.
1.2 Schema	Figure 1 was modified to include children aged ≥6 to <12 years. Dosing for adolescents/children ≥15 kg and <30 kg was selected to be 300 mg q4w.	Based on Health Authorities input regarding overall pediatric development plan and their recommendation to extend the inclusion to younger pediatrics, the age of participants was revised to be at least 6 years old and the dosage of IMP was selected to be 300 mg q4w for adolescents/children ≥15 kg and <30 kg.

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of activities (SoA)	Some notes were modified to include specific information related to participants aged ≥6 to 12 years old.	Specified assessments will not be conducted in children (aged less than 12 years old); while they remain appropriate for adolescents and adults, as clinical assessments done by patients themselves, they are not suitable for the younger pediatric group.
	Medical history: Footnote e was modified to record fungal stain assessment.	Fungal stain assessment as supporting evidence is optional, so the criterion was combined with criterion I02 d. However, the information is recorded in medical history.
	Nasal endoscopy assessment will be performed only at screening, Week 0, Week 24, and Week 52 for children aged ≥6 to <12 years old.	To reduce the frequency of an invasive procedure in children aged ≥6 to <12 years old, nasal endoscopy at Week 12 and Week 36 will not be performed in this age group.
	Nasal endoscopy: Footnote i for nasal polyp score (NPS) ≥3 for both unilateral and bilateral disease was modified to NPS score ≥2 out of 4 for unilateral polyps or 3 out of 8 for bilateral polyps.	To allow the enrolment of patients with unilateral AFRS, specific criteria for NPS for this subgroup were updated.
	CT scan note and footnote k: The information requiring performing a CT scan within 48 hours prior to the use of SCS was removed.	As per Health Authorities request, the CT scan to be performed between Week 36 and Week 52 in case of SCS use was removed.
	Addition of footnote x related to Visit 2 for q4w administrations.	This footnote was added for q4w administrations and IMP training.
2.2 Background	Rationale for background information was added for children aged ≥6 to <12 years.	Based on Health Authorities input regarding overall pediatric development plan and their recommendation to extend the inclusion to younger pediatrics, the age of participants was revised to be at least 6 years old.
3.1 Appropriateness of measurements	Inclusion criteria related to NPS ≥3 for both unilateral and bilateral disease was modified to NPS score ≥2 out of 4 for unilateral polyps or 3 out of 8 for bilateral polyps and Lund Mackay (LMK) ≥12 for both unilateral and bilateral disease was modified to LMK ≥9 for patients with unilateral polyps or ≥12 for patients with bilateral polyps.	To allow the enrolment of patients with unilateral AFRS, specific criteria for NPS and LMK for this subgroup were updated.
4.1 Overall design	Study design and dosage of dupilumab was updated to include children aged ≥6 years old.	Based on Health Authorities input regarding overall pediatric development plan and their recommendation to extend the inclusion to younger pediatrics, the age of participants was revised to be at least 6 years old and the dosage of IMP was selected to be 300 mg q4w for adolescents/children ≥15 kg and <30 kg.
4.2 Scientific rationale for study design	Inclusion criteria related to NPS of ≥3 out of 8 was modified to NPS score ≥2 out of 4 for unilateral polyps or 3 out of 8 for bilateral polyps and LMK ≥12 out of 24 was modified to LMK ≥9 out of 12 for unilateral polyps or ≥12 out of 24 for bilateral polyps.	To allow the enrolment of patients with unilateral AFRS, specific criteria for NPS and LMK for this subgroup were updated.

Section # and Name	Description of Change	Brief Rationale
4.3 Justification for dose	Information on dosing and exposures for dupilumab derived from previously conducted AD studies in children was added to justify the dosing for children used in this study.	Based on Health Authorities input regarding overall pediatric development plan and their recommendation to extend the inclusion to younger pediatrics, the age of participants was revised to be at least 6 years old and the dosage of IMP was selected to be 300 mg q4w for adolescents/children ≥15 kg and <30 kg as per dupilumab AD studies with the same population.
5.1 Inclusion criteria	I 01. Participant age modified from ≥12 years to ≥6 years. I 05. Body weight modified from ≥30 kg to ≥15 kg.	Based on Health Authorities input regarding overall pediatric development plan and their recommendation to extend the inclusion to younger pediatrics, the age of participants was revised to be at least 6 years old.
	I 02.e) was removed and combined with inclusion criterion I 02.d). A footnote was added in the Schedule of Activity - Medical History to record this information.	Fungal staining has high variability (10-100% false positive rate) and low specificity. In practice this means that a negative fungal stain does not rule out the diagnosis of AFRS, while saprophytic fungal growth is not necessarily diagnostic of AFRS. This uncertainty is reflected in the fact that fungal culture is only considered supportive evidence in the Bent and Kuhn diagnostic criteria in contrast to the other four criteria which are key for the diagnosis (elevated specific IgE, polyps, CT, and eosinophilic mucin).
	I 03.a) Endoscopic NPS of at least 3 out of 8 (either unilateral or bilateral polyps) was modified to NPS score ≥2 out of 4 for unilateral polyps or 3 out of 8 for bilateral polyps.	To allow the enrolment of patients with unilateral AFRS, specific criteria for NPS and LMK for this subgroup were updated.
	I 03.b) LMK score at inclusion was modified to include either LMK score of 9 unilateral sinus opacification or 12 bilateral sinus opacification.	To allow the enrolment of patients with unilateral AFRS, specific criteria for NPS and LMK for this subgroup were updated.
	I 07. Addition of a specific Assent Form for children aged ≥6 to <12 years.	Based on Health Authorities input regarding overall pediatric development plan and their recommendation to extend the inclusion to younger pediatrics, a specific Assent Form should be used for these children.
5.2 Exclusion criteria	E 02 blood boil example was removed and replaced by hemangioma.	Blood boil is not the correct medical term for the condition.
	E15 was modified to provide a more precise description of prior dupilumab use that leads to exclusion.	Precision concerning prior dupilumab use was added in the exclusion criterion.
6.1 Study Intervention(s) administered	Addition of a new dosing regimen for dupilumab and matching placebo for adolescents/children ≥15 kg and <30 kg.	Based on Health Authorities input regarding overall pediatric development plan and their recommendation to extend the inclusion to younger pediatrics, the age of participants was extended to be at least 6 years old. The dosing for these children was added.

Section # and Name	Description of Change	Brief Rationale
6.3 Measures to minimize bias: Randomization and blinding	Added children to the adolescent stratification factor.	Based on Health Authorities input regarding overall pediatric development plan and their recommendation to extend the inclusion to younger children, the age stratification was clarified to include children with adolescents.
	Added another stratification factor in adults of disease pattern (unilateral/bilateral in endoscopy at screening).	To ensure treatment balance within disease pattern.
	Code breaking: The sentence “Investigator could decide at his/her discretion to contact the Sponsor to discuss the situation in case of unblinding participant’s intervention assignment” was removed	As per EMA GCP Inspectors Working Group (GCP IWG) and the Clinical Trial Facilitation Group (CTFG), the responsibility to break the treatment code in emergency situations resides solely with the Investigator. Consequently, the Sponsor can't require or insist on being involved in the decision to unblind, stall or delay in any way the unblinding of trial subject treatment in emergency situations.
6.5.3 Rescue medicine	Information related to use of SCS during the specific period from Week 36 to Week 52 was removed.	As per Health Authorities request, the CT scan to be performed between Week 36 and Week 52 in case of SCS use was removed.
8 Study assessments and procedures	PRO assessment order was added.	PRO assessment order was added to be consistent with footnote in SoA.
	Blood sample volume was specified for children	Based on Health Authorities input regarding overall pediatric development plan and their recommendation to extend the inclusion to younger children, the age of participants was extended to be at least 6 years old. The blood sample volume for these children was added.
8.1.2.1 Lund Mackay score	Information related to use of SCS during the specific period from Week 36 to Week 52 was removed.	As per Health Authorities request, the CT scan to be performed between Week 36 and Week 52 in case of SCS use was removed.
9.3 Populations for analysis	The following was added: PRO endpoints will be analyzed using the ITT population in adults and adolescents.	PRO questionnaires are not applicable for children aged ≥6 and <12 years.
9.4.1 General considerations for Statistical Analysis	Added clarification that all primary and select secondary efficacy endpoints in the multiplicity hierarchical testing procedure will be performed at an alpha of 0.01 level.	As per Health Authorities request to clarify that the multiplicity plan will conform to the same overall alpha of 0.01.
9.4.2 Primary endpoint(s) and 9.4.3 Secondary endpoint(s)	Removed the estimand from the endpoint column in Table 7 and Table 8 and added an intercurrent event handling strategy for prohibited biologics and other prohibited medications.	As per Health Authorities request to clarify the strategy is associated with the intercurrent event and not the endpoint, and to propose intercurrent event handling strategies for prohibited biologic use and other prohibited medications.
	Added disease pattern (unilateral/bilateral in endoscopy at screening) as a factor in the statistical analysis model.	To account for this new randomization stratification factor.
10.2 Appendix 2: Clinical laboratory tests	HBcAb IgM and IgG were removed	Only HBcAb total test is performed at Central Laboratory whereas HBcAb IgM and IgG tests are not performed at Central Laboratory.

Section # and Name	Description of Change	Brief Rationale
10.4 Appendix 4: Contraceptive guidance and collection of pregnancy information	For male participants with partners who become pregnant, the sentence "this applies to male participants who receive dupilumab" was removed.	As the study is double-blinded, this sentence is not accurate.

10.12.2 Amended protocol 02 (23 November 2021)

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

The primary purpose of the amendment is to institute changes to allow more flexible criteria for participant enrolment, while maintaining the necessary inclusion/exclusion criteria to achieve the scientific aims of the study and maintain patient safety.

Inclusion/exclusion criteria were modified in order to be more in line with the current clinical practice of investigators in terms of diagnosis and management of patients with allergic fungal rhinosinusitis (AFRS).

Additional changes including statistical analysis of the secondary endpoint(s) are presented in the table below. The Sponsor changed the handling of surgery for AFRS or starting prohibited biologics from worst possible score to worst observation carried forward to better reflect the clinical scenario of treatment failure.

Minor changes and clarifications and typographical errors are not mentioned in the table below.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Section 1.3 Schedule of activities (SOA)	Footnote a: Extension of the screening period from 28 days ±3 days to a maximum of 42 ±3 days in case of particular circumstances to allow patients to complete study procedures (eg, skin testing, mucin collection).	To allow adequate time for certain test results to be available, ie. fungal sensitization by skin testing or eosinophilic mucin present in sinus tissue.
Section 5.1 Inclusion criteria	Removal of "without fungal invasion" from Inclusion criteria 02 B&K criteria d: d) Eosinophilic mucin/mucus ~~without fungal invasion into sinus tissue (~~identified within 5 years prior to screening or at screening~~)~~ with or without positive fungal stain.	Patients with known or risk factors for fungal invasion are already excluded from participating in the study with the following exclusion criteria: E03, E05, E06, and E07, therefore, an additional inclusion criteria for histological proof of fungal invasion into sinuses is not deemed necessary to exclude these patients from the study.

Section # and Name	Description of Change	Brief Rationale
Section 5.1 Inclusion criteria	Revision of inclusion criterion I04 previously reported as “Prior sino-nasal surgery(ies) for AFRS” to “History of sino-nasal surgery(ies)” with addition of a note providing examples of sino-nasal surgery.	The AFRS disease process evolves with time and due to the similarity of symptoms patients may undergo sino-nasal intervention for CRS or nasal polyps and the diagnosis of AFRS based on Bent Kuhn criteria is only made post-surgically based on histopathology. Therefore, a modification in this criteria is made, to allow enrollment of patients who may not have in the historical sino-nasal surgical report specified "surgery for AFRS" (eg. for the first surgery) but for whom a histopathological diagnosis of AFRS was made at or after surgery and before randomization in the study.
Section 5.4 Screen failures	Extension of the duration of validity of the screening CT scan to 90 days in case of rescreening if the rescreening is performed outside of the 90 days window, the CT scan must be repeated.	To avoid re-exposing patients to radiation in case of rescreening, given that CT scan images are not likely to change significantly during a 3-month period.
Section 8.1.7	Addition of the following text: If UPSIT is planned on the same day as nasal endoscopy and the endoscopy is conducted under local anesthetics the assessment with UPSIT must be performed before anesthetics use to ensure that the effect of anesthetics will not interfere with UPSIT interpretation.	Instruction added to avoid any impact of the anesthetics on the UPSIT assessment.
Section 9.4.3 Secondary endpoint(s) and 1.1 Synopsis	Change of intercurrent event handling strategy for undergoing surgery for AFRS or starting prohibited biologics: “data collected after surgery or starting prohibited biologics will be excluded and the worst possible score (eg, 24 for LMK) will be assigned to the Week 52 value” changed to “data collected after surgery or starting prohibited biologics will be set to missing and the worst post-baseline score value on or before surgery or starting prohibited biologics will be used to impute the missing Week 52 value (ie worst observation carried forward [WOCF] approach). For participants with no post-baseline values, the baseline value will be used (composite strategy).”	To change the intercurrent event handling strategy for surgery for AFRS or use of prohibited biologics to include each patient's own worst data in order to better reflect the clinical scenario of treatment failure.
Section 10.2 Appendix 2 Clinical Laboratory tests and Section 1.3 Schedule of activities (SOA)	Revision of the footnote e in the Table 9-Protocol-required laboratory assessments and the footnote q in the Schedule of Activities to remove HBsAb test and to precise wording for the testing.	Clarification on hepatitis DNA/RNA assessments. Removal of HBsAb assessment from the entire protocol, as only HBsAg and HBcAb results are used for the assessment of HBV DNA. Removal of the wording “false positivity” for patients with positive HBcAb or HCVAb and negative DNA/RNA as this wording is not appropriate for antibodies status.
Section 10.12 Appendix 12: Protocol amendment history	The overall rationale and table with summary of changes for Amended protocol 01 were moved from the Cover page to Section 10.12.	This is aligned with Sanofi procedures.

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