NCT05049122

CLINICAL TRIAL PROTOCOL

Protocol title:	**A single-arm, 52-weeks, Phase 4 study to assess the efficacy and safety of dupilumab in patients with chronic rhinosinusitis with nasal polyposis (CRSwNP) who are not adequately controlled with existing therapies**
Protocol number:	**LPS16872**
Amendment number:	**Not applicable**
Compound number (INN/Trademark):	**SAR231893 (dupilumab/Dupixent®)**
Brief title:	**Dupilumab in Japanese patients with chronic rhinosinusitis with nasal polyp (SINUS-M52)**
Study phase:	**Phase 4**
Sponsor name:	**Sanofi K.K.**
Legal registered address:	**3-20-2, Nishi Shinjuku, Shinjuku-ku, Tokyo 163-1488 Japan**
Monitoring team's representative name and contact information	

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1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Protocol title:

A single-arm, 52-weeks, Phase 4 study to assess the efficacy and safety of dupilumab in patients with chronic rhinosinusitis with nasal polyposis (CRSwNP) who are not adequately controlled with existing therapies

Brief title: Dupilumab in Japanese patients with chronic rhinosinusitis with nasal polyp (SINUS-M52)

Rationale:

Dupilumab blockade of interleukin-4 (IL-4) and IL-13 signaling has demonstrated a favorable efficacy and safety profile for the treatment of a variety of atopic disease states, including atopic dermatitis (AD), asthma, and CRSwNP, where type-2 inflammation is a key driver of the underlying disease process. This study will assess the efficacy and safety profile of dupilumab administered as monotherapy to Japanese CRSwNP participants whose disease is not adequately controlled with existing therapies (systemic corticosteroids [SCS] and surgery).

Dupilumab has been approved for the treatment of CRSwNP that is not adequately controlled with existing therapies by the health authority in Japan on the condition that the efficacy and safety of dupilumab monotherapy will be assessed after approval; the efficacy and safety data in the global program were developed with intranasal corticosteroid (INCS) concomitantly administered with dupilumab. Intranasal corticosteroid is not approved for CRSwNP in Japan. Their use for CRSwNP is an off-label use in Japan. The objective of this Phase 4 study is to assess the efficacy and safety of dupilumab as monotherapy (without concomitant INCS) in participants with CRSwNP.

Objectives and endpoints:

Objectives	Endpoints
Primary	
• To assess the efficacy of 24-week treatment with dupilumab 300 mg every 2 weeks (q2w) to reduce nasal polyp score (NPS) in participants with chronic rhinosinusitis with nasal polyposis (CRSwNP) who do not use concomitant intranasal corticosteroid (INCS)	• Proportion of participants with NPS improvement from baseline ≥1 at Week 24
Secondary	
• To assess the efficacy of 24-week treatment with dupilumab 300 mg q2w on other efficacy endpoints in participants with CRSwNP who do not use concomitant INCS	**Key secondary efficacy endpoints:** • Change from baseline to Week 24 in bilateral NPS • Change from baseline to Week 24 in nasal congestion/obstruction (NC) symptom severity score using the CRSwNP nasal symptom diary • Change from baseline to Week 24 in opacification of sinuses assessed by computerized tomography (CT) scan using the Lund Mackay (LMK) score **Other secondary efficacy endpoints:** • Change from baseline to Week 24: - Total symptom score (TSS), a composite score derived from the nasal symptom diary (includes nasal congestion, loss of sense of smell, anterior and posterior rhinorrhea) - Loss of smell symptom severity score using the nasal symptom diary - Visual analogue scale for rhinosinusitis
• To evaluate the safety of 24-week treatment with dupilumab in participants with CRSwNP	• Incidence of treatment-emergent adverse events (TEAEs), treatment-emergent serious adverse events (TESAEs), and TEAEs leading to treatment discontinuation
Tertiary/exploratory	
• To assess the efficacy of 52-week treatment with dupilumab under different dosing regimens to participants with CRSwNP who do not use concomitant INCS	• Proportion of participants with NPS improvement from baseline ≥1 at Week 52 • Change from baseline to Week 52 in bilateral NPS • Change from baseline to Week 52 in NC symptom severity score using the CRSwNP nasal symptom diary • Change from baseline to Week 52 in opacification of sinuses assessed by CT scan using the LMK score • Change from baseline to Week 52 in TSS
• To evaluate the safety of 52-week treatment with dupilumab in participants with CRSwNP	• Incidence of TEAEs, TESAEs, and TEAEs leading to treatment discontinuation

Abbreviations: CRSwNP: chronic rhinosinusitis with nasal polyposis; CT: computerized tomography; INCS: intranasal corticosteroid; LMK: Lund Mackay; NC: nasal congestion/obstruction; NPS: nasal polyp score; q2w: every 2 weeks; TEAE: treatment-emergent adverse event; TESAE: treatment-emergent serious adverse events, TSS: total symptom score.

Overall design:

This is a Phase 4, open-label, single-arm, multicenter, efficacy and safety study of dupilumab monotherapy in participants with CRSwNP that is not adequately controlled with existing therapies.

This study will investigate the efficacy and safety of dupilumab 300 mg every 2 weeks (q2w) at Week 24, without concomitant administration of INCS.

In addition, in line with Japan label, the study is designed to assess the long-term (52 weeks) efficacy and safety of an initial treatment regimen of dupilumab 300 mg q2w for 24 weeks without INCS, followed by a less frequent dosing regimen (300 mg every 4 weeks [q4w]) up to Week 48 for those participants who demonstrate stable disease* at Week 24. Other participants will receive the q2w regimen up to Week 50.

**Stable disease definition: nasal polyp score (NPS) improvement from baseline to both Weeks 16 and 24 is ≥ 2 points.*

During the study, participants who report deterioration requiring medical or surgical intervention may go to the study site for clinical evaluation. An unscheduled visit may be used for this purpose, and if necessary, the Investigator may consider one of the treatment alternatives described in Section 6.8.1.

Brief summary:

This is a Phase 4, open-label, single-arm, multicenter study to evaluate the efficacy and safety of dupilumab monotherapy in participants aged 18 or older with CRSwNP that is not adequately controlled with existing therapies.

Number of participants:

Approximately 25 participants will be enrolled.

Intervention groups and duration:

Study intervention(s)

- Dupilumab 300 mg q2w
- Dupilumab 300 mg q4w

For participants who have stable disease, the dosing interval can be changed from q2w to q4w at the discretion of the Investigator at Week 24. Participants who change from q2w to q4w will not be permitted to return to the q2w regimen during this study and will receive the q4w regimen until Week 48. Other participants will receive the q2w regimen up to Week 50. The participants will be followed up to Week 52.

Duration of study period (per participant):

- Screening Period (2 to 4 weeks): between Screening Visit (Visit 1) and the first dose of investigational medicinal product (IMP) (Visit 2)
- Intervention Period (up to 52 weeks±3 days)

Investigational medicinal product(s):

- Dupilumab 300 mg

Formulation:

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

Route of administration: subcutaneous (SC) injection

Dose regimen:

- One injection of 300 mg q2w up to Week 24 (all participants)
- One injection of 300 mg q4w after Week 24 (participants who have stable disease at Week 24)
- One injection of 300 mg q2w after Week 24 (participants who cannot achieve stable disease)

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

Statistical considerations:

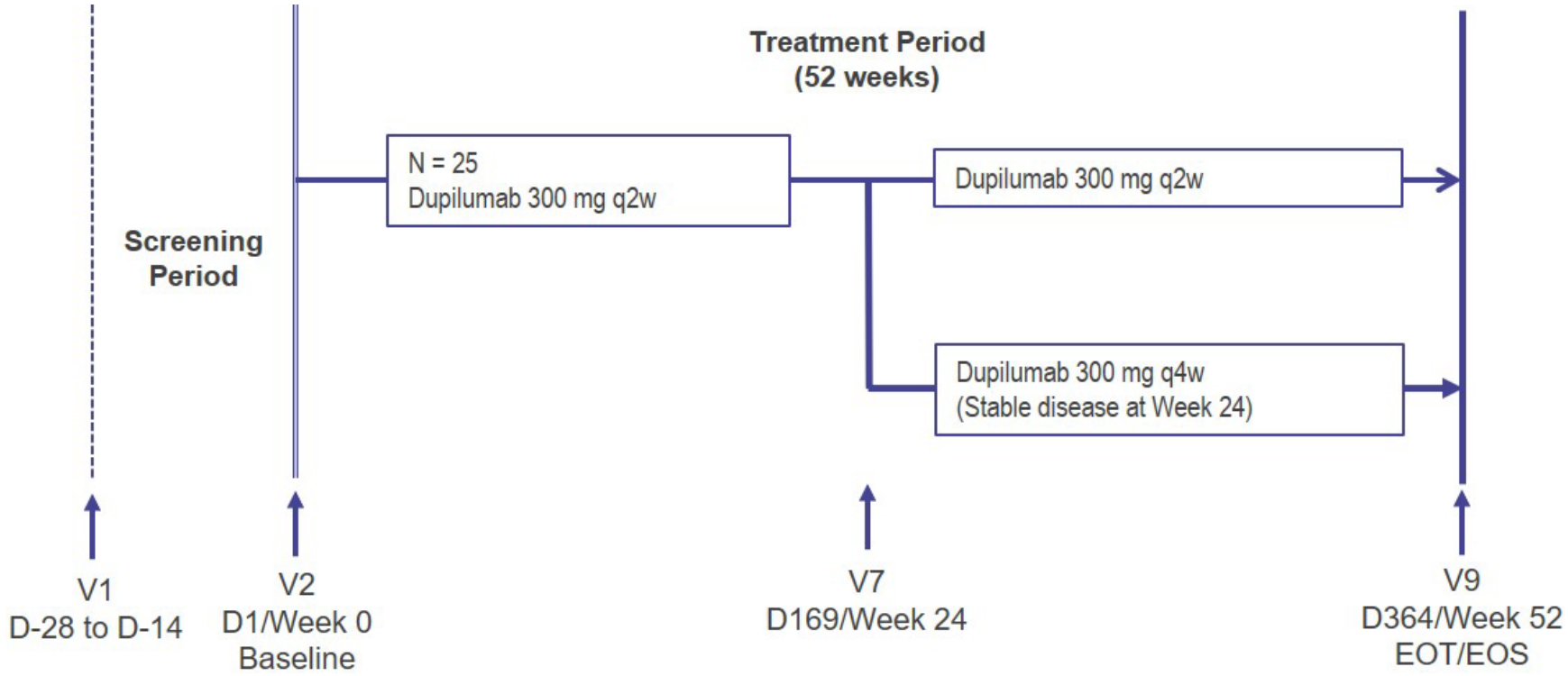
This postmarketing study is to assess whether dupilumab used without INCS will show similar efficacy to that of dupilumab used with INCS in EFC14280, using the point estimates of the proportion of responders (NPS improvement from baseline ≥1) at Week 24. Formal statistical tests for hypotheses (null/alternative) will not be performed.

- **Primary endpoint:**
  - The proportion of responders (NPS improvement from baseline ≥1) at Week 24.
- **Key secondary endpoints:**
  - Change from baseline to Week 24 in bilateral NPS
  - Change from baseline to Week 24 in nasal congestion/obstruction (NC) symptom severity score using the CRSwNP nasal symptom diary
  - Change from baseline to Week 24 in opacification of sinuses assessed by computerized tomography (CT) scan using the Lund Mackay (LMK) score

Data Monitoring/Other committee: No

1.2 SCHEMA

Figure 1 - Graphical study design



Abbreviations: D: day; EOS: end of study, EOT: end of treatment; q2w: every 2 weeks; q4w: every 4 weeks; V: visit.

1.3 SCHEDULE OF ACTIVITIES (SOA)

Procedure	D-28 to D-14	Intervention Period							
		W0 D1	W2 D15 (±3 days)	W4 D29 (±3 days)	W8 D57 (±3 days)	W16 D113 (±3 days)	W24 D169 (±3 days)	W40 D281 (±3 days)	W52 D364 (±3 days) EOT/EOS
Visit	**V1 (Screening)**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**
Informed consent	X								
Inclusion and exclusion criteria	X	X							
Patient demographics	X								
Physical examination	X						X		X
Medical/surgical/medication history[a]	X								
Record planned surgery for NP, SCS use, and other rescue medication use		←							→
Prior/concomitant medications	X	X	X	X	X	X	X	X	X
Call IVRS (IWRS)[b]	X	←							→
IMP administration[c]		←							→
		All participants: q2w up to W24 Participants with stable disease at W24: q4w from W24 up to W48 Participants who cannot achieve stable disease at W24: q2w from W24 up to W50							
Nasal endoscopy[d]	X	X		X	X	X	X	X	X

Procedure	D-28 to D-14	Intervention Period							
		W0 D1	W2 D15 (±3 days)	W4 D29 (±3 days)	W8 D57 (±3 days)	W16 D113 (±3 days)	W24 D169 (±3 days)	W40 D281 (±3 days)	W52 D364 (±3 days) EOT/EOS
Visit	**V1 (Screening)**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**
CT scan	X[e]						X		X
Nasal Symptom Diary[f] (includes nasal congestion, loss of smell, anterior and posterior rhinorrhea; TSS derived from these 4 items)		← daily diary →							
VAS for rhinosinusitis		X	X	X	X	X	X	X	X
Vital signs[g]	X	X			X	X	X	X	X
12-Lead ECG (local reading)	X								
AE review		←							→
SAE review		←							→
Laboratory assessments (including hematology, biochemistry, and urinalysis)[h]	X	X			X		X		X
Hepatitis B and C; HIV testing; TB testing[i]	X					X[j]	X[j]	X[j]	X[j]
Pregnancy test (WOCBP only)[k]	X	X		X	X	X (W12, 16)	X (W20, 24)	X (W28, 32, 36, 40)	X (W44, 48, 52)

Abbreviations: AE: adverse event; CT: computerized tomography; D: day; e-CRF: electronic case report form; ECG: electrocardiogram; EOS: end of study; EOT: end of treatment; HBcAb: hepatitis B core antibody; HBsAb: hepatitis B surface antibody; HBsAg: hepatitis B surface antigen; HCV Ab: hepatitis C virus antibody; HIV: human immunodeficiency virus; IgM: immunoglobulin M; IGAR: Interferon-gamma release assay; IMP: investigational medicinal product; IVRS/IWRS: interactive voice/web response system; MRI: magnetic resonance image; NE: nasal endoscopy; NERD: non-steroid anti-inflammatory drug exacerbated respiratory disease; NP: nasal polyposis; NPS: nasal polyp score; q2w: every 2 weeks; q4w: every 4 weeks; SAE: serious adverse event; SCS: systemic corticosteroids; TB: tuberculosis; TSS: total symptom score; V: visit; VAS: visual analogue scale; W: week; WOCBP: women of childbearing potential.

a Past medical history, including allergic comorbidities (asthma, aspirin sensitivity, allergic rhinitis, etc.). Surgeries for NP, including number, type and dates of sinonasal surgeries, and polypectomies, in the past will be recorded. Systemic corticosteroid use (number of courses, doses, route 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 e-CRF. NERD will be assessed through a specific questionnaire (Appendix 11 [Section 10.11]).

b Call IVRS/IWRS to register visit and obtain next IMP kit numbers assignment or report potential definitive IMP stop.

c Investigational medicinal product will be administered q2w (after Week 24, some participants can be administered q4w). Between visits, at site or home administration is allowed after the second dose.
Investigational medicinal product will be administered after the completion of all scheduled clinical assessments at the visit or at home. The planned last dose is at Week 48 or 50.
For participants who have stable disease at Week 24, the dosing interval can be changed from q2w to q4w at the discretion of the Investigator; the reason for the change in dosing regimen should be recorded in the e-CRF. Other participants will receive the q2w regimen until Week 50. Stable disease is defined as NPS improvement from baseline to both Weeks 16 and 24 of ≥2 points.

d Nasal endoscopy: endoscopy (including use of decongestants before the procedure) will be performed after all other efficacy assessments have been completed for each visit. Standard video sequences will be downloaded by the Investigator to the central reader's secured internet site. For eligibility, central reading of V1 will be used. At V2, the Investigator will review the V1 results from the central reader to confirm entry criteria and reconfirm eligibility based on a review of the inclusion/exclusion criteria and the V2 endoscopy local reading. To confirm eligibility at V2, only the V1 central reading will be made available to the site. In addition, at V2, the Investigator will perform the NE to confirm eligibility score and enter the result in the e-CRF. Thus, the participant will be considered eligible based on a V1 central reading followed by a V2 local reading NPS score of 5 or more and at least 2 on each side.

e Computerized tomography scan to be done during the Screening Period.

f Captured daily.

g Vital signs, including systolic and diastolic blood pressures (mmHg), pulse rate (beats per minute), respiratory rate (breaths per minute), and body temperature (forehead [temporal] temperature; degrees Celsius), and body weight (kg) will be measured at V1 and V2 and subsequent visits prespecified in the SoA. Height (cm) will be measured at V1 only. Vital signs will be measured prior to receiving IMP at the clinic visits in the sitting position, preferably using the same arm at each visit.

h Hematology: platelet count, red blood cell count, hemoglobin, hematocrit, and total white blood cell count with five-part differential count. Clinical chemistry: blood urea nitrogen, creatinine, glucose (indicate if fasting or nonfasting), uric acid, total cholesterol, total protein, albumin, total bilirubin (in case of values above the normal range, differentiation in conjugated and nonconjugated bilirubin), alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, lactate dehydrogenase, electrolytes (sodium, potassium, chloride), and creatine phosphokinase. Routine urinalysis: specific gravity, pH, glucose, protein, blood, ketones, urobilinogen, nitrite by dipstick, and microscopic examination (if blood or protein is abnormal).

i Hepatitis screen: HBsAg, HBsAb, HBcAb or HBcAb IgM and total; HCV Ab. HIV screen: anti-HIV-1 and HIV-2 antibodies. TB blood testing: IGRA.
In case of results showing HBsAg (negative) and HBcAb total or HBcAb IgM (positive), HBV DNA testing may be performed prior to enrollment to rule out a false positive if the Investigator believes the participant is a false positive or to clarify the serological status if the Investigator finds it unclear to interpret in the absence of known HBV infection.
In case of results showing HCV Ab (positive), HCV RNA testing may be performed to rule out a false positive, if the Investigator believes the participant is a false positive.
An IGRA will be performed for diagnosis of both latent and active TB only for participants without a history of active/latent TB.

j Participant who are HBcAb (positive) and HBV DNA (negative) at Visit 1 will require HBV DNA monitoring at Visits 6, 7, and 8 and the EOT/EOS Visit. If the HBV DNA result becomes positive during the study, the participant will be temporarily discontinued from IMP administration and should be referred to a hepatologist. Investigational medicinal product may be restarted under careful consideration of participant's risks and benefits based on hepatologist evaluation and current treatment guidelines and after consultation with the Medical Monitor.

k Serum pregnancy test at V1 and urine pregnancy tests q4w thereafter. A negative result must be obtained during the Screening Period before IMP administration. Urinary pregnancy test could be performed at home as part of visit with or without the assistance of a home care provider. In the case of a positive urine pregnancy test, the study intervention 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.

2 INTRODUCTION

Dupilumab is a fully human monoclonal antibody directed against the IL-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 the blockade of IL-4 and IL-13 intracellular signaling.

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

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

2.1 STUDY RATIONALE

This is a Phase 4, open-label, single-arm, multicenter, efficacy and safety study of dupilumab monotherapy in participants with CRSwNP whose disease is not adequately controlled with existing therapies (SCS and surgery).

Dupilumab has been approved for the treatment of CRSwNP that is not adequately controlled with existing therapies by the health authority in Japan on the condition that the efficacy and safety of dupilumab monotherapy will be assessed after approval; the efficacy and safety data in the global program were developed with INCS concomitantly administered with dupilumab; no efficacy and safety data for dupilumab used as monotherapy were collected in the pivotal Phase 3 studies. Intranasal corticosteroid is not approved for CRSwNP in Japan. Their use for CRSwNP is an off-label use in Japan. The objective of this Phase 4 study is to assess the efficacy and safety of dupilumab as monotherapy (without concomitant INCS) in participants with CRSwNP.

This study will primarily investigate the efficacy of dupilumab 300 mg q2w at Week 24, without concomitant administration of INCS in CRSwNP participants. The safety of 24-week treatment with dupilumab will also be investigated.

In addition, in line with the Japan label, the study is designed to assess the long-term (52 weeks) efficacy and safety of an initial treatment regimen of dupilumab 300 mg q2w for 24 weeks, followed by a less frequent dosing regimen (300 mg q4w) up to Week 48 for those participants who demonstrate stable disease* at Week 24. Other participants will receive the q2w regimen until Week 50.

**Stable disease definition: nasal polyp score (NPS) improvement from baseline to both Weeks 16 and 24 is ≥ 2 points.*

2.2 BACKGROUND

The study background is described in Section 2.1.

2.3 BENEFIT/RISK ASSESSMENT

Dupilumab has shown clinically relevant benefit in several type 2-driven immunological disorders such as AD, asthma, and CRSwNP. A satisfactory safety profile has been observed so far in completed and currently ongoing studies.

More detailed information about the known and expected benefits and risks and adverse events (AEs) considered as expected of dupilumab may be found in the Package Insert.

2.3.1 Risk assessment

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

Dupilumab has an extensive safety database. As of 28 September 2020, 10 773 participants had been enrolled into the development program for dupilumab and are included in the safety population. The estimated number of participants exposed to dupilumab in clinical studies was 9110 (356 in healthy volunteer studies, 4130 in AD studies, 3319 in asthma studies, 470 in CRSwNP studies, 226 in eosinophilic esophagitis studies, 176 in the grass/peanut allergy studies, 355 in the chronic obstructive pulmonary disease (COPD) studies, 36 in prurigo nodularis (PN) studies, and 42 in the chronic spontaneous urticaria (CSU) study).

Based on the sales figures and the World Health Organization defined daily dose of 21.4 mg/day, the cumulative postmarketing exposure to dupilumab could be estimated to be 249 341 patient years from 01 January 2017 through 30 September 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, dry eye, eye pruritus, eosinophilia, pyrexia, headache, arthralgia, anaphylaxis, serum sickness-like reaction, and serum sickness. These ADRs were generally mild or moderate, transient, and manageable. These ADRs were not observed consistently in all indications. More significant serious allergic reactions were very rare. Importantly, no increased overall risk of serious infection 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 or serum sickness-like reaction in the adult AD program and anaphylaxis related to dupilumab in the adult asthma clinical studies.

Participants 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, participants with pre-existing helminth infections should be treated for their helminth infection before initiating therapy with dupilumab.

Other potential risks based on the safety profile in particular indications such as eosinophilia in asthma participants treated with dupilumab monotherapy were reported in 2 asthma studies. However, eosinophil counts declined to near baseline levels during study treatment. It is anticipated that dupilumab used as monotherapy in Japanese participants with CRSwNP will have a favorable safety profile, as observed in the Phase 3 global clinical program for this disease (with concomitant INCS administration) and across other type 2-driven immunological disorders.

2.3.2 Benefit assessment

Dupilumab solution for injection is currently authorized:

- In over 40 countries worldwide, including the United States (US) for use in adults with inadequately controlled CRSwNP, the European Union (EU) as an add-on therapy with INCS for the treatment of adults with severe CRSwNP for whom therapy with SCS and/or surgery does not provide adequate disease control, and in Japan for use in adults with CRSwNP (only participants whose disease is not adequately controlled with existing therapies). Review of this indication is ongoing in several other countries worldwide.
- In over 60 countries worldwide including the US, EU (Centralised Procedure), and Japan for the treatment of adults with inadequately controlled moderate-to-severe AD. In the US and EU, it has also been authorized for use in adolescent patients (≥12 years of age) with inadequately controlled moderate-to-severe AD. Further, in the US and EU as well as some additional countries, dupilumab is approved for the treatment of children aged 6 to <12 years with AD.
- In over 40 countries worldwide for the asthma indication. In the US for use in adults and adolescents (≥12 years of age) with moderate-to-severe eosinophilic or oral steroid dependent asthma, in the EU for use in adults and adolescents with severe asthma with type-2 inflammation characterized by raised blood eosinophils and/or raised fractional exhaled nitric oxide, and in Japan for use in adults and adolescents with severe or refractory bronchial asthma. The review of dupilumab for this indication is ongoing in several other countries worldwide.

As part of the dupilumab CRSwNP clinical development program, two Phase 3 studies in participants with severe CRSwNP have demonstrated that dupilumab 300 mg q2w coadministered with INCS is significantly better than placebo for the reduction of polyp size, sinus opacification, and severity of symptoms and that it is generally well tolerated.

However, in previous Phase 3 studies, the placebo group to which only INCS was administered showed a trend of slight improvement in NC symptom severity but no trend of improvement in NPS and LMK score. The change in NPS and NC symptom severity during the screening period (4 weeks) in which only INCS was administered was small in both the group of participants who had used INCS prior to screening and the participants who started INCS during the screening

period. Since the efficacy of INCS in participants with CRSwNP in these Phase 3 studies was extremely limited, the efficacy observed was most likely attributed to dupilumab. Therefore, dupilumab administered as monotherapy, without INCS, is expected to have similar efficacy.

2.3.3 Overall benefit: risk conclusion

The target population of this study is patients with uncontrolled CRSwNP without concomitant INCS. 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 the study will provide an opportunity for these patients to be treated with a novel therapy that has proven efficacy in other disease states (eg, AD, asthma) and more importantly in two large Phase 3 studies in CRSwNP.

The Sponsor recognizes that the "Coronavirus Disease 2019" (COVID-19) pandemic is having an impact on the conduct of clinical studies. The Sponsor is monitoring the situation closely and may suspend study screening activities until the impact of the COVID-19 pandemic is deemed manageable and no longer interfering with the conduct of studies at individual sites and participants can safely participate in this study. To ensure the integrity of the studies and safety of the participants, there is a contingency plan in place to address any potential impact of COVID-19 that may arise during the conduct of the study (refer to Appendix 7 [Section 10.7]).

Based on the aforementioned potential benefits to patients participating in this study and the appropriate precautions and mitigations that have been instituted to manage any potential impact of COVID-19 on the conduct of the study and the safety of the participants, the Sponsor assesses that the overall benefit-risk balance is positive for the conduct of and patient participation in this study.

3 OBJECTIVES AND ENDPOINTS

Table 1 - Objectives and endpoints

Objectives	Endpoints
Primary	
• To assess the efficacy of 24-week treatment with dupilumab 300 mg every 2 weeks (q2w) to reduce nasal polyp score (NPS) in participants with chronic rhinosinusitis with nasal polyposis (CRSwNP) who do not use concomitant intranasal corticosteroid (INCS)	• Proportion of participants with NPS improvement from baseline ≥1 at Week 24
Secondary	
• To assess the efficacy of 24-week treatment with dupilumab 300 mg q2w on other efficacy endpoints in participants with CRSwNP who do not use concomitant INCS	Key secondary efficacy endpoints: • Change from baseline to Week 24 in bilateral NPS • Change from baseline to Week 24 in in nasal congestion/obstruction (NC) symptom severity score using the CRSwNP nasal symptom diary • Change from baseline to Week 24 in opacification of sinuses assessed by computerized tomography (CT) scan using the Lund Mackay (LMK) score Other secondary efficacy endpoints: • Change from baseline to Week 24: - Total symptom score (TSS), a composite score derived from the nasal symptom diary (includes nasal congestion, loss of sense of smell, anterior and posterior rhinorrhea) - Loss of smell symptom severity score using the nasal symptom diary - Visual analogue scale for rhinosinusitis
• To evaluate the safety of 24-week treatment with dupilumab in participants with CRSwNP	• Incidence of treatment-emergent adverse events (TEAEs), treatment-emergent serious adverse events (TESAEs), and TEAEs leading to treatment discontinuation
Tertiary/exploratory	
• To assess the efficacy of 52-week treatment with dupilumab under different dosing regimens to participants with CRSwNP who do not use concomitant INCS	• Proportion of participants with NPS improvement from baseline ≥1 at Week 52 • Change from baseline to Week 52 in bilateral NPS • Change from baseline to Week 52 in NC symptom severity score using the CRSwNP nasal symptom diary • Change from baseline to Week 52 in opacification of sinuses assessed by CT scan using the LMK score • Change from baseline to Week 52 in TSS
• To evaluate the safety of 52-week treatment with	• Incidence of TEAEs, TESAEs, and TEAEs leading to

Objectives	Endpoints
dupilumab in participants with CRSwNP	treatment discontinuation

Abbreviations: CRSwNP: chronic rhinosinusitis with nasal polyposis; CT: computerized tomography; INCS: intranasal corticosteroid; LMK: Lund Mackay; NC: nasal congestion/obstruction; NPS: nasal polyp score; q2w: every 2 weeks; TEAE: treatment-emergent adverse event; TESAE: treatment-emergent serious adverse events, TSS: total symptom score.

3.1 APPROPRIATENESS OF MEASUREMENTS

Refer to Section 4.2.2 for the rationale for the endpoints. The primary objective of this study is to assess the efficacy of dupilumab monotherapy in CRSwNP participants. The primary efficacy endpoint is the proportion of participants with improvement in NPS improvement (≥1 point) at Week 24. A 1-point improvement in NPS was defined as a clinically meaningful difference based on the results of the pivotal Phase 3 study (EFC14280). The secondary objectives of this study are to assess the efficacy and safety of dupilumab monotherapy in CRSwNP participants. The secondary efficacy endpoints, the change from baseline in the NPS, LMK score, and NC symptom severity scores to Week 24, were primary endpoints in EFC14280. These endpoints are to be evaluated to show the similar efficacy of dupilumab monotherapy compared to dupilumab with INCS coadministration.

4 STUDY DESIGN

4.1 OVERALL DESIGN

This is a Phase 4, open-label, single-arm, multicenter, efficacy and safety study of dupilumab monotherapy in participants with CRSwNP that is not adequately controlled with existing therapies.

This study will investigate the efficacy and safety of dupilumab 300 mg q2w at Week 24, without concomitant administration of INCS.

In addition, in line with Japan label, the study is designed to assess the long-term efficacy (52 weeks) and safety of an initial treatment regimen of dupilumab 300 mg q2w for 24 weeks without INCS, followed by a less frequent dosing regimen (300 mg q4w) up to Week 48 for those participants who demonstrate stable disease (NPS improvement from baseline to both Weeks 16 and 24 ≥2 points) at Week 24. Other participants will receive the q2w regimen until Week 50.

During the study, participants who report deterioration requiring medical or surgical intervention may go to the study site for clinical evaluation. An unscheduled visit may be used for this purpose, and if necessary, the Investigator may consider one of the treatment alternatives described in Section 6.8.1.

Study duration for each participant will be a total of up to 56 weeks.

The study includes 2 study periods:

- Screening Period (2 to 4 weeks): between the Screening Visit (Visit 1) and the first dose of IMP (Visit 2); to determine a participant's eligibility
- Intervention Period (up to 52 weeks ±3 days): to treat participants with dupilumab starting at baseline (Visit 2)

Patients who fulfill the inclusion criteria and do not meet any of the exclusion criteria will be enrolled to receive the IMP (Section 5).

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

4.2.1 Rationale for intervention with dupilumab

Dupilumab blockade of IL-4 and IL-13 signaling has demonstrated a favorable efficacy and acceptable safety profile for the treatment of a variety of atopic disease states, including AD (1), asthma (2), and CRSwNP (3), where type-2 inflammation is a key driver of the underlying disease process. Notably, in the dupilumab CRSwNP clinical development program, two Phase 3 studies in participants with severe CRSwNP have demonstrated that dupilumab 300 mg q2w, when used

concomitantly with INCS, is significantly better than placebo for the reduction of polyp size, sinus opacification, and severity of symptoms and is generally well tolerated.

The primary objective of this study is to assess the efficacy of dupilumab without INCS administered to CRSwNP participants whose disease is not adequately controlled with existing therapies. The safety of dupilumab monotherapy will also be investigated.

4.2.2 Rationale for study design, key study assessments/endpoints

Efficacy will be determined using the primary endpoint of the proportion of participants with improvement in NPS (≥1 point) at Week 24. A 1-point improvement in NPS is defined as a clinically meaningful difference based on the results of the Phase 3 study (EFC14280). Additionally, as key secondary efficacy endpoints, the change from baseline in the NPS, LMK, and NC symptom severity scores up to Week 24 will be measured. These secondary endpoints were primary endpoints in EFC14280. These endpoints should be evaluated to show the similar efficacy of dupilumab alone compared to dupilumab with INCS coadministration.

This study will collect data on the primary and secondary efficacy endpoints at Week 52 as well for both the q2w and q4w (after Week 24) dosing regimens.

4.3 JUSTIFICATION FOR DOSE

Dupilumab will be administered in accordance with the approved dose in Japan.

The recommended dose of dupilumab for adult CRSwNP patients is 300 mg given q2w; however, after the disease condition is stable, 300 mg given q4w could be used.

4.4 END OF STUDY DEFINITION

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

A participant is considered to have completed the study if he/she has completed all phases of the study, including the last visit or the last scheduled procedure shown in the Schedule of Activities (SoA ; Section 1.3).

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 who is at least 18 years of age at the time of signing the informed consent

Type of participant and disease characteristics

I 02. Participant who has bilateral sinonasal polyposis despite prior treatment with SCS anytime within the past 2 years; and/or has a medical contraindication/intolerance to SCS; and/or has had prior surgery for nasal polyposis at Screening Visit (Visit 1) and has:

- An endoscopic bilateral NPS at Visit 1 of at least 5 out of a maximum score of 8 (with a minimum score of 2 in each nasal cavity)
- Ongoing symptoms of:

  Nasal congestion/blockade/obstruction for at least 8 weeks before Visit 1 that is moderate or severe (NC symptom severity score 2 or 3) at Visit 1 and a weekly average severity of greater than 1 (based on the average of the assessments 1 week before Visit 1) at the time of enrollment (Visit 2)

  AND

  Loss of smell or rhinorrhea (anterior/posterior) for at least 8 weeks before Visit 1

Weight

I 03. Participant whose body weight is >30 kg at the time of screening

Sex, contraceptive/barrier method, and pregnancy testing requirements

I 04. Participant who is male or female

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

- Female participants
  - 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 (at a minimum until 12 weeks after the last dose of IMP).

- A WOCBP must have a negative highly sensitive pregnancy test (urine or serum as required by local regulations; refer to Section 8.2.5) at both Visit 1 and Visit 2 before the first dose of IMP.
- If a urine test on Day 1 cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. 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 05. Participant who is 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. If the participant is less than 20 years of age, a specific ICF must also be signed by the participant's parent/legally authorized representative (LAR).

5.2 EXCLUSION CRITERIA

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

Medical conditions

E 01. Participant with conditions/concomitant diseases making them nonevaluable at Visit 1 or for the primary efficacy endpoint such as:

- Antrochoanal polyps
- Nasal septal deviation that would occlude at least 1 nostril
- Acute sinusitis, nasal infection, or upper respiratory infection within 2 weeks prior to Visit 1 (participant can be rescreened after resolution of symptoms)
- Ongoing rhinitis medicamentosa
- Eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome), granulomatosis with polyangiitis (Wegener’s granulomatosis), Young’s syndrome, Kartagener’s syndrome or other dyskinetic ciliary syndromes, or concomitant cystic fibrosis

- Radiologic suspicion or confirmed invasive or expansive fungal rhinosinusitis
- Clinically significant/active underlying hepatobiliary disease
- Alanine aminotransferase (ALT) >3 × upper limit of normal (ULN)
- Creatine phosphokinase (CPK) >10 × ULN
- Platelets <100 000 cells/mm^3
- Neutrophils <1500 cells/mm^3
- Serum creatinine >1.7 × ULN

E 02. Participant with nasal cavity malignant tumor and benign tumors (eg, papilloma, blood boil)

E 03. Participants diagnosed with, suspected of, or at high risk of endoparasitic infection, and/or use of antiparasitic drug within 2 weeks before Visit 1 or during the Screening Period

E 04. Participant who has history of human immunodeficiency virus (HIV) infection or positive HIV screen (anti-HIV-1 and HIV-2 antibodies) serology at Visit 1

E 05. Participant who has severe concomitant illness(es) that, in the Investigator's judgment, would adversely affect the participant'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), and other severe endocrinological, gastrointestinal, metabolic, pulmonary, or lymphatic diseases. The specific justification for participants excluded under this criterion will be noted in study documents (chart notes, electronic case report forms [e-CRFs], etc).

E 06. Participant who has known or suspected immunodeficiency, including history of invasive opportunistic infections (eg, tuberculosis [TB], histoplasmosis, listeriosis, coccidioidomycosis, pneumocystosis, and aspergillosis), despite infection resolution, or otherwise recurrent infections of abnormal frequency or prolonged duration suggesting an immune compromised status, as judged by the Investigator

E 07. Participant who has current diagnosis of active or latent TB, nontuberculous mycobacterial infection, or a history of incompletely treated TB unless it is well documented by a specialist that the participant has been adequately treated and can now start treatment with a biologic agent, in the medical judgment of the Investigator and/or infectious disease specialist

E 08. Participant who has active chronic or acute infection requiring treatment with systemic antibiotics, antivirals, or antifungals within 2 weeks before Visit 1 or during Screening Period

E 09. Participant who has history of malignancy without complete remission (ie, participant who required treatment 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 10. Participant who has known or suspected alcohol and/or drug abuse

E 11. Participant who has history of systemic hypersensitivity or anaphylaxis to dupilumab or any of its excipients

E 12. Participant who has a planned major surgical procedure during the participant's participation in this study

E 13. Participant who has undergone any and/or sinus intranasal surgery (including polypectomy) within 6 months before Visit 1

E 14. Participant who has had a sinonasal surgery changing the lateral wall structure of the nose making impossible the evaluation of NPS

E 15. Participant who has any other medical or psychological condition including relevant laboratory or cardiovascular 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 study, may make participant'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, e-CRF, etc.).

Prior/concomitant therapy

E 16. Participants who have participated in a prior dupilumab clinical study or have been treated with commercially available dupilumab

E 17. Participants 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) within 4 weeks before Visit 1 or 5 half-lives, whichever is longer
- Any investigational monoclonal antibody within 5 half-lives or within 6 months before Visit 1 if the half-life is unknown
- Anti-IgE therapy (omalizumab) within 4 months before Visit 1

E 18. Participant who received treatment with a live (attenuated) vaccine within 4 weeks before 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 treatment (EOT) or end of study (EOS) or moved to before the start of the study without compromising the health of the participant.

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

Participants who have their vaccination moved to before the start of the study can be enrolled into the study only after a gap of 4 weeks following administration of the vaccine.

E 19. Participant who has received leukotriene antagonists/modifiers within 4 weeks before Visit 1, unless participant is on a continuous treatment for at least 30 days

E 20. Participant who has initiated allergen immunotherapy within 3 months before Visit 1 or has planned to begin therapy or change its dose during the screening or intervention period

E 21. Participant who receives concomitant treatment prohibited in the study (see Section 6.8)

E 22. Participant who has received either intravenous immunoglobulin therapy and/or plasmapheresis within 30 days before Visit 1

Diagnostic assessments

E 23. Participants with any of the following results at Visit 1:

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

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

c) Positive hepatitis C virus (HCV) antibody with positive HCV RNA.

Noncompliance with diary completion

E 24. Participants who do not demonstrate the following for acceptable compliance: completing the diary for any 4 mornings in the 7 days immediately preceding the Baseline Visit (Visit 2)

Other exclusions

E 25. Individuals accommodated in an institution because of regulatory or legal order; prisoners or participants who are legally institutionalized

E 26. 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 with study procedures

E 27. Participants who are employees of the clinical study site, other individuals directly involved in the conduct of the study, or immediate family members of such individuals (in

conjunction with Section 1.61 of International Council for Harmonisation - Good Clinical Practice [ICH-GCP] Ordinance E6)

E 28. Any specific situation during study impleentation/course that may lead to ethical concerns

E 29. Participant who has 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 in this study.

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently enrolled. 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 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).

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Rescreened participants should be assigned a new participant number for every screening/rescreening event.

There is no requirement for a waiting period between the screen failure date and the rescreening date. The interactive voice/web response system (IVRS/IWRS) report will flag rescreened participants. The Investigator will obtain information about subsequent scheduled visits via the IVRS/IWRS, which will be available 24 hours a day.

Participants who fail screening during the Screening Period may be rescreened for study eligibility only once for the following criteria:

- They do not meet the inclusion criterion of having a weekly average NC symptom severity score >1 at Visit 2.
- They have an acute illness such as acute sinusitis, nasal infection, or upper respiratory infection (E 01). These participants can be rescreened only after complete resolution of symptoms.
- They have taken one of the prohibited treatments listed in Section 6.8 during the Screening Period.

Participants who are rescreened must sign a new consent form, and all of the Visit 1 procedures must be repeated (refer to Section 10.1.3 for further instructions related to rescreening) unless a prior assessment is performed within the time frame permitted prior to study entry or the Visit 1

baseline CT scan of sinuses is performed. Participants with positive test results for HIV or hepatitis will not be allowed to rescreen.

All participants must fulfill all eligibility criteria before enrollment into the study; no waiver will be allowed for enrollment.

If certain dynamic laboratory tests do not meet the eligibility criteria, these laboratory assessments may be repeated, at the discretion of the Investigator, if the results are judged to be likely to return to acceptable range for study inclusion within the Screening Visit window.

For participants who do not fulfill other exclusion criteria, rescreening should be discussed with the Sponsor. In all cases, a given participant can only be rescreened once.

5.5 CRITERIA FOR TEMPORARILY DELAYING SCREENING

During a regional or national emergency declared by a governmental agency, if the site is unable to adequately follow protocol-mandated procedures, contingency measures are proposed in Appendix 7: Contingency measures for a regional or national emergency that is declared by a governmental agency (Section 10.7) should be considered for screening.

6 STUDY INTERVENTION(S) 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

Approximately 25 participants will be enrolled and will be assigned to study intervention as described below:

- Dupilumab 300 mg q2w up to Week 24 (all participants)
- Dupilumab 300 mg q4w after Week 24 (participants who have stable disease at Week 24)
- One injection of 300 mg q2w after Week 24 (participants who cannot achieve stable disease)

For participants who have stable disease (NPS improvement from baseline to both Weeks 16 and 24 ≥2 points), the dosing interval can be changed from q2w to q4w at the discretion of the Investigator at Week 24. Participants who proceed from the q2w regimen to the q4w regimen will receive the q4w regimen up to Week 48 and will not be permitted to return to the q2w regimen during this study. Other participants will receive q2w regimen up to Week 50. All participants will be followed up to Week 52.

At Visit 2, the Investigator (or designee) will prepare and perform the first IMP injection in front of the participant (or parent/LAR/caregiver). The IMP will be administered following clinic procedures. Participants will be monitored at the study site for at least 30 minutes after the injection for signs of hypersensitivity reaction.

After the second dose of IMP, home administration of IMP q2w (by participant, caregiver, or health care professional) is possible if the participant (or caregiver) has been appropriately trained at the study site. Training must be documented when it is completed successfully, and training injections must be recorded in the participant's study file. In case of emergency (eg, natural disaster, pandemic), different training methods (eg, training remotely with instruction provided by phone) can be performed (and will be documented in the participant's study file). When IMP is administered at home, the participants must be advised by the site staff to self-monitor for potential signs and symptoms that may suggest a hypersensitivity reaction for at least 30 minutes after administration.

If the participant (or caregiver) is unable or unwilling to administer IMP, arrangements must be made for qualified site personnel and/or healthcare professionals to administer IMP for the doses that are not scheduled to be given at the study site. If the participant or caregiver(s) do not become comfortable with injecting the IMP at home or if the Investigator determines that participant (or caregiver) administering an injection at home is not appropriate, injections can be performed at the site by way of unscheduled visits.

Subcutaneous injection sites should be alternated among the 4 quadrants of the abdomen (avoiding the navel and waist areas), the upper thighs. and the upper arms, such that the same site is not injected twice consecutively. Injection in the upper arms can be done only by a trained person (caregiver trained by Investigator or designee) or health care professional but not the participants themselves.

Post-trial access to IMP will not be provided.

Table 2 - Overview of study interventions administered

Arm name	Dupilumab
Intervention name	Dupilumab 300 mg
Type	Biological
Dose formulation	A 150 mg/mL dupilumab solution in a prefilled syringe to deliver 300 mg in 2 mL
Unit dose strength(s)	300 mg
Dosage level(s)	300 mg q2w or q4w ±3 days
Route of administration	Subcutaneous
Use	Experimental
IMP or NIMP	IMP
Packaging and labeling	One glass prefilled syringe packed in a participant kit box. Both the glass prefilled syringe and the box will be labeled as required per country requirement.
Former names	Dupixent

Abbreviation: IMP: investigational medicinal product; NIMP: noninvestigational medicinal product; q2w: every 2 weeks; q4w: every 4 weeks

The IMP may be supplied at the site or from the Investigator, site, or Sponsor to the participant via a Sponsor-approved courier company where allowed by local regulations and agreed upon by the participant.

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

For a regional or national emergency declared by a governmental agency that results in travel restrictions, confinement, or restricted site access, contingency measures are included in Appendix 7: Contingency measures for a regional or national emergency that is declared by a governmental agency (Section 10.7).

6.1.1 Packaging and labeling

Dupilumab 300 mg will be supplied at each visit as glass prefilled syringes packed in one participant kit box. The number of kits to be supplied to each participant at each visit is based on the Investigator's instruction.

The content of the labeling is in accordance with the local regulatory specifications and requirements.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 Storage and handling

1. The Investigator or designee must confirm that appropriate temperature conditions have been maintained during transit for all study intervention received and that 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 it. 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).

It is the responsibility of the Investigators to inform the participants regarding the mandatory storage requirements for the IMP. No temperature monitoring will be performed at the participants' homes.

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 8.3.8).

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 [DTP] 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 study protocol, or dispose of IMP in any other manner.

6.2.3 Treatment accountability and compliance

The Investigator or designee will keep accurate records of the quantities of the IMP dispensed and returned, used and unused by each participant.

- Proper recording of treatment kit numbers as required on the appropriate e-CRF page for accounting purposes.
- All medication treatment kits (whether empty or unused) are returned by the participant at each visit when a treatment dispensing is planned and at the EOT/EOS Visit.
- The completed patient diary (returned to the site at each visit), returned IMP treatment kit boxes, used and unused, along with any unused prefilled syringes will be used for drug accountability purposes. Participants will also return used prefilled syringes to the site in a sharps container.
- The Investigator (or designee) will track treatment accountability/compliance by diary and by counting the number of used and unused treatment kits and syringes and will complete the appropriate page of the patient treatment log.
- The monitor in charge of the study will then check the data entered on the IMP administration page by comparing them with the IMPs that have been retrieved and the patient treatment log forms. Reconciliation will occur with the paper diary as appropriate depending on the study visit/period.

6.2.4 Return and/or destruction of treatments

Whenever possible, all partially used, used, or unused IMP provided by the Sponsor will be destroyed on-site according to the standard practices of the site. A detailed treatment log of the destroyed IMP supplied by the Sponsor will be established with the Investigator (or the pharmacist) and countersigned by the Investigator and the monitoring team. The Investigator will not destroy any IMP supplied by the Sponsor unless the Sponsor provides written authorization. When destruction at the site cannot be performed, all IMP supplied by the Sponsor will be retrieved by the Sponsor. A detailed treatment log of the returned IMP supplied by the Sponsor will be established with the Investigator (or the pharmacist) and countersigned by the Investigator and the monitoring team.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

This is an open-label, single-arm study; randomization and blinding will not be implemented.

6.4 STUDY INTERVENTION COMPLIANCE

- Methods used by the Investigator or his/her delegate to ensure that the IMP was administered

- IMP accountability:
  - Intervention units are returned by the participant at each visit. In case of DTP process, the intervention units can be returned by the carrier (if defined in the contract).
  - The Investigator counts the number of prefilled syringes remaining in the returned packs and fills in the intervention log form.
  - The Investigator records the dosing information on the appropriate page(s) of the e-CRF.
  - The monitor in charge of the study then checks the e-CRF data by comparing them with the IMP that he/she has retrieved and the intervention log forms.
  - Proper placement of tear-off label for accounting purposes.

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. 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 patient diary (returned to the site at each visit) and by returned IMP treatment kit boxes, both used and unused, along with any unused prefilled syringes during the site visits and documented in the source documents and relevant form. Deviation(s) from the prescribed dosage regimen should be recorded (refer to Section 6.2.3 for details).

A record of the quantity of IMP dispensed to and administered 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.

6.5 DOSE MODIFICATION

For participants who have stable disease (NPS improvement from baseline to both Weeks 16 and 24 is ≥2 points), the dosing interval can be changed from q2w to q4w at the discretion of the Investigator at Week 24. Participants who proceed to the dosing interval from q2w to q4w will not be permitted to return to the q2w regimen during this study. The maximum dose will not exceed dupilumab 300 mg q2w.

However, any dose reduction is not allowed other than above.

6.5.1 Retreatment criteria

Not applicable.

6.6 CONTINUED ACCESS TO INTERVENTION AFTER THE END OF THE STUDY

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

6.7 TREATMENT OF OVERDOSE

For this study, any dose of dupilumab greater than twice the intended dose during an interval of less than 11 days will be considered an overdose.

No antidote is available for dupilumab. The Sponsor does not recommend specific treatment for an overdose. Symptomatic overdoses (serious or nonserious) are required to be reported as AE of special interests (AESI) (refer to Section 8.3.6).

In the event of an overdose, the Investigator should:

- Contact the Sponsor immediately.
- Evaluate the participant to determine, in consultation with the Sponsor, whether study intervention should be interrupted.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities until dupilumab can no longer be detected systemically.
- Document appropriately in the e-CRF.

6.8 CONCOMITANT THERAPY

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

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

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

Prohibited medications

The following concomitant treatments are not permitted during the Screening Period and throughout the study unless otherwise specified:

- Intranasal corticosteroids within 5 half-lives or at least 30 days, whichever is longer, before Visit 1, during the Screening Period, and up to Week 52 (however, INCS can be used for other coexisting diseases [eg, allergic rhinitis] after Week 24, as needed, to keep more participants for the assessment of exploratory endpoints with 52-week treatment)

- Any systemic immunosuppressive treatment, including but not limited to methotrexate, cyclosporine, mycophenolate, tacrolimus, gold, penicillamine, sulfasalazine, hydroxychloroquine, azathioprine, and cyclophosphamide, within 4 weeks before Visit 1 or 5 half-lives, whichever is longer, during the Screening Period, and up to Week 52
- Anti-IgE therapy (omalizumab) within 4 months before Visit 1, during the Screening Period, and up to Week 52 and other biologics for immuno-inflammatory conditions within 4 weeks before Visit 1 or 5 half-lives, whichever is longer, and up to Week 52
- Allergen immunotherapy during the Screening Period and up to Week 52 (except if initiated more than 3 months prior to Visit 1 and dose stable for 1 month prior to Visit 1)
- Long-term courses (>2 weeks) of SCS are prohibited from Visit 1 onward
- Short-term courses (≤2 weeks) of SCS are prohibited only during the Screening Period, and they are allowed as rescue medication after Visit 2
- Live, attenuated vaccines within 4 weeks before Visit 1, during the Screening Period, and up to Week 52 (Appendix 8 [Section 10.8])
- Systemic antibiotic for >2 weeks during the study
- Use of intranasal decongestants, except for preparation of nasal endoscopy (NE)

Participants who receive any of the prohibited treatments or undergo surgery during the Screening Period will not start the intervention period. They may, however, be rescreened following the procedures described in the SoA (Section 1.3).

Participants who use INCS between Visit 2 and Week 24 for whatever reason will discontinue the IMP administration.

Permitted concomitant medication

The following treatments are allowed throughout the study unless otherwise specified:

- Intranasal corticosteroids to treat other coexisting diseases (such as allergic rhinitis) are allowed after Week 24 as needed.
- Nasal normal saline.
- Single topical decongestant administration such as oxymetazoline hydrochloride (to reduce swelling and widen the path for the endoscope) and topical anesthetics such as lidocaine are allowed before endoscopy.
- Short-acting β2-adrenergic receptor agonists, long-acting β2-adrenergic receptor agonists, and long-acting muscarinic acetylcholine receptor antagonists.
- 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 before Visit 1.
- Allergen immunotherapy in place for ≥3 months before Visit 1 is permitted.
- Paracetamol/Acetaminophen, at doses of ≤2 g/day, is permitted for use any time during the study.

Other concomitant medication may be considered on a case-by-case basis by the Investigator in consultation with the Medical Monitor if required.

Rescue medication including antibiotics, short courses of SCS for treatment of CRSwNP as described in Section 6.8.1, or short courses of SCS to treat other serious coexisting diseases (such as asthma exacerbation) or for AEs is allowed.

6.8.1 Rescue medicine and procedures

During the study intervention period, based on clinical evaluation, in case of worsening of signs and/or symptoms requiring medical intervention, the following rescue medications/procedures may be employed as per Investigator's judgment:

1. Systemic (eg, oral) corticosteroids up to 2 weeks
2. Antibiotics for the treatment of acute sinusitis less than 2 weeks after Visit 2
3. Sinonasal surgery

Participants receiving rescue treatment other than surgery during the study should continue on IMP unless the Investigator decides to withdraw the study intervention. Before starting treatment with SCS, participants should come to the study site for the clinical assessments including endoscopy.

For participants who undergo or plan to have surgery for NP, the 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 intervention and assessed as soon as possible using the procedures normally planned for the EOT/EOS Visit as described in the SoA (Section 1.3).

If the surgery is to be performed during the intervention period, an AE or SAE page will be completed. If surgery is scheduled after the planned EOS, the EOT/EOS Visit will not be delayed. The surgery will be followed up by the Investigator or the participant's physician with general medical practice.

In any case, participants who prematurely discontinue the treatment will be encouraged to return to the study site for the efficacy and safety assessments planned at the EOT/EOS Visit (refer to SoA [Section 1.3]).

The date and time of rescue medication administration as well as the name and dosage regimen of the rescue medication must be recorded. For participants who undergo sinonasal surgery for NP, the reason (worsening signs and/or symptoms during the study), the expected and real surgery

dates, and the type and outcome of surgery will be recorded. For participants who plan to have sinonasal surgery for NP, the reason (worsening signs and/or symptoms during the study), the expected and real surgery dates, and the type of surgery will also be recorded in the e-CRF.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

The IMP should be continued whenever possible. In case the IMP is stopped, it should be determined whether the stop can be made temporarily; permanent IMP discontinuation should be a last resort. Any IMP discontinuation should be fully documented in the e-CRF. In any case, the participant should remain in the study as long as possible.

7.1.1 Permanent discontinuation

In rare instances, it may be necessary for a participant to permanently discontinue study intervention. If study intervention is permanently discontinued, the participant will remain in the study to be evaluated for the assessments planned for the EOT/EOS Visit, with the exception of the CT scan. 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.

Participants must be withdrawn from the study (ie, from any further IMP or study procedure) for the following reasons:

- At their own request or at the request of their LAR (an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective participant to the participant's participation in the procedures involved in the research)
- If, in the Investigator's opinion, continuation in the study would be detrimental to the participant's well-being
- In case of surgery for NP
- At the specific request of the Sponsor
- In the event of a critical protocol deviation, at the request of the Investigator or the Sponsor
- In the event of an anaphylactic systemic allergic reaction that is related to IMP and that requires treatment
- In the event that the participant is diagnosed with a malignancy during the study, excluding carcinoma in situ of the cervix or squamous or basal cell
- Pregnancy
- Any opportunistic infection, such as TB or other infections whose nature or course may suggest an immunocompromised status (refer to Appendix 9 [Section 10.9])
- Met liver chemistry stopping criteria (Section 7.1.2)

Handling of participants after permanent intervention discontinuation

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.

If possible, and after the permanent discontinuation of intervention, the participants will be assessed as soon as possible using the procedures normally planned for the EOT/EOS Visit (refer to SoA [Section 1.3]).

All cases of permanent intervention discontinuation must be recorded by the Investigator on the appropriate pages of the e-CRF when considered as confirmed.

7.1.2 Liver chemistry stopping criteria

Details of the liver chemistry stopping criteria are provided in Appendix 5 (Section 10.5).

Discontinuation of study intervention for abnormal liver tests is required by the Investigator when a participant meets one of the conditions outlined in the algorithm (ie, ALT >3 × ULN) or in the presence of abnormal liver chemistries not meeting protocol-specified stopping rules if the Investigator believes that it is in best interest of the participant.

7.1.3 Temporary discontinuation

Temporary intervention discontinuation may be considered by the Investigator because of suspected AEs or disruption of the clinical study due to a regional or national emergency declared by a governmental agency (Appendix 7: Contingency measures for a regional or national emergency that is declared by a governmental agency [Section 10.7]). For all temporary intervention discontinuations, the duration should be recorded by the Investigator on the appropriate pages of the e-CRF.

In addition, any of the following conditions will be a cause for temporary treatment discontinuation:

- Infections or infestations that do not respond to medical treatment should have IMP discontinued until the infection is resolved
- Any laboratory abnormality that meets the temporary treatment discontinuation criteria as per Appendix 5 (Section 10.5)

For a participant who requires HBV DNA monitoring, if the HBV DNA result becomes positive during the study, the participant will temporarily discontinue IMP and should be referred to a hepatologist. Investigational medicinal product may be restarted under careful consideration of the participant's risks and benefits based on hepatologist evaluation and current treatment guidelines and after consultation with Medical Monitor (refer to footnote j in the SoA [Section 1.3]).

Temporary intervention discontinuation decided by the Investigator corresponds to more than 1 dose not being administered to the participant. If the IMP is interrupted for more than 2 doses, then the participant should permanently discontinue the study intervention.

7.1.4 Rechallenge

Reinitiation of intervention with the IMP will be done under close and appropriate clinical and/or laboratory monitoring once the Investigator has considered, according to his/her best medical judgment, that the IMP was unlikely to have been responsible for the AE in question and that the selection criteria for the study are still met (refer to Section 5).

For a regional or national emergency declared by a governmental agency, contingency measures are included in Appendix 7: Contingency measures for a regional or national emergency that is declared by a governmental agency (Section 10.7).

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

- A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, or compliance reasons. This is expected to be uncommon.
- At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted. See the SoA (Section 1.3) for data to be collected at the time of EOT/EOS and for any further evaluations that need to be completed.
- 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.

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.

All study withdrawals should be recorded by the Investigator in the appropriate screens of the e-CRF 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. Withdrawal of consent for 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 retreated 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/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 study site for a required study visit:

- The site must attempt to contact the participant, reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule, and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant (where possible, 3 documented attempts via 2 different methods [phone, text, e-mail, certified letter, etc] should be done). 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.
- Site personnel or an independent third party will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants enrolled, including those who did not get study intervention. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented, and the participant will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

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, urine tests) and obtained before signing of the ICF may be utilized for screening or baseline purposes, provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

For a regional or national emergency declared by a governmental agency, contingency measures are included in Appendix 7: Contingency measures for a regional or national emergency that is declared by a governmental agency (Section 10.7).

8.1 EFFICACY ASSESSMENTS

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

8.1.1 Nasal endoscopy: nasal polyp score

The NPS (4, 5, 6) is assessed by central video recordings of NE. The NPS is the sum of the right and left nostril scores, as evaluated by means of NE. Nasal polyp is graded based on polyp size described in Table 3.

Table 3 - Endoscopic nasal polyp score

Polyp Score	Polyp Size
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 of the inferior nasal cavity

Nasal endoscopy should be performed at the end of the scheduled visits before the administration of IMP and should be preceded by local administration of anesthetic drugs in combination with a decongestant.

Standard video sequences will be downloaded or sent to a centralized reader. Centralized imaging data assessments and scoring by independent physician reviewer(s) for the imaging data will be performed for all endoscopies. To confirm eligibility at Visit 2, only the Visit 1 central reading will be made available to the site. In addition, at Visit 2, the Investigator will perform the NE to confirm the eligibility score and enter the result in the e-CRF. Thus, the participant will be considered eligible based on a Visit 1 central reading followed by a Visit 2 local reading NPS score of 5 or more and at least 2 on each side.

For the analysis of the primary endpoint, the central reading of Visit 2 will be used for comparison with the Week 24 reading. The sites will remove participant-identifying information from the imaging data header prior to sending the imaging data to the central reader.

Nasal endoscopy will be conducted at the Screening Visit (Visit 1), Visit 2, and Visits 4 to 9.

Further details on NE will be available in a separate operational manual provided to the sites.

8.1.2 Nasal congestion/obstruction symptom severity score

Nasal congestion/obstruction will be assessed by the participant using a diary on a daily basis from Visit 1 and throughout the study, on a 0 to 3 categorical scale (where 0 = no symptoms, 1 = mild symptoms, 2 = moderate symptoms and 3 = severe symptoms) (7):

Nasal congestion/obstruction will be scored as a reflective score (evaluation of symptom severity over the past 24 hours) by the participants (Table 4).

Table 4 - Nasal congestion/obstruction symptom severity score

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 diary will be dispensed at Visit 1, and the diary will be checked by the study site at each visit.

A NC symptom severity score ≥2 at Visit 1 and a weekly average severity greater than 1 at the time of enrollment (Visit 2) are required and will be provided to the site to determine participant eligibility. The participant must have 4 or more measurements collected within 7 days prior to enrollment; the baseline will be the average of these measurements (E 24).

For the baseline to EOT/EOS analysis, the average of the symptom severity scores from the most recent 4 weeks before a scheduled visit will be used.

8.1.3 Computerized tomography scan: Lund Mackay score

The LMK system is based on localization with points given for degree of opacification: 0 = normal, 1 = partial opacification, 2 = total opacification. These points are then applied to the maxillary, anterior ethmoid, posterior ethmoid, sphenoid, and frontal sinus on each side. The osteomeatal complex (OC) is graded as 0 = not occluded or 2 = occluded. Adding the scores of these 6 parameters will derive a maximum score of 12 per side (left and right). The total score of the 2 sides will be used for analysis. This scoring system has been validated in several studies (8, 9, 10).

For participants in whom the OC is missing (because of a previous surgery), the reader should consider the location of the previous OC and provide a score (as if the OC were there).

Computerized tomography scan should be performed anytime during the Screening Period before the first administration of IMP and at Visits 7 and 9 (Weeks 24 and 52). Whenever possible, a cone beam CT scan should be utilized.

Details for CT will be available in a separate operational manual provided to the sites.

8.1.4 Nasal symptom diary: Disease specific daily symptom assessment and total symptom score

On a daily basis from Visit 1 and throughout the study, the participant will use a diary to:

- Respond to the morning individual rhinosinusitis symptom questions using a 0 to 3 categorical scale (where 0 = no symptoms, 1 = mild symptoms, 2 = moderate symptoms, and 3 = severe symptoms) (11):
  - Congestion and/or obstruction
  - Loss of sense of smell
  - Anterior rhinorrhea (runny nose)
  - Posterior rhinorrhea (postnasal drip)

The total symptom score (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, and rhinorrhea (average of anterior/posterior nasal discharge).

8.1.5 Visual analogue scale for rhinosinusitis

The visual analogue scale (VAS) for rhinosinusitis is used to evaluate the total severity (7). Rhinosinusitis disease can be divided into MILD, MODERATE, and SEVERE based on total severity VAS score (0 to 10 cm):

- MILD = VAS 0 to 3
- MODERATE = VAS >3 to 7
- SEVERE = VAS >7 to 10

The participant will be asked to indicate on a VAS the answer to the question below:

"How troublesome are your symptoms of your rhinosinusitis?"

The VAS ranges from 0 (Not troublesome) to 10 (Worst thinkable troublesome) (Appendix 10 [Section 10.10]).

8.2 SAFETY ASSESSMENTS

This section presents safety assessments other than AEs, which are presented in Section 8.3.

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

8.2.1 Physical examinations

Physical examinations will include an assessment of general appearance, skin, eyes, ear/nose/throat, heart, chest, abdomen, reflexes, lymph nodes, spine, and extremities. All deviations from normal will be recorded, including those attributable to the participant's disease.

Physical examinations will be performed at Visits 1, 7, and 9.

8.2.2 Vital signs

Vital signs including systolic and diastolic blood pressure (mmHg), pulse rate (beats per minute), respiratory rate (breaths per minute), and body temperature (forehead [temporal] temperature; degrees Celsius); and body weight (kg) will be measured at Visit 1, Visit 2, and Visits 5 to 9. Height (cm) will be measured at screening (Visit 1) only. Vital signs will be measured in the sitting position at each visit and will be measured prior to receiving IMP using preferably the same arm at each visit.

8.2.3 Electrocardiograms

A standard 12-lead electrocardiogram (ECG) will be performed at the sites at the Screening Visit (Visit 1). In case of an abnormal ECG finding, the Investigator should enter details into the e-CRF. At Visit 2, the Investigator should use his/her medical judgment to consider whether the participant is eligible for the study.

8.2.4 Clinical safety laboratory assessments

- See Appendix 2 (Section 10.2) for the list of clinical laboratory tests to be performed and the SoA (Section 1.3) for their timing and frequency.
- The Investigator must review the laboratory report and record any clinically significant changes occurring during the study as an AE. The laboratory reports must be filed with the source documents. Abnormal laboratory findings associated with the underlying disease are not considered clinically significant, unless judged by the Investigator to be more severe than expected for the participant's condition.

- All laboratory tests with values that are considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator.
  - 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 tests, 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 tests 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 e-CRF.

8.2.5 Pregnancy testing

A serum pregnancy test will be performed at Visit 1, and urine pregnancy tests will be performed at Visit 2 and q4w thereafter. A negative result must be obtained at both Visit 1 and Visit 2 prior to the first administration of IMP. A urinary test could be performed at home as part of visit with or without the assistance of a home care provider. In case of positive urinary test, the study intervention 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.

- Refer to Section 5.1 Inclusion Criteria for pregnancy testing entry criteria; the Investigator is responsible for the review of medical history, menstrual history, and recent sexual activity to decrease the risk for including a woman with an early undetected pregnancy.
- Additional serum or urine pregnancy tests may be performed, as determined necessary by the Investigator or required by local regulation, to establish the absence of pregnancy at any time during the participant's participation in the study.

8.2.6 Suicidal ideation and behavior risk monitoring

Not applicable.

8.2.7 Hypersensitivity monitoring

Allergic reaction is a potential risk associated with the administration of most therapeutic monoclonal antibody treatments.

Allergic reactions may be defined as allergic reaction-mediated signs and symptoms experienced by participants during or shortly after a pharmacologic or biologic agent is given. These reactions may present in a variety of ways, including dizziness, headache, anxiety, dyspnea, hypotension, tachycardia, pruritus, rash, urticaria/angioedema, flushing, nausea or vomiting, and joint pain with fever. Allergic reactions may begin within a few hours and persist up to 24 hours after dosing.

Refer to Appendix 12 (Section 10.12), which describes the clinical criteria for the diagnosis of anaphylaxis.

Participants should be monitored for at least 30 minutes after each study site IMP administration for any signs or symptoms of a hypersensitivity reaction. Any instance of allergic reaction should be reported as an AESI (Section 8.3.6). Any anaphylactic reactions or acute allergic reactions that require immediate treatment will be an AESI with immediate reporting (within 24 hours), and study medication must be permanently discontinued. Trained personnel and medications should be available to treat anaphylaxis or any severe allergic reaction if it occurs. Furthermore, the study participants will be advised, when the IMP is administered at home, to self-monitor for potential signs and symptoms that may suggest a hypersensitivity reaction for at least 30 minutes after administration.

Anaphylactic reactions or systemic allergic reactions that are related to IMP and require treatment must be reported as an AESI (within 24 hours; for further details, see AESI definition in Section 8.3.6), and study medication must be permanently discontinued.

8.2.8 Injection site reaction assessments

Based on the SC mode of administration of high doses of protein and on a higher incidence of local injection site reactions observed at the highest dose level (300 mg weekly) in dupilumab studies, severe injection site reactions are considered a potential risk. Participants who experience an injection site reaction must be closely monitored for the possibility of a more intense injection site reaction with a future injection. Any severe injection reaction that lasts over 24 hours will be reported as an AESI (Section 8.3.6) with immediate notification.

Prophylactic treatment/premedication for an injection site reaction is not permitted.

8.3 ADVERSE EVENTS, SERIOUS ADVERSE EVENTS AND OTHER SAFETY REPORTING

The definitions of AEs and SAEs can be found in Appendix 3 (Section 10.3). The definition of AESI is provided in Section 8.3.6.

The definitions of unsolicited and solicited AEs can be found in Appendix 3 (Section 10.3).

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's LAR).

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 all AEs that are considered related to the study intervention or study procedures or that cause the participant to discontinue the study intervention (see Section 7).

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

8.3.1 Time period and frequency for collecting AE and SAE information

All AEs (serious or nonserious) will be collected from the signing of the ICF until the EOT/EOS Visit at the time points specified in the SoA (Section 1.3).

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

The Investigator should take appropriate measures to follow all AEs until clinical recovery is complete and laboratory results have returned to normal, until progression has been stabilized, or until death, in order to ensure the safety of the participants. This may imply that observations will continue beyond the last planned visit per protocol and that additional investigations may be requested by the monitoring team up to the time as noticed by the Sponsor.

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

8.3.2 Method of detecting AEs and SAEs

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

8.3.3 Follow-up of AEs and SAEs

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

8.3.4 Regulatory reporting requirements for SAEs

- Prompt notification by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRBs), and the Investigators.

- Serious adverse events that are considered expected will be specified in the Package Insert.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.
- An Investigator who receives an investigator safety report describing an SAE, SUSAR, or any other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with Package Insert and will notify the IRB, 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 EOT/EOS.
- If a pregnancy is reported, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the female participant's 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 and will be reported as such.
- The participant or pregnant female partner will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant or pregnant female partner and the neonate, and the information will be forwarded to the Sponsor.
- 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 10.3.4. While the Investigator is not obligated to actively seek this information in former study participants or pregnant female partners, he/she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue the study intervention.

8.3.6 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 are 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 the SAE notification described in Section 10.3.4, even if it does not fulfill a seriousness criterion.

Adverse event of special interests for this study include the following:

- Anaphylactic or systemic allergic reactions that are related to IMP and that require treatment (refer to Appendix 12 [Section 10.12] for the definition of anaphylaxis)
- Severe injection site reactions that last longer than 24 hours
- Conjunctivitis, blepharitis, or keratitis
- Serum sickness or serum sickness-like reaction
- Clinically symptomatic eosinophilia (or eosinophilia associated with clinical symptoms)
- Any infection meeting at least 1 of the following criteria:
  - Any SAE of serious infection
  - Requires parenteral (intravenous, intramuscular, SC) antimicrobial therapy
  - Requires oral antimicrobial therapy for longer than 2 weeks
  - Is a parasitic infection
  - Is an opportunistic infection (refer to Appendix 9 [Section 10.9])

  Note: Antimicrobial therapy refers to antibiotic, antiviral, and antifungal agents.
- Significant elevation of alanine aminotransferase (ALT)
  - ALT >5 × ULN in participants with baseline ALT ≤2 × ULN

    or
  - ALT >8 × ULN if baseline ALT >2 × ULN
- Pregnancy of a female participant 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 study or in a female partner of a male participant entered in the clinical study. It will be qualified as an SAE only if it fulfills one of the seriousness criteria (see Appendix 3 [Section 10.3]).
  - 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 (See Appendix 4 [Section 10.4]).
- 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 intended dose during an interval of less than 11 days. The circumstances (ie, accidental or intentional) should be clearly specified in the verbatim and symptoms, if any, entered on separate AE forms.

Of note, asymptomatic overdose has to be reported as a standard AE.

8.3.7 Guidelines for management of specific laboratory abnormalities

Decision trees for the management of certain laboratory abnormalities by Sanofi are provided in Appendix 5 (Section 10.5).

The following laboratory abnormalities should be monitored, documented, and managed according to the related flow chart in protocol appendices.

- Neutropenia
- Thrombocytopenia
- Increase in ALT
- Increase in serum creatinine
- Increase in creatine phosphokinase (CPK)

8.3.8 Guidelines for reporting product complaints

Any defect in the IMP must be reported as soon as possible by the Investigator to the monitoring team, which will complete a product complaint form within the 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 PHARMACOKINETICS

Pharmacokinetics parameters are not evaluated in this study.

8.5 GENETICS

Genetics are not evaluated in this study.

8.6 BIOMARKERS

Biomarkers are not evaluated in this study.

8.7 IMMUNOGENICITY ASSESSMENTS

Immunogenicity is not evaluated in this study.

8.8 HEALTH ECONOMICS OR MEDICAL RESOURCE UTILIZATION AND HEALTH ECONOMICS

Health economics or medical resource utilization and health economics parameters are not evaluated in this study.

8.9 USE OF DATA FOR FUTURE RESEARCH

Not applicable.

9 STATISTICAL CONSIDERATIONS

This postmarketing study is to assess whether dupilumab used without INCS will show similar efficacy to that of dupilumab used with INCS in EFC14280, using the point estimates of the proportion of responders (NPS improvement from baseline ≥1) at Week 24. Formal statistical analysis for hypothesis (null/alternative) will not be performed.

9.1 SAMPLE SIZE DETERMINATION

In EFC14280, the proportion of responders (NPS improvement from baseline ≥1) at Week 24 was 62.0% in the dupilumab group. Based on this result, the proportion of responders (NPS improvement from baseline ≥1) at Week 24 in this postmarketing study will be at least 50.0% to justify the similar effect size between EFC14280 and this study.

It is necessary for 20 participants to achieve this similar responder rate (at least 50%) with a 90% probability of success. The sample size was adjusted up to 25 to account for a 20% drop-out rate.

9.2 POPULATIONS FOR ANALYSES

The populations for analyses are defined in Table 5.

Table 5 - Populations for analyses

Population	Description
Screened	All participants who sign the informed consent form (ICF)
Enrolled	The enrolled population includes all participants with a treatment kit number allocated and recorded in the interactive response technology (IRT) database, regardless of whether the treatment kit was used or not. Participants treated without a treatment kit number being allocated will not be considered enrolled and will not be included in any efficacy population.
Intent-to-treat (ITT)	Enrolled population with chronic rhinosinusitis with nasal polyp (CRSwNP)
Modified intent-to-treat (mITT)	All participants in ITT allocated to study intervention administered at least 1 dose of study intervention
Per protocol (PP)	All participants in mITT allocated to study intervention administered at least 1 dose of study intervention, and who did not receive intranasal corticosteroids (INCS) up to Week 24
Per protocol with extension term (PPE)	All participants in mITT allocated to study intervention administered at least 1 dose of study intervention during the intervention period after Week 24, and who did not receive INCS throughout the study
Safety (SAF)	All participants allocated to study intervention administered at least 1 dose of study intervention before Week 24
Safety for extension term (SAFE)	All participants allocated to study intervention administered at least 1 dose of study intervention during the intervention period after Week 24

Abbreviations: CRSwNP: chronic rhinosinusitis with nasal polyp; ICF: informed consent form; INCS: intranasal corticosteroids; IRT: interactive response technology; ITT: intent-to-treat; mITT: modified ITT; PP: per protocol; PPE: per protocol with extension term; SAF: safety; SAFE: safety for extension term

Efficacy analyses for the treatment period up to Week 24 will be performed using the per protocol (PP) population. Efficacy analyses for the treatment period after Week 24 will be performed using the per protocol with extension term (PPE) population. Additionally, supportive efficacy analyses will be performed using the modified intent-to-treat (mITT) population.

Safety data up to Week 24 will be reported for the safety (SAF) population. Safety data collected after Week 24 will be reported for the safety for extension term (SAFE) population.

Participants exposed to study intervention before or without being enrolled will not be considered enrolled and will not be included in any efficacy or safety populations. The safety experience of these participants will be reported separately.

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

For any participant enrolled more than once, only the data associated with the first enrollment will be used in any efficacy or safety population. The safety experience associated with any later enrollment will be reported separately.

9.3 STATISTICAL ANALYSES

The statistical analysis plan (SAP) will be finalized prior to database lock and will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

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

9.3.1 General considerations

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

The observation period will be divided into 2 segments:

- The **pre-treatment period** is defined as the period up to first IMP administration.
- The **treatment-emergent period** is defined as the period from the first IMP administration to the last visit in the study.

Dose regimen groups in the extension term after Week 24 will be defined as follows:

- 300 mg q2w group: participants who were administered at least 1 dose of the 300 mg q2w regimen and never experienced q4w administration during the extension term after Week 24
- 300 mg q4w group: participants who were administered at least 1 dose of the 300 mg q4w regimen during the extension term after Week 24

During the treatment term, including efficacy variable after Week 24, continuous variables and binary variables for efficacy by each visit will be summarized using descriptive statistics and frequency table in both the PP and mITT populations.

9.3.2 Primary efficacy endpoint

- The proportion of responders (NPS improvement from baseline ≥1) at Week 24.

The number of participants and percentage with the 95% confidence interval (CI) for the primary endpoint will be provided at Week 24 in the PP population.

Participants who undergo surgery for NP or receive SCS for any reason will be considered nonresponders for time points after undergoing surgery or receiving SCS. Participants who have missing data at Week 24 will be considered nonresponders.

Details of supportive analyses will be provided in the SAP.

9.3.3 Key secondary efficacy endpoints

- Change from baseline to Week 24 in bilateral NPS
- Change from baseline to Week 24 in NC symptom severity score using the CRSwNP nasal symptom diary (refer to Section 8.1.2 for the details of NC symptom severity score assessment)
- Change from baseline to Week 24 in opacification of sinuses assessed by CT scan using the LMK score (refer to Section 8.1.3 for the details of LMK score)

Handling of missing data

Each of the 3 key secondary efficacy endpoints will be analyzed using a hybrid method of worst-observation carried forward (WOCF) and multiple imputation. For participants taking selected prohibited medications and/or rescue medications or who undergo surgery (details of selection will be specified in the SAP, refer to Section 6.8.1), their data after the medication usage or surgery will be set to missing, and the worst postbaseline value on or before the time of the medication usage or surgery will be used to impute the missing Week 24 value (for participants whose postbaseline values are all missing, the baseline will be used to impute). Participants who discontinue the treatment prematurely are encouraged to follow the planned clinical visits, and in those participants who did not take the selected prohibited medications and/or rescue medications or undergo surgery, all data collected after treatment discontinuation will be used in the analysis. For these participants, missing data may still happen despite all efforts to collect the data after treatment discontinuation. For participants who discontinue due to lack of efficacy, all data collected after discontinuation will be used in the analysis, and a WOCF approach will be used to impute the missing Week 24 value if needed. For participants who discontinue not due to lack of efficacy, a multiple imputation approach assuming missing at random will be used to impute the missing Week 24 value, and this multiple imputation will use all participants, excluding participants who have taken the selected prohibited medications and/or rescue medications or undergone surgery on or before Week 24 and excluding participants who discontinue due to lack of efficacy on or before Week 24. All of the imputed complete data will be analyzed by descriptive statistics with the 95% CI. The summarized mean changes obtained from each imputed dataset will be combined using Rubin's rule for a single estimate.

Other secondary efficacy endpoints

- Change from baseline to Week 24 in TSS
- Change from baseline to Week 24 in loss of smell severity score
- Change from baseline to Week 24 in VAS for rhinosinusitis

The other secondary efficacy endpoints will be analyzed using the same hybrid approach as the 3 key secondary efficacy endpoints.

9.3.4 Exploratory efficacy endpoints

Descriptive statistics for the exploratory efficacy endpoints (NPS, NC symptom severity score, LMK score, and TSS) will be presented by dose regimen group and overall for the extension term after Week 24.

Details of exploratory efficacy analyses will be provided in the SAP.

9.3.5 Safety analysis

All safety analyses up to Week 24 will be analyzed for the SAF. Safety data collected during the extension term after Week 24 up to Week 52 will be reported for the SAFE. Safety analyses for the extension term will be presented by dose regimen group and overall.

The number and percentage of participants with at least 1 treatment-emergent AE (TEAE), treatment-emergent serious AE (TESAE), and TEAE leading to treatment discontinuation will be tabulated. Multiple occurrences of the same event in the same participant will be counted once in the tables. The denominator for computing percentages will be the safety populations. Serious AEs and AEs leading to withdrawal from the withdrawal that occur before or after the "treatment-emergent period" will be summarized separately. Definitions for AESI and the method to identify AESIs will be specified in the SAP.

Descriptive statistics of values and change from baseline values for each laboratory and vital signs parameters will be summarized at each time point. The number and percentage of participants with at least 1 incidence of potentially clinically significant abnormality (PCSA) at any time during the treatment-emergent period will be summarized.

9.3.5.1 Adverse events

General common rules for adverse events

The AEs will be analyzed in the following 2 categories:

- Pre-treatment AEs: AEs that developed, worsened, or became serious during the pre-treatment period.
- Treatment-emergent AEs: AEs that developed, worsened, or became serious during the treatment-emergent period.

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

Analysis of all adverse events

An AE incidence table will be provided for all types of TEAEs: all TEAEs, all treatment-emergent AESIs (defined with a preferred term [PT] or a prespecified grouping), all treatment-emergent SAEs, and all TEAEs leading to permanent treatment discontinuation.

The AE summaries will be generated with the number (%) of participants experiencing at least one event. Participants who die during the study will also be listed.

9.3.5.2 Laboratory variables and vital signs

Quantitative analyses

For laboratory variables, vital signs, descriptive statistics for results, and changes from baseline will be provided for each planned visit, with the last value and the worst value (minimum and/or maximum value depending on the parameter) during the treatment-emergent period. These analyses will be performed using central measurements (when available) or local measurements for laboratory variables.

Analyses according to PCSA

Potentially clinically significant abnormality analyses will be performed based on the PCSA list currently in effect at Sanofi at the time of database lock. Analyses according to PCSA will be performed based on the worst value during the treatment-emergent period, using all measurements (either local or central, and scheduled, nonscheduled, or repeated). For laboratory variables and vital signs, the incidence of participants with at least one PCSA during the treatment-emergent period will be summarized, regardless of the baseline level, according to the following baseline status categories:

- Normal/missing
- Abnormal according to PCSA criterion or criteria

9.3.5.3 Product complaints

Product complaints will be summarized in the safety population.

9.3.6 Other analysis

For a regional or national emergency declared by a governmental agency, contingency measures are included in Appendix 7: Contingency measures for a regional or national emergency that is declared by a governmental agency (Section 10.7).

9.4 INTERIM ANALYSES

No interim analysis is planned.

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])
  - Good Postmarketing Study Practice (GPSP)
- The protocol, protocol amendments, ICF, and other relevant documents (eg, advertisements) must be submitted to an IRB by the Investigator and reviewed and approved by the IRB before the study is initiated.
- Any amendments to the protocol will require IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation 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 annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB
  - Determining whether an incidental finding (as per Sanofi policy) should be returned to a participant and, if it meets the appropriate criteria, to ensure the finding is returned (an incidental finding is a previously undiagnosed medical condition that is discovered unintentionally and is unrelated to the aims of the study for which the tests are being performed). The following should be considered when determining the return of an incidental finding:
    - The return of such information to the study participant (and/or his/her designated healthcare professional, if so designated by the participant) is consistent with all applicable national, state, or regional laws and regulations in the country where the study is being conducted, and

  - The finding reveals a substantial risk of a serious health condition or has reproductive importance, AND has analytical validity, AND has clinical validity.
  - The participant in a clinical study has the right to opt out of being notified by the Investigator of such incidental findings. In the event that the participant has opted out of being notified and the finding has consequences for other individuals, eg, the finding relates to a communicable disease, Investigators should seek independent ethical advice before determining next steps.
  - In case the participant has decided to opt out, the Investigator must record in the site medical files that she/he does not want to know about such findings.
- Notifying the IRB of SAEs or other significant safety findings as required by IRB procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB, European regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (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 study 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 study participants or on the scientific value of the study) 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 participants or their LAR, and answer all questions regarding the study, including what happens to the participant when his/her participation ends.
- Participants must be informed that their participation is voluntary. Participants or their LAR will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Privacy and Data Protection requirements including those of the GDPR and of the French law, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- In case of ICF amendment while the participants are still included in the study, they must be reconsented to the most current version of the ICF(s).Where participants are not in the

study anymore, teams in charge of the amendment must define if those participants must or not reconsent 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) must be provided to the participant or their LAR, where applicable.

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

For a regional or national emergency declared by a governmental agency, contingency procedures may be implemented for the duration of the emergency (Appendix 7: Contingency measures for a regional or national emergency that is declared by a governmental agency [Section 10.7]). The participants or their LAR should be verbally informed prior to initiating any changes that are to be implemented for the duration of the emergency (eg, study visit delays/treatment extension, use of local labs).

10.1.4 Data protection

All personal data collected and/or processed in relation to this study will be handled in compliance with all applicable Privacy & Data Protection laws and regulations, including the GDPR. The study Sponsor is the Sanofi company responsible for ensuring compliance with this matter, when processing data from any individual who may be included in the Sanofi databases, including Investigators, nurses, experts, service providers, Ethics Committee members, etc.

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

Protection of participant data

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

Participant race and ethnicity will be collected in this study because they are expected to modify the drug response/because they are required by regulatory agencies (eg, on Japanese population for the Pharmaceuticals and Medical Devices Agency in Japan).

- 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 applicable data protection laws. The level of disclosure must also be explained to the participant as described in the informed consent.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB 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 study 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 precontractual 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 intragroup 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 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 e-mail, 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 studies and results on publicly accessible websites, based on company commitments, international and local legal and regulatory requirements, and other clinical trial disclosure commitments established by pharmaceutical industry associations. These websites include clinicaltrials.gov, EU clinicaltrialregister (eu.ctr), and sanofi.com, as well as some national registries.

In addition, results from clinical studies 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 clinicalstudydatarequest.com.

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

Professionals involved in the study or in the drug development program

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 e-CRF 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 electronically signing the CRF.

- Guidance on completion of e-CRFs will be provided in CRF Completion Guideline.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the e-CRF.
- The Investigator must permit study-related monitoring, audits, IRB review, and regulatory agency inspections and provide direct access to source data documents.
- Quality tolerance limits (QTLs) will be predefined in the Centralized Monitoring Plan to identify systematic issues that can impact participant safety and/or reliability of study results. These predefined parameters will be monitored during the study and important deviations from the QTLs and remedial actions taken will be summarized in the clinical study report.
- 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).
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 25 years after the signature of the final study report unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.7 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 e-CRF 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.
- Definition of what constitutes source data can be found in Section 10.1.8.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the e-CRF.

- Study monitors will perform ongoing source data verification to confirm that data entered into the e-CRF 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.

10.1.8 Definition of source data

Source data is all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study. 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.

All the data collected in the e-CRF should be transcribed directly from source documents. Data collected from the study-associated laboratories, endoscopy, CT scan, and patient diary will be considered source data.

10.1.9 Study and site start and closure

First act of recruitment

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.

Study/Site termination

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

10.1.10 Publication policy

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

10.2 APPENDIX 2: CLINICAL LABORATORY TESTS

- The tests detailed in Table 6 will be performed by the local laboratories.
- 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.

Table 6 - Protocol-required laboratory tests

Laboratory tests	Parameters
Hematology	
	Platelet count
	RBC count
	Hemoglobin
	Hematocrit
	Total WBC count with differential:
	Neutrophils
	Lymphocytes
	Monocytes
	Eosinophils
	Basophils
Clinical chemistry[a]	
	BUN
	Creatinine
	Glucose (Indicate if fasting, or nonfasting)
	Uric acid
	Total cholesterol
	Total protein
	Albumin
	Total bilirubin (in case of values above the normal range, differentiation in conjugated and nonconjugated bilirubin)
	ALT/SGPT
	AST/SGOT
	Alkaline phosphatase[b]
	Lactate dehydrogenase
	Sodium
	Potassium
	Chloride
	Creatine phosphokinase
Routine urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, urobilinogen, nitrite by dipstick • Microscopic examination (if blood or protein is abnormal)
Pregnancy testing	• Serum and urine hCG pregnancy test (as needed for women of childbearing

Laboratory tests	Parameters
	potential)
Other screening tests	• Serology: - HBsAg, HBcAb or HBcAb IgM and total[c] - HBsAb - HCVAb[d] - HIV screen (anti-HIV-1 and HIV-2 antibodies) - TB blood testing (IGRA)[e]

Abbreviations: ALT: alanine aminotransferase; AST: aspartate aminotransferase; BUN: blood urea nitrogen; HBcAb: hepatitis B core antibody; HBsAb: hepatitis B surface antibody; HBsAg: hepatitis B surface antigen; HBV: hepatitis B; hCG: human chorionic gonadotropin; HCVAb: hepatitis C virus antibody; HIV: human immunodeficiency virus; IgM: immunoglobulin M; IGRA: interferon-gamma release assay; RBC: red blood cell, SAE: serious adverse event; SGOT: serum glutamic-oxaloacetic transaminase; SGPT: Serum glutamic-pyruvic transaminase; TB: tuberculosis; WBC: white blood cell.

NOTES :

a Details of liver chemistry stopping criteria and required actions and follow-up are given in Section 7.1.2 and Appendix 5 (Section 10.5). All events of ALT or bilirubin which may indicate severe liver injury (possible Hy's Law) must be reported as an SAE.

b If alkaline phosphatase is elevated, consider fractionating.

c In case of results showing HBsAg (negative), and HBcAb total or HBcAb IgM (positive), an HBV DNA testing will be performed and should be confirmed prior to enrollment. Participants who are HBcAb (positive) and HBV DNA (negative) at Visit 1 will require HBV DNA monitoring at Visits 6, 7, and 8 and at the participant's last visit (refer to SoA [Section 1.3]).

d In case of results showing HCV Ab (positive), HCV RNA testing will be performed and should be confirmed prior to enrollment.

e An IGRA is required only for participants without history of active/latent TB.

Investigators must document their review of each laboratory safety report.

10.3 APPENDIX 3: AES AND SAES: 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 participant 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.

Definition of unsolicited and solicited AE

- An unsolicited AE is an AE that was not solicited using a participant diary and that is communicated by a participant, participant's parent, or LAR who has signed the informed consent. Unsolicited AEs include serious and nonserious AEs.
- Potential unsolicited AEs may be medically attended (ie, symptoms or illnesses requiring hospitalization, or emergency room visit, or visit to/by a health care provider). The participant, participant's parent, or LAR will be instructed to contact the site as soon as possible to report medically attended event(s), as well as any events that, though not medically attended, are of participant, participant's parent, or LAR's concern. Detailed information about reported unsolicited AEs will be collected by qualified site personnel and documented in the participant's records.
- Unsolicited AEs that are not medically attended nor perceived as a concern by participant, participant's parent, or LAR will be collected during interview with the participant, participant's parent, or LAR and by review of available medical records at the next visit.
- Solicited AEs are predefined local and systemic events for which the participant is specifically questioned, and which are noted by the participants in their diary.

Events <u>meeting</u> the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital sign 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), eg:
  - Symptomatic, and/or
  - Requiring either corrective treatment or consultation, and/or
  - Leading to IMP discontinuation or modification of dosing, and/or
  - Fulfilling a seriousness criterion, and/or

- Defined as an AESI.

- 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

An SAE is defined as any AE 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 admitted (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 or significant 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) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e) Is a congenital anomaly/birth defect

f) Other situations:

- Medical or scientific judgment should be exercised by the Investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

  Note: The following list of medically important events is intended to serve as a guideline for determining which condition has to be considered as a medically important event. The list is not intended to be exhaustive:

  - Intensive treatment in an emergency room or at home for:
    - Allergic bronchospasm
    - Blood dyscrasias (ie, agranulocytosis, aplastic anemia, bone marrow aplasia, myelodysplasia, pancytopenia, etc.)
    - Convulsions (seizures, epilepsy, epileptic fit, absence, etc.).
  - Development of drug dependence or drug abuse
  - ALT >3 × ULN + total bilirubin >2 × ULN or asymptomatic ALT increase >10 × ULN
  - Suicide attempt or any event suggestive of suicidality
  - Syncope, loss of consciousness (except if documented as a consequence of blood sampling)
  - Bullous cutaneous eruptions

- 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.
- 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 required form.
- 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 to interfere with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. "Severe" is a category used 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 that 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 Package Insert 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 representatives. 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 representatives.**
- The Investigator may change his/her opinion of causality in light of follow-up information and send an 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, the Investigator will provide the Sponsor's representatives with a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally submitted documents.
- 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

Serious adverse event 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) 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 are:

  FAX: 0120-305-260/03-6301-3052

  E-mail: jp.adamsSAE@sanofi.com

SAE reporting to the Sponsor via paper data collection tool

- Facsimile transmission of the SAE paper data collection tool 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 data collection tool within the designated reporting time frames.
- Contacts for SAE reporting are:

  FAX: 0120-305-260/03-6301-3052

  E-mail: jp.adamsSAE@sanofi.com

For AESIs, the Sponsor will be informed immediately (ie, within 24 hours), per SAE notification described above, even if not fulfilling a seriousness criterion.

10.4 APPENDIX 4: CONTRACEPTIVE AND BARRIER GUIDANCE AND COLLECTION OF PREGNANCY INFORMATION

10.4.1 Definitions

A woman is considered WOCBP (fertile) from the time of menarche until becoming postmenopausal (see below) unless permanently sterile (see below).

A postmenopausal state is defined as the period of time after a woman has experienced no menses for 12 consecutive months without an alternative medical cause.

- A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT).
- Females on HRT and whose menopausal status is in doubt will be required to use one of the nonestrogen 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.

- Permanent sterilization methods include:
  - 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, gonadal dysgenesis), Investigator discretion should be applied to determining study entry eligibility.

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

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

10.4.2 Contraception guidance

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
Highly effective methods[b] that have low user dependency *Failure rate of <1% per year when used consistently and correctly.*
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS) [c]
• Bilateral tubal occlusion
• Azoospermic partner (vasectomized or due to a medical cause) *Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.* Note: documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
Highly effective methods[b] that are user dependent *Failure rate of <1% per year when used consistently and correctly.*
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c] –oral –intravaginal –transdermal –injectable
• Progestogen-only hormone contraception associated with inhibition of ovulation[c] –oral –injectable
• 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.)*
Effective methods[d] that are not considered highly effective *Failure rate of ≥1% per year when used consistently and correctly.*
• Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action
• Male or female condom with or without spermicide
• Cervical cap, diaphragm, or sponge with spermicide
• A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods) [c]
a Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies. *b* Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently

and correctly. *c* Male condoms must be used in addition to hormonal contraception. *d* Considered effective, but not highly effective - failure rate of ≥1% per year. NOTE: Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception. Male condom and female condom should not be used together (due to risk of failure from friction).

10.4.3 Collection of pregnancy information

Male participants with partners who become pregnant

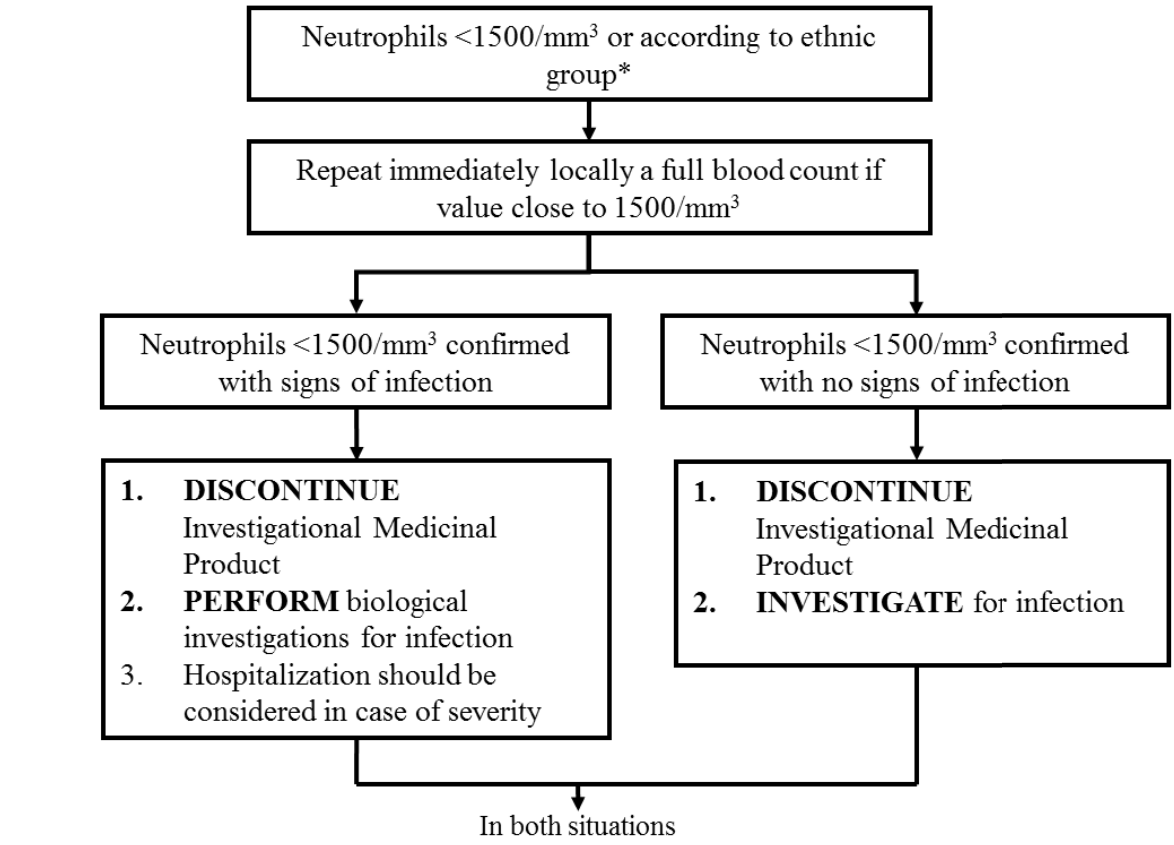
- The Investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive study intervention.
- After obtaining the necessary signed informed consent from 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. 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 estimated 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 will be reported as an AE or SAE. A spontaneous abortion 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 of the protocol. While the Investigator is not obligated to actively seek this information in former study participants, he/she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study intervention.

10.5 APPENDIX 5: LIVER AND OTHER SAFETY: SUGGESTED ACTIONS AND FOLLOW-UP ASSESSMENTS AND STUDY INTERVENTION RECHALLENGE GUIDELINES

NEUTROPENIA

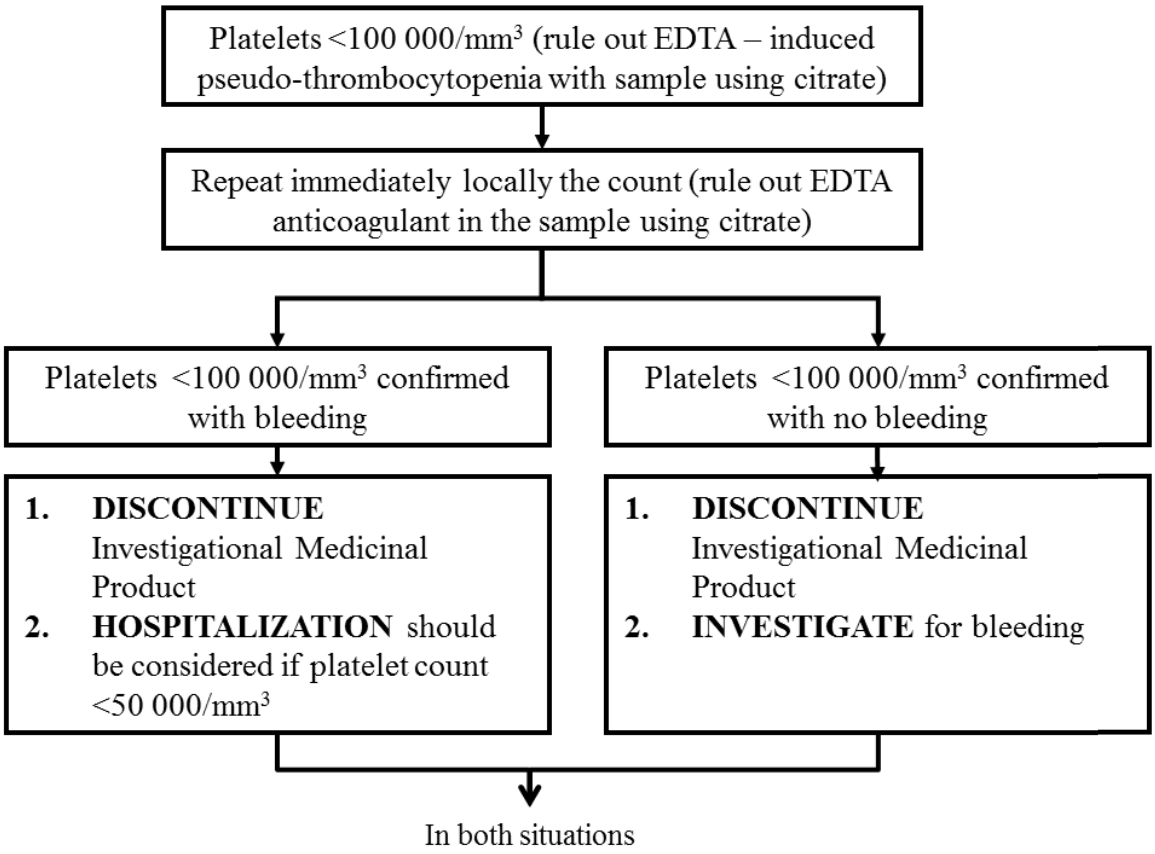


3. **INFORM** the local monitor
4. **INVESTIGATE** previous treatments particularly long-term, even a long time ago, exposure to toxic agents, e.g., benzene, X-rays, etc.
5. **PERFORM** and collect the following investigations (results):
   - RBC and platelet counts, Absolute Neutrophil Count (ANC)
   - Infectious serologies to be performed locally, according to clinical symptoms / medical history
6. **DECISION** for bone marrow aspiration: to be taken in specialized unit
7. **COLLECT/STORE** one sample following handling procedures described in PK sections **(for studies with PK sampling)**
8. **MONITOR** the leukocyte count 3 times per week for at least one week, then twice a month until it returns to normal

***** For individuals of African descent, the relevant value of concern is <1000/mm3

Neutropenia is to be recorded as an AE only if at least 1 of the criteria listed in the general guidelines for reporting AEs in Section 10.3 is met.

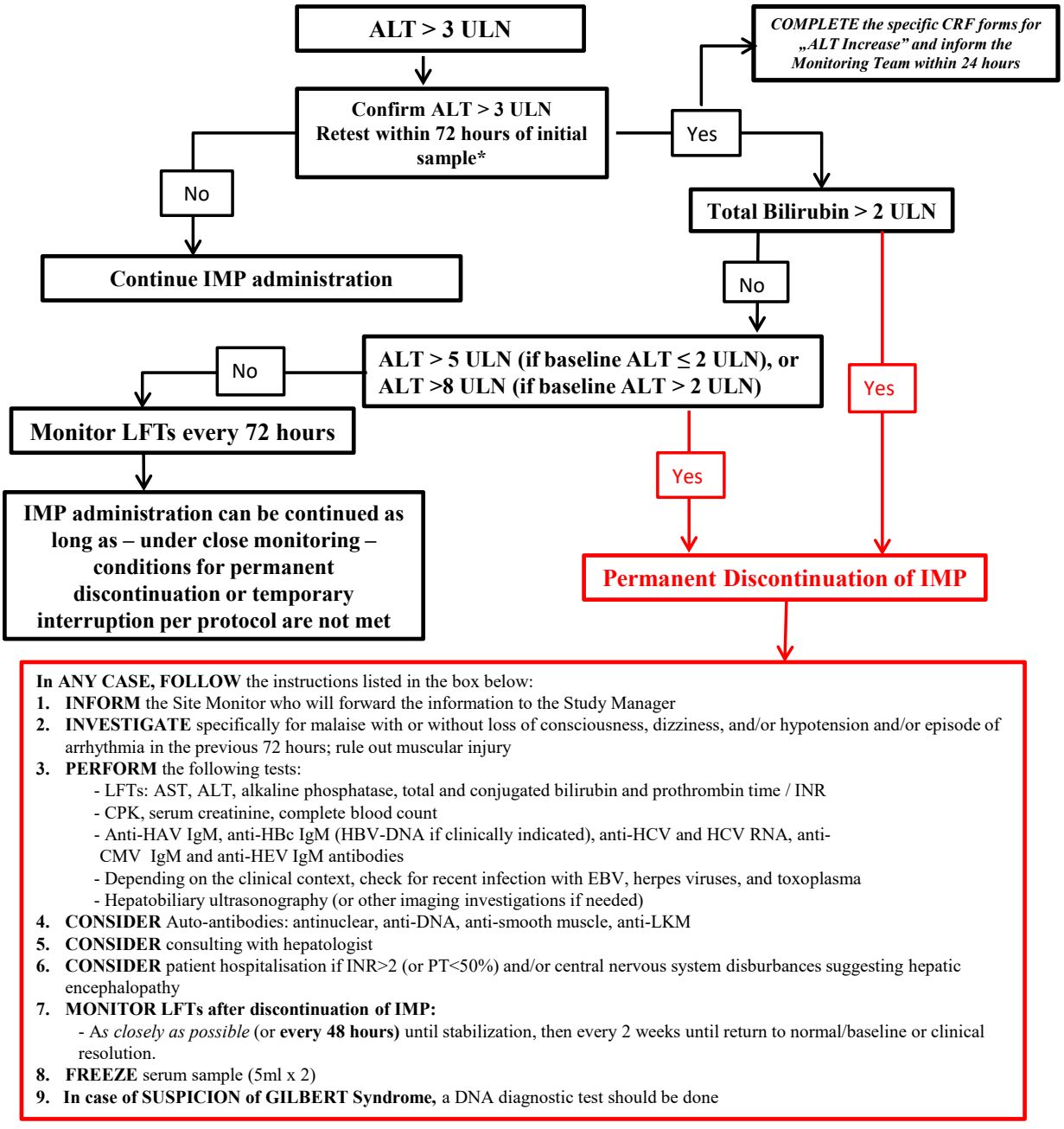
THROMBOCYTOPENIA



3. **INFORM** the local Monitor
4. **QUESTION** about alcohol habits, any drug intake including quinine (drinks), heparin administration, aspirin, immunotherapy, etc.
5. **PERFORM** or collect the following investigations:
   - Complete blood count, schizocytes, creatinine
   - Locally:
     - Bleeding time and coagulation tests (INR or PT, aPTT, D-Dimers)
     - Infectious serologies to be performed according to clinical symptoms / medical history
6. **COLLECT/STORE** one sample following handling procedures described in PK sections **(for studies with PK sampling)**
7. **DECISION** for bone marrow aspiration to be taken in specialized unit
8. **MONITOR** the platelet count every day for at least one week and then regularly until it returns to normal

Thrombocytopenia is to be recorded as an AE only if at least 1 of the criteria listed in the general guidelines for reporting AEs in Section 10.3 are met.

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:**
   - A*s closely as possible* (or **every 48 hours)** until stabilization, then every 2 weeks until return to normal/baseline or clinical resolution.
8. **FREEZE** serum sample (5ml x 2)
9. **In case of SUSPICION of GILBERT Syndrome,** a DNA diagnostic test should be done

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

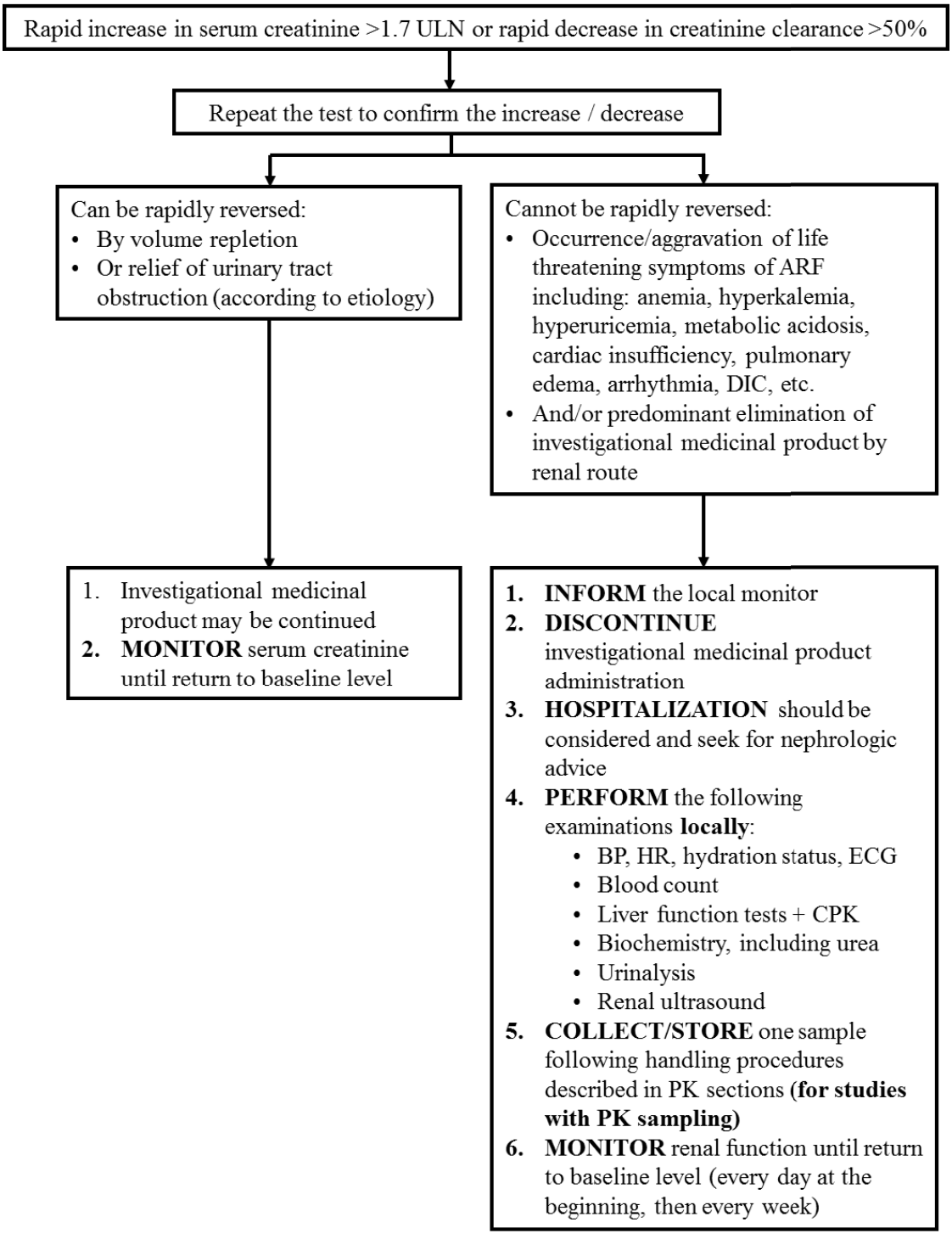
Note:

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

See Section 10.3 for guidance on safety reporting.

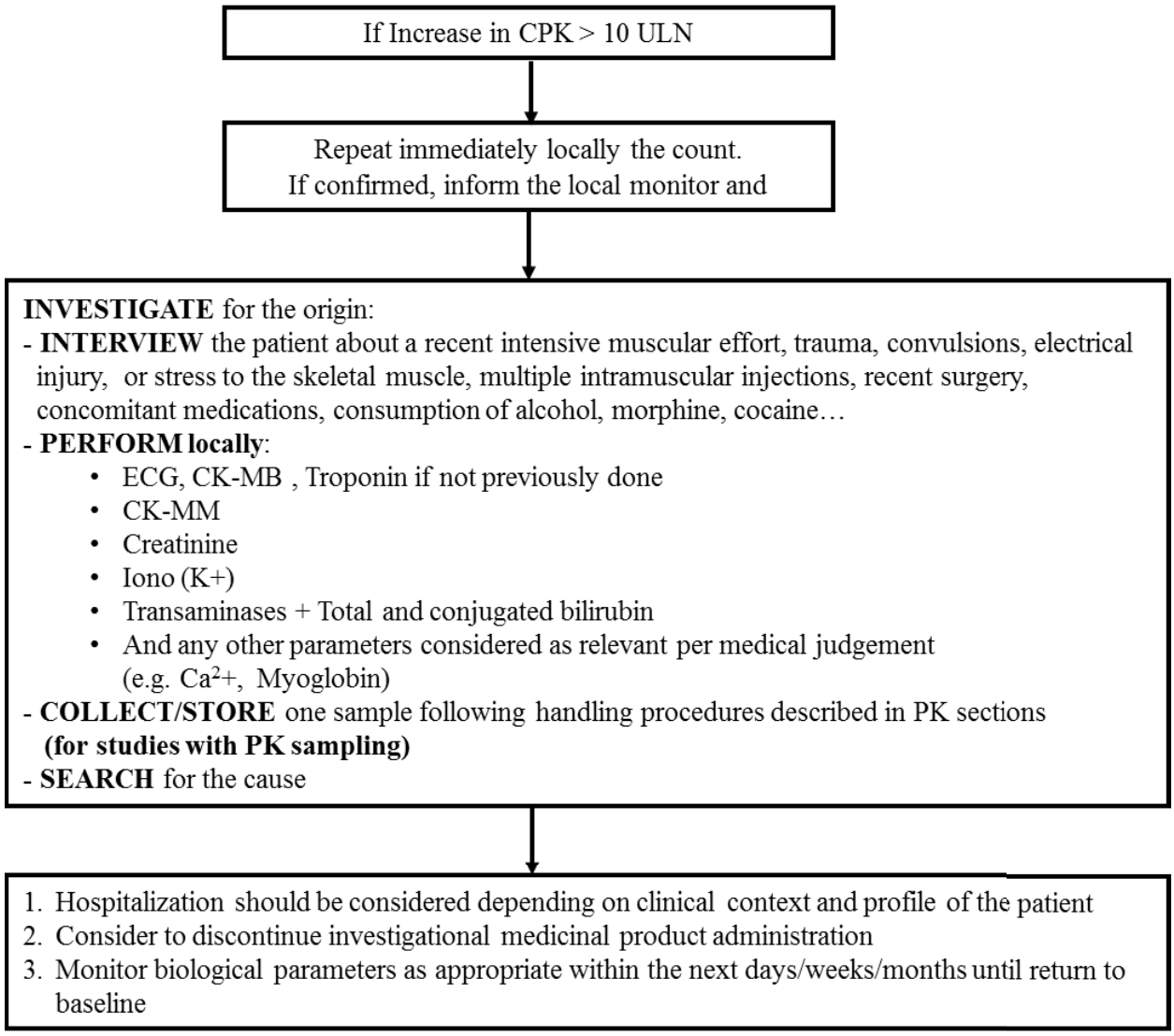
Normalization is defined as ≤ULN or baseline value, if baseline value is >ULN.

INCREASE IN SERUM CREATININE in patients with normal baseline (creatininemia between 45 µmol/L and 84 µmol/L)



Increase in serum creatinine is to be recorded as an AE only if at least 1 of the criteria listed in the general guidelines for reporting AEs in Section 10.3 are met.

INCREASE IN CPK OF NON-CARDIAC ORIGIN AND NOT RELATED TO INTENSIVE PHYSICAL ACTIVITY



Increase in CPK is to be recorded as an AE only if at least 1 of the criteria in the general guidelines for reporting AEs in Section 10.3 are met.

10.6 APPENDIX 6: COUNTRY-SPECIFIC REQUIREMENTS

Not applicable.

10.7 APPENDIX 7: CONTINGENCY MEASURES FOR A REGIONAL OR NATIONAL EMERGENCY THAT IS DECLARED BY A GOVERNMENTAL AGENCY

A regional or national emergency declared by a governmental agency (eg, public health emergency, natural disaster, pandemic, terrorist attack) may prevent access to the clinical study site.

Contingency procedures are suggested below and in other sections (Section 5.5, Section 6.1, Section 7.1.3, Section 7.1.4, Section 8, Section 9.3.6, and Section 10.1.3) for an emergency that prevents access to the study site to ensure the safety of the participants and to consider continuity of the clinical study conduct, protect study integrity, and assist in maintaining compliance with GCP in Conduct of Clinical Trials Guidance. Sponsor agreement MUST be obtained prior to the implementation of these procedures for the duration of the emergency.

During the emergency, if the site will be unable to adequately follow protocol-mandated procedures, screening may be temporarily delayed (see also Section 5.5).

Attempts should be made to perform all assessments in accordance with the approved protocol to the extent possible. In case this is not possible due to a temporary disruption caused by an emergency, focus should be given to those assessments that are necessary to ensure the safety of participants and those that are important to preserving the main scientific value of the study.

Procedures to be considered in the event of a regional or national emergency declared by a governmental agency:

- If on-site visits are not possible, visit windows may be extended for assessment of safety and/or efficacy data that cannot be obtained remotely (eg, nasal endoscopy, CT scan, vital signs, laboratory assessments, serum pregnancy test) and should be documented in the participant's study file.
- Use of local clinic or laboratory locations may be allowed.
- Arrangements can be made for qualified site personnel and/or health care professionals (eg, visiting nurse service) for vital signs, blood sample collection, and IMP administration, if allowed by local regulations and approved by the participant.

As an alternative to on-site IMP dispensing, 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.

During a regional or national emergency declared by a governmental agency, reinitiation of IMP can only occur once the Investigator has determined, according to his/her best judgment, that the contribution of the IMP to the occurrence of the epidemic event (eg, COVID-19) was unlikely.

The participants or their LAR should be verbally informed prior to initiating any changes that are to be implemented for the duration of the emergency (eg, study visit delays/treatment extension, use of local labs).

Contingencies implemented due to emergency will be documented and a sensitivity analysis may be conducted (details will be specified in the SAP).

10.8 APPENDIX 8: LIST OF PROHIBITED LIVE ATTENUATED VACCINES

The list below is indicative and not exhaustive.

- Bacillus chickenpox (Varicella)
- Intranasal influenza (FluMist-Influenza); inactive influenza vaccine delivered by injection is permitted
- Measles (Rubeola)
- Measles-mumps-rubella (MMR) combination
- Measles-mumps-rubella-varicella (MMRV) combination
- Mumps
- Oral polio (Sabin)
- Oral typhoid
- Rotavirus
- Rubella
- Smallpox (Vaccinia)
- Varicella zoster (shingles)
- Yellow fever

10.9 APPENDIX 9: LIST OF OPPORTUNISTIC INFECTIONS

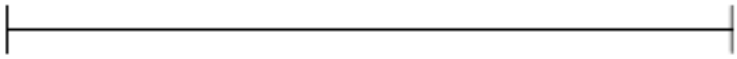
The list below is indicative and not exhaustive.

- Aspergillosis
- Blastomyces dermatitidis (endemic in the south-eastern and south-central states of the USA, along the Mississippi and Ohio Rivers)
- Candidiasis – only systemic or extensive mucosal or cutaneous cases
- 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 in tropical areas and the Tennessee-Ohio-Mississippi river basins)
- Listeriosis
- Mycobacterium avium
- Nontuberculosis mycobacteria
- Pneumocystis pneumonia

10.10 APPENDIX 10: VISUAL ANALOGUE SCALE

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

How troublesome are your symptoms of rhinosinusitis?



Not troublesome 10 cm **Worst thinkable troublesome**

10.11 APPENDIX 11: QUESTIONS FOR PARTICIPANTS WITH CRSWNP TO ASSIST DETERMINATION OF NERD DIAGNOSIS

The following questions are to assist the determination of nonsteroid anti-inflammatory drug exacerbated respiratory disease (NERD) diagnosis in participants with CRSwNP (12, 13, 14, 15):

QUESTION 1 - ***Have you ever had respiratory, nasal and/or bronchial, symptoms following the intake of aspirin or/and non-steroidal anti-inflammatory drugs (NSAID)?***

• **NO, I usually take aspirin or NSAID drugs →** the patient has not NERD.

• **NO, I don't take aspirin or NSAID drugs →** the patient unlikely has NERD but cannot be totally ruled out.

• **YES, only to one drug →** the patient likely has NERD. However, a potential IgE-mediated allergy to a specific NSAID should be further investigated

• **YES, to 2 or more drugs →** the patient most likely has NERD.

QUESTION 2 - ***While having a positive clinical history of NERD, have you ever undergone an aspirin provocation test, either nasal, bronchial, or oral?***

• **NO →** conclusion can be only obtained from clinical history.

• **YES, negative →** the patient unlikely has NERD but cannot be totally ruled out.

• **YES, positive →** confirms the patient has NERD.

DIAGNOSIS OF NERD:

• **Conditional**: only based on clinical history (question 1).

• **Strong**: based in both clinical history and provocation test (questions 1 and 2).

10.12 APPENDIX 12: DEFINITION OF ANAPHYLAXIS

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

(Adapted from Second symposium on the definition and management of anaphylaxis: Summary report— Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium [16])

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.

10.13 APPENDIX 13: ABBREVIATIONS

AD:	atopic dermatitis
ADR:	adverse drug reaction
AE:	adverse event
AESI:	adverse event of special interests
ALT:	alanine aminotransferase
AST:	aspartate aminotransferase
BUN:	blood urea nitrogen
CI:	confidence interval
CIOMS:	Council for International Organizations of Medical Sciences
COPD:	chronic obstructive pulmonary disease
COVID-19:	Coronavirus Disease 2019
CPK:	creatine phosphokinase, creatine phosphokinase
CRSwNP:	chronic rhinosinusitis with nasal polyposis
CSU:	chronic spontaneous urticaria
CT:	computerized tomography
DTP:	direct to patient
ECG:	electrocardiogram
e-CRF:	electronic case report form
EOS:	end of study
EOT:	end of treatment
EU:	European Union
FSH:	follicle-stimulating hormone
GDPR:	General Data Protection Regulation
GPSP:	Good Postmarketing Study Practice
HBcAb:	hepatitis B core antibody
HBsAb:	hepatitis B surface antibody
HBsAg:	hepatitis B surface antigen
HBV:	hepatitis B virus
hCG:	human chorionic gonadotropin
HCV:	hepatitis C virus
HCVAb:	hepatitis C virus antibody
HIV:	human immunodeficiency virus
HRT:	hormonal replacement therapy
ICF:	informed consent form
ICH:	International Council for Harmonisation
IGAR:	interferon-gamma release assay
IgM:	immunoglobulin M
IL:	interleukin
IL-4Rα:	interleukin-4 receptor alpha subunit
IMP:	investigational medicinal product
INCS:	intranasal corticosteroid
IRB:	Institutional Review Board

IVRS:	interactive voice response system
IWRS:	interactive web response system
LAR:	legally authorized representative
LMK:	Lund Mackay
mITT:	modified intention-to-treat
NC:	nasal congestion obstruction
NE:	nasal endoscopy
NERD:	nonsteroid anti-inflammatory drug exacerbated respiratory disease
NIMP:	noninvestigational medicinal product
NPS:	nasal polyp score
NSAID:	nonsteroid anti-inflammatory drug
OC:	osteomeatal complex
PCSA:	potentially clinically significant abnormality
PN:	prurigo nodularis
PP:	per protocol
PPE:	per protocol with extension term
PT:	preferred term
q2w:	every 2 weeks
q4w:	every 4 weeks
QTL:	quality tolerance limit
SAE:	serious adverse event
SAF:	safety population
SAFE:	safety population for extension term
SAP:	statistical analysis plan
SC:	subcutaneous
SCS:	systemic corticosteroid
SGOT:	serum glutamic-oxaloacetic transaminase
SGPT:	serum glutamic-pyruvic transaminase
SoA:	Schedule of Activities
SUSAR:	suspected unexpected serious adverse reaction
TB:	tuberculosis
TEAE:	treatment-emergent adverse event
TESAE:	treatment-emergent serious adverse event
TSS:	total symptom score
ULN:	upper limit of normal
US:	United States
VAS:	visual analogue scale
WBC:	white blood cell
WOCBP:	woman of childbearing potential
WOCF:	worst-observation carried forward

10.14 APPENDIX 14: PROTOCOL AMENDMENT HISTORY

Not applicable.

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