CLINICAL TRIAL PROTOCOL

Protocol title:	**A randomized, double-blind, placebo-controlled, parallel-group, 52-week Phase 3 trial to investigate the efficacy, safety, and tolerability of itepekimab in adult participants with inadequately-controlled chronic rhinosinusitis with nasal polyps**
Protocol number:	**EFC18418**
Amendment number:	**Not applicable**
Compound number (INN/Trademark):	**SAR440340** **Itepekimab/Not applicable**
Brief title:	**A Phase 3 study to assess the efficacy, safety, and tolerability of itepekimab (anti-IL-33 mAb) in participants with inadequately-controlled chronic rhinosinusitis with nasal polyps**
Acronym:	**CEREN-1**
Study phase:	**Phase 3**
Sponsor name: **Legal registered address:**	**Sanofi US Services Inc.** **55 Corporate Drive** **Bridgewater, NJ 08807**
Monitoring team's representative name and contact information	**Renny Raj** **Email: Renny.Raj@sanofi.com; Phone: 445-888-5173**

Regulatory agency identifier number(s):

IND:	134401
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Other:	Not applicable

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LIST OF ABBREVIATIONS

ACQ:	Asthma Control Questionnaire
ADA:	antidrug antibody(ies)
ADE:	adverse device effect
AE:	adverse event
AECOPD:	acute exacerbation(s) of chronic obstructive pulmonary disease(s)
AERD:	aspirin-exacerbated respiratory disease(s)
AESI:	adverse event of special interest
ALT:	alanine transferase
ANCOVA:	analysis of covariance
AST:	aspartate transferase
AxMP:	auxiliary medicinal product
BD:	bronchodilator
CFR:	Code of Federal Regulations
CI:	confidence interval
COPD:	chronic obstructive pulmonary disease(s)
CRS:	chronic rhinosinusitis
CRSsNP:	chronic rhinosinusitis without nasal polyp
CRSwNP:	chronic rhinosinusitis with nasal polyp(s)
CS:	corticosteroid(s)
CSR:	clinical study report
CT:	computed tomography
CXCL:	chemokine (C-X-C motif) ligand
DMC:	Data Monitoring Committee
DNA:	deoxyribonucleic acid
DPO:	data protection officer
ECG:	electrocardiography
eCRF:	electronic case report form
eDiary:	electronic diary
EOS:	end of study
EOT:	end of treatment
EQ-5D:	EuroQol-5 Dimensions
EQ-5D-5L:	EuroQol-5 Dimensions-5 Level
ETD:	early treatment discontinuation
EU:	European Union
FDA:	Food and Drug Administration
FEV1:	forced expiratory volume in 1 second
FSH:	follicle stimulating hormone
GCP:	Good Clinical Practice
GDPR:	General Data Protection Regulation
GPS:	Genetic Pathway Score
HBcAb:	hepatitis B core antibody(ies)
HBV:	hepatitis B virus
HCV:	hepatitis C virus

HIV:	human immunodeficiency virus
HR:	hazard ratio
HRQoL:	Health-Related Quality of Life
HRT:	hormone replacement therapy
IA:	interim analysis
IB:	Investigator brochure
ICD:	international classification of diseases
ICF:	informed consent form
ICH:	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IE:	intercurrent event
IEC:	Independent Ethics Committee
Ig:	immunoglobulin(s)
IL:	interleukin(s)
IM:	intramuscular
IMP:	investigational medicinal product
INCS:	intranasal corticosteroid(s)
IRB:	Institutional Review Board
IRT:	interactive response technology
ISF:	Investigator study file
ISR:	injection site reaction(s)
IV:	intravenous
JAK:	Janus kinase
LABA:	long-acting beta-agonist(s)
LAMA:	long-acting muscarinic antagonist(s)
LMK:	Lund Mackay Score
LOAC:	loss of asthma control
LoF:	loss of function
LS:	least squares
LTS:	long-term study
mAb:	monoclonal antibody(ies)
MFNS:	mometasone furoate nasal spray
MH:	Mantel-Haenszel
MI:	multiple imputation
NCS:	Nasal Congestion Score
NP:	nasal polyp
NPS:	Nasal Polyp Score
NSAID:	nonsteroidal anti-inflammatory drug
PCR:	polymerase chain reaction
PCSA:	potentially clinically significant abnormality
PFS:	prefilled syringe(s)
PGIC:	Patient Global Impression of Change
PGIS:	Patient Global Impression of Severity
PK:	pharmacokinetic(s)
PoC:	proof-of-concept
PRO:	patient-reported outcomes

PROMIS:	Patient-Reported Outcomes Measurement Information System
Q2W:	every 2 weeks
Q4W:	every 4 weeks
QoL:	quality of life
QTL:	quality tolerance limit(s)
RNA:	ribonucleic acid
RR:	risk ratio
SAE:	serious adverse event
SAP:	statistical analysis plan
SC:	subcutaneous
SCS:	systemic corticosteroid(s)
SD:	standard deviation
SD-SF-8b:	Sleep Disturbance-Short Form-8b
SEM:	standard error of the mean
SNOT:	Sino-Nasal Outcome Test
SUSAR:	suspected unexpected serious adverse reaction
TB:	tuberculosis
TE:	treatment-emergent
TEAE:	treatment-emergent adverse event
TNF:	tumor necrosis factor
TSLP:	thymic stromal lymphopoietin
TSS:	Total Symptom Score
ULN:	upper limit of normal range
UPSIT:	University of Pennsylvania Smell Identification Test
US:	United States
WOCBP:	woman/women of childbearing potential
WPAI-SHP:	Work Productivity and Activity Impairment-Specific Health Problem

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Protocol title:

A randomized, double-blind, placebo-controlled, parallel-group, 52-week Phase 3 trial to investigate the efficacy, safety, and tolerability of itepekimab in adult participants with inadequately-controlled chronic rhinosinusitis with nasal polyps

Brief title:

A Phase 3 study to assess the efficacy, safety, and tolerability of itepekimab (anti-IL-33 mAb) in participants with inadequately-controlled chronic rhinosinusitis with nasal polyps

Regulatory agency identifier number(s):

IND:	134401
NCT:	Not applicable
WHO:	U1111-1306-4858
EUDAMED:	Not applicable
EU trial number:	2024-516814-39
Other:	Not applicable

Rationale:

The CRS is an inflammatory disease of the mucosa of the nasal cavity and paranasal sinuses characterized by 12 weeks or more of at least 2 of the 4 cardinal symptoms: nasal obstruction, anterior or posterior nasal discharge, reduction or loss of sense of smell, and facial pain/pressure/fullness. In the US and Europe, it is estimated that CRS affects approximately 10% of the population (1, 2). Phenotypically CRS is divided mainly into 2 types based on the presence or absence of NP: CRS with NP (CRSwNP) and CRS without NP (CRSsNP).

CRSwNP is a complex inflammatory condition of the nasal and paranasal sinus mucosa. The etiology of CRSwNP is multifactorial and involves a combination of genetic, environmental, and immunological factors. A subset of patients with CRSwNP have asthma and AERD, which involves hypersensitivity to aspirin and other NSAIDs. Patients with concomitant asthma and AERD have more severe and difficult to control disease. In CRSwNP, there is a predominant type 2 inflammatory endotype (eosinophilic), however some patients present with non-type 2 inflammation (eg, macrophages, neutrophils) (3). In the US 87% of patients with CRSwNP have type 2 endotype (4), with relatively similar percentages in Europe (85%) and Australia (75%) (5). In Asia, while the contribution of type 2 inflammation has increased over time, the percentage of non-type 2 inflammation varies between 17% and 58% (5). However, recent studies show that the proportion of eosinophilic CRSwNP in China is as high as 73.7%, which is comparable to the data from Western countries (6, 7) Currently approved biologics for CRSwNP predominantly target type 2 inflammation (eg, anti-IL-5, anti-IL4-Rα, anti-IgE), however there is a significant proportion of patients that has an incomplete response to therapy. For example, in the SINUS trials of dupilumab in CRSwNP, ~35% of participants did not have an improvement of at least

1 point in the NPS, and ~54% did not have an improvement of at least 2 points in NPS (8). The development of novel therapies that aim to target type 2 and non-type 2 inflammatory pathways may provide an improved response to treatment.

IL-33 is a pro-inflammatory cytokine that triggers and amplifies inflammatory responses in both innate and adaptive immune systems, when epithelial cells are stressed or damaged due to exposure to inflammatory triggers. Multiple lines of evidence support the important role of IL-33 in CRSwNP. In a murine model of CRS, there was an increase in IL-33 expression in epithelial cells and in infiltrating immune cells, and IL-33 blockade resulted in decreased polypoid lesions, mucosal edema and thickness, subepithelial collagen layer and numbers of goblet cells (9). Moreover, in an animal model of AERD, one of the most recalcitrant forms of CRSwNP, levels of IL-33 were increased, and IL-33 blockade resulted in improved lung resistance after aspirin exposure (10). Additionally, these pre-clinical data are supported by translational data showing elevated IL-33 expression in both eosinophilic and non-eosinophilic CRSwNP, and by single cell RNA sequencing data showing elevated IL-33 expression in basal and endothelial cells from CRSwNP tissues (11).

Lastly and importantly, data from Regeneron Genetics Center using a new 5-variant IL-33 signaling GPS showed that NP (ICD10 code J33, 9061 cases and 422 513 allergy-free controls) was among the most significant associations with the IL-33 GPS. Specifically, data showed that individuals in the top 20% of the GPS, who are predicted to have higher IL-33 signaling, had 49% higher risk of NP ($p = 8 \times 10^{-62}$) and, for comparison, 22% higher risk of asthma ($p = 3 \times 10^{-115}$). When considering the rare IL-33 LoF variant separately, heterozygote carriers had 52% lower risk of NP ($p = 3 \times 10^{-7}$). These novel associations, which remained highly significant after excluding from the analysis individuals who have co-morbid asthma, establish NP as a novel indication for IL-33 blockade.

Itepekimab is a human IgG4P mAb, that binds IL-33 with subnanomolar affinity and thereby inhibits IL-33 signaling. In a mouse model of chronic airway inflammation, blocking IL-33 with itepekimab-normalized inflammatory markers associated with type 1 and type 2 inflammation, including eosinophils, neutrophils, and $ST2^+$ $CD4^+$ T cells (12). Moreover, in PoC studies, itepekimab showed efficacy in reducing both the rates of loss of asthma control in patients with moderate-to-severe asthma and the rates of COPD exacerbation in former smokers with COPD, highlighting the broad (type 2 and non-type 2) anti-inflammatory potential of IL-33 blockade with itepekimab (13).

To develop itepekimab as a potential treatment for CRSwNP, two Phase 3 studies (EFC18418 and EFC18419) are planned to support registration of itepekimab in the proposed CRSwNP indication. The objective of each of the Phase 3 studies is to investigate the efficacy and safety profile of 2 different dosage regimens of itepekimab compared to placebo over a period of 52 weeks in participants with CRSwNP treated with INCS with significant symptoms despite previous surgery and/or treatment with SCS.

Objectives and endpoints:

Objectives	Endpoints
Primary	
• To evaluate the efficacy of itepekimab compared with placebo on NP size and nasal congestion.	• Change from baseline to Week 24 in the endoscopic NPS. • Change from baseline to Week 24 in the NCS (co-primary).
Secondary	
• To evaluate the long-term efficacy of itepekimab compared with placebo on NP size.	• Change from baseline to Week 52 in endoscopic NPS (key secondary).
• To evaluate the long-term efficacy of itepekimab compared to placebo on nasal congestion.	• Change from baseline to Week 52 in NCS (key secondary).
• To evaluate the efficacy of itepekimab compared with placebo on sinus opacification.	• Change from baseline to Week 24 in opacification of sinuses assessed by CT scan using the LMK score.
• To evaluate the efficacy of itepekimab compared to placebo on symptoms of CRSwNP.	• Change from baseline to Weeks 24 and 52 in the TSS (nasal congestion/obstruction, anterior/posterior rhinorrhea, and loss of sense of smell).
• To evaluate the efficacy of itepekimab compared to placebo on sense of smell.	• Change from baseline to Weeks 24 and 52: - Loss of smell severity score using the daily CRSwNP sinonasal symptom eDiary. - UPSIT score.
• To evaluate the efficacy of itepekimab compared to placebo on health-related quality of life.	• Change from baseline to Weeks 24 and 52 in SNOT-22 total score.
• To evaluate the efficacy of itepekimab compared to placebo on sleep disturbance.	• Change from baseline to Weeks 24 and 52 in PROMIS SD-SF-8b scores.
• To evaluate the ability of itepekimab compared to placebo to reduce the risk of worsening/acute sinusitis requiring treatment with SCS or sinus surgery.	• Proportion of participants with CRSwNP requiring SCS or surgery for CRS. • Annualized rate of SCS course[a] or surgery for CRS during the planned study intervention period. • Time to first either SCS or surgery for CRS.
• To evaluate the effect of itepekimab compared to placebo on asthma in the subgroup of participants with comorbid asthma.	• Change from baseline to Weeks 24 and 52 in pre-BD FEV1 (in mL) in participants with co-morbid asthma. • Change from baseline to Weeks 24 and 52 in ACQ-5 score in participants with co-morbid asthma.
• To evaluate the effect of itepekimab compared to placebo in the subgroup of participants with AERD.	• Change from the baseline to Week 24 and 52 in NPS and NCS in the subgroup of participants with AERD. • Proportion of participants with AERD requiring SCS or surgery for CRS during the planned study intervention period. • Annualized rate of SCS course or surgery for CRS during the planned study intervention period in participants with AERD.

Objectives	Endpoints
	• Time to first either SCS or surgery for CRS in participants with AERD. • Change from baseline to Weeks 24 and 52 in pre-BD FEV1 (in mL) in participants with AERD.
• To evaluate the efficacy of itepekimab compared to placebo.	• Proportion of NPS responders at Weeks 24 and 52 (defined as participants with improvement by at least 1 point in NPS). • Proportion of NPS responders at Weeks 24 and 52 (defined as participants with improvement by at least 2 points in NPS).
• To evaluate the safety and tolerability of itepekimab compared to placebo in participants with CRSwNP.	• Incidence of TEAEs, TESAEs, TEAESIs and TEAEs leading to treatment discontinuation.
• To evaluate the PK of itepekimab.	• Itepekimab concentration in serum.
• Assessment of immunogenicity to itepekimab over time compared to placebo.	• Incidence of treatment-emergent anti-itepekimab antibody (ADA) responses throughout the study.

Abbreviations: ACQ = asthma control questionnaire; ADA = anti-drug antibody; AERD = aspirin-exacerbated respiratory disease; BD = bronchodilator; CRS = chronic rhinosinusitis; CRSwNP = chronic rhinosinusitis with nasal polyposis; CT = computed tomography; FEV = forced expiratory volume; LMK = Lund Mackay Score; NCS = Nasal Congestion Score; NP = nasal polyp; NPS = Nasal Polyposis Score; PK = pharmacokinetic(s); PROMIS = Patient-Reported Outcomes Measurement Information System; SCS = systemic corticosteroids; SD-SF = sleep disturbance short form; SNOT = Sino-Nasal Outcome Test; TEAE = treatment-emergent adverse event; TESAE = treatment-emergent serious adverse event; TEAESI = treatment-emergent adverse events of special interest; TSS = total symptoms score; UPSIT = University of Pennsylvania Smell Identification Test.

a Initiation of rescue therapy as defined in Section 6.9.1. A course of SCS is considered continuous if intervention is separated by less than 7 days.

For China, please see Section 10.8.1 details.

Overall design synopsis:

EFC18418 is a Phase 3 multinational randomized, double-blind, placebo-controlled trial with 3 parallel groups aimed at evaluating the efficacy, safety, and tolerability of 2 different dosing regimens of itepekimab in participants diagnosed with CRSwNP. During the study, participants will receive MFNS as INCS. In Japan, participants on INCS (MFNS or other INCS) will continue taking their daily INCS with a stable dose through all periods of the study. In Japan, participants not on INCS prior to screening, will receive MFNS during screening and throughout the study. In China, participants will continue their stable daily dose of INCS (which may include MFNS or other INCS) during the screening period and throughout the study. The study interventions consist of SC administration of itepekimab at a dose of 300 mg Q2W, itepekimab at a dose of 300 mg Q4W, or a matching placebo. A total of approximately 210 participants will be randomized in 1:1:1 fashion, and the intervention duration will be 52 weeks. Following the intervention period, an optional long term extension study may be available for participants in this study. Participants who are eligible and willing to participate in this study will directly roll over without a 20-week follow up period. For other participants (and in case the long- term extension study is not started or approved), participants will have a 20-week follow up period. It is estimated that approximately 95 sites may participate in this study.

Brief summary:

EFC18418 is a multinational, randomized, double-blind, placebo-controlled, parallel-group, Phase 3 study with 3 treatment groups. The purpose of the study is to evaluate the efficacy, safety and tolerability of 2 dosing regimens of itepekimab compared to placebo as add-on therapy to INCS in male and female participants with CRSwNP aged 18 years of age and older.

Study details include:

- The study duration (4-week screening, 52-week treatment, 20-week safety follow-up) will be up to 76 weeks. For participants transitioning to the LTS18420 study, the study duration will be 56 weeks.
- The treatment duration will be up to 52 weeks.
- The number of visits will be 9 site visits and 20 phone/home visits.

Number of participants:

Approximately 210 participants will be randomized.

Study arms and duration:

Participants who satisfy the inclusion criteria will be randomized (1:1:1) to one of the following IMP intervention group to be administered for the planned 52-week intervention duration:

- Itepekimab 300 mg, administered as a single SC injection Q2W.
- Itepekimab 300 mg, administered as a single SC injection Q4W with alternating SC injection of matching placebo at the 2-week interval between active IMP.
- Placebo, administered as a single SC injection of matching placebo to itepekimab Q2W.

Randomization will be stratified by asthma/AERD status (no asthma, asthma only, asthma & AERD), and region (Asia or rest of the world) (Appendix 14 Section 10.14 for AERD diagnosis).

Study intervention(s)

Investigational medicinal product(s)

Sterile itepekimab or matching placebo will be provided in PFS for SC administration. Each PFS contains a deliverable volume of 2 mL with an itepekimab concentration of 150 mg/mL or 0 mg/mL.

- Formulation: 2 mL solution for injections (150 mg/mL).
- Route(s) of administration: SC.
- Dose regimen: all participants will receive Q2W dosing to maintain the blind. Participants on Q4W will receive alternating doses of IMP and placebo.

AxMP

Mometasone nasal spray

- Formulation: Mometasone (50 µg/actuation) metered-dose nasal spray.
- Route(s) of administration: intranasal.
- Dose regimen: 2 actuations per nostril twice a day (total daily dose of 400 µg), starting at Visit 1, unless they are unable to tolerate or there is a specific regulatory requirement preventing use of this dose in which case they can stay on a lower dose regimen (200 µg) of MFNS.

Devices

The itepekimab PFS is classified as a combination product with an integral medical device where the principal mechanism of action is that of itepekimab. Medical devices for diagnostic interventions (eg, ECG) are not considered as 'investigational devices' in the context of this study.

Post-trial access to study medication

After the end of the study, a separate long-term study (LTS18420) may be offered to participants who completed the study and are still taking the IMP. This long-term study will allow to assess long-term safety and efficacy of the itepekimab and will be described in a separate protocol.

If the long-term study is not conducted, and depending on the participant’s unmet medical need, the non-availability of suitable alternative therapies, and an assessment of what is known about the benefits and risks of itepekimab, participants who have successfully completed their participation in this clinical trial will be eligible for post-trial access to itepekimab.

The Investigator/treating physician will determine if access to itepekimab is the best medical option for the participant and will then submit a request to the Sponsor, if allowed by local regulations.

Provision of itepekimab will be in compliance with all applicable national and local laws and regulations, including safety reporting obligations.

A participant will not be eligible for post-trial provision of itepekimab if his/her participation in the trial is terminated prematurely.

The Sponsor’s post-trial access responsibilities will need to be periodically re-evaluated. Based on new information about the investigational product (including adverse reactions), the continued health benefit to the individual and market availability of the product or alternative therapies, post-trial access may be terminated. This includes situations where the trial may be stopped due to safety concerns or other issues.

<u>Duration of study intervention</u>

Every participant will receive 52 weeks of intervention in the study.

Statistical considerations:

- **Co-primary endpoint:**

The co-primary endpoints are the change from baseline to Week 24 in bilateral endoscopic NPS and in NCS.

They will be analyzed by fitting an ANCOVA model with the baseline covariate and factors for treatment, asthma/AERD and region. Statistical inference obtained from all imputed data will be combined using Rubin's rule. Descriptive statistics including number of participants, mean, standard error, and LS means will be provided. In addition, difference in LS means and the corresponding 95% CI will be provided along with the p-values.

Intercurrent events:

- The following IEs will be handled with a composite variable strategy. Data after the IE will be assigned to the worst possible score:
  a) Use of selected prohibited/rescue medication (eg, prohibited biologic therapy).
  b) Nasal/sinus surgery prior to Week 24.
- The following IEs will be handled with a treatment policy strategy. All assessments after starting such IE and before or at Week 24 will be included:
  a) Use of SCS for any reason.
  b) Study intervention discontinuation.
  c) Use of other prohibited/rescue medications prior to Week 24.

Missing data handling:

After applying the rules for IEs, if there is still missing data, then the missing data will be handled as follows:

- For participants who discontinue IMP before Week 24 without use of selected prohibited/rescue medication (eg, prohibited biologic therapy) or nasal/sinus surgery prior to Week 24: MI approach will be used to impute missing endpoint value at Week 24, and this MI will use all participants from the same randomized arm, excluding participants who use selected prohibited/rescue medication (eg, prohibited biologic therapy) or nasal/sinus surgery prior to Week 24.

Each of the imputed complete datasets will be analyzed by fitting an ANCOVA model with the baseline covariate and factors for treatment, asthma/AERD and region. Statistical inference obtained from all imputed data will be combined using Rubin's rule. Descriptive statistics including number of participants, mean, standard error, and LS means will be provided.
In addition, difference in LS means and the corresponding 95% CI will be provided along with the p-values.

- **Main secondary endpoints:**

  a) **Continuous efficacy endpoints** including change from baseline in NPS and in NCS at Week 52, change from baseline in LMK score at Week 24, change from baseline in TSS, in Loss of Smell Symptom Severity score, in UPSIT score, in SNOT-22 total score and in PROMIS SD-SF-8b at Week 24 and Week 52: these endpoints will be analyzed in the same fashion as the co-primary endpoints described in Section 9.2.2.2.

  b) **Proportion endpoints,** including proportion of participants with CRSwNP requiring SCS or surgery for CRS during the planned study intervention period and proportions of NPS responders, will be analyzed using an MH method stratified by asthma/AERD strata and region. The estimate of the MH weighted risk difference and corresponding Wald 95% CI and Wald test using Sato variance will be provided. All data collected after study intervention discontinuation will be used in the analysis. Participants who discontinue the study without an event will be considered as no event.

  c) **Time to first SCS use or surgery for CRS** will be analyzed using a Cox regression model. The time to the first event will be included as the dependent variable while intervention group, screening asthma/AERD strata and region will be used as covariates. The HR will be estimated for comparison of each itepekimab regimen to placebo. The Kaplan-Meier method will be used to derive the probabilities that a participant would experience an event up to specific time points for each intervention group.

  d) **The annualized number of SCS course or surgery for CRS** during the planned study treatment will be analyzed using a negative binomial regression model. The model will include the number of SCS course or surgery for CRS during the planned study treatment period as the response variable, with intervention group, asthma/AERD strata and regions. Log transformed treatment duration will be the offset variable. The estimated annualized number of SCS courses or surgery for CRS for each treatment group and its 95% CI will be derived from the negative binominal model. The event rate ratio of each itepekimab regimen versus placebo and the corresponding 95% CI and p-values will be provided.

- **Interim analysis:**

  A non-binding futility IA will be planned after a minimum of approximately 90 pooled participants in the Phase 3 studies (EFC18418 and EFC18419) have completed at least a minimum of 24 weeks. More details in Section 9.3.

Data Monitoring/Other committee: Yes

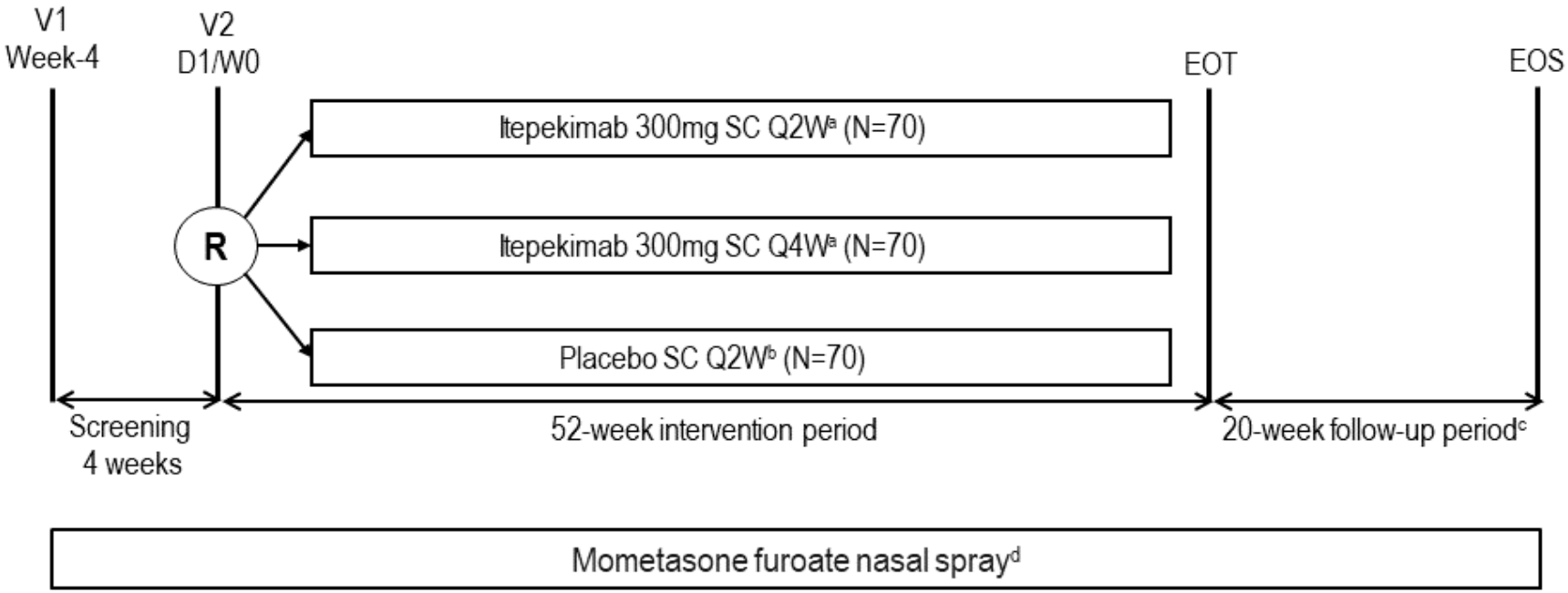
An independent DMC, which operates separately from the Sponsor, will monitor the study. The DMC functions are according to a DMC Charter and consists of external experts with relevant expertise in the diseases being studied, biostatistics, or clinical research. The main role of the DMC is to review safety and efficacy data throughout the trial, in order to evaluate the balance between benefits and risks.

The DMC will also examine the trial results and provide appropriate recommendations to the Sponsor regarding the conduct of the clinical trial.

In their advisory capacity, the DMC provides recommendations to the Sponsor.
It is the responsibility of the Sponsor to promptly review and consider the DMC's recommendations in a timely manner. The recommendations may pertain to continuing the trial as planned, making modifications to the trial design or procedures, or even potentially terminating the trial if deemed necessary.

1.2 SCHEMA

Figure 1 - Graphical study design



Abbreviations: D = day; EOS = end of study; EOT = end of treatment; IMP = investigational medicinal product; MFNS = mometasone furoate nasal spray; N = number; Q2W = once every 2 weeks; Q4W = once every 4 weeks; R = randomization; SC = subcutaneous; V = visit; W = week.

a Itepekimab 300 mg administered as 1 SC injection Q2W. Q4W dosing will receive alternating doses of the active IMP and placebo Q2W.

b Placebo, administered as 1 SC injection of matching placebo to itepekimab SC Q2W.

c For participants not entering the long-term extension study.

d MFNS administered as 2 actuations per nostril twice a day (total daily dose of 400 µg), starting at Visit 1, unless they are unable to tolerate or there is a specific regulatory requirement preventing use of this dose in which case they can stay on a lower dose regimen (200 µg) of MFNS. In Japan, participants on INCS (MFNS or other INCS) will continue taking their daily INCS with a stable dose through all periods of the study. In Japan, participants not on INCS prior to screening, will receive MFNS during screening and throughout the study. China participants should be on daily treatment with intranasal corticosteroids (INCS) which may include MFNS, prior to screening and will continue their daily INCS with a stable dose as background treatment during the screening and throughout the study.

1.3 SCHEDULE OF ACTIVITIES (SOA)

Procedure	Screening[a]	Intervention Period										EOT/ETD[b]	Follow-up (20 weeks) /EOS[c]	Notes
Week	**-4**	**0**	**2**	**4**	**6, 8, 10**	**12**	**14, 16, 18, 20, 22**	**24**	**26, 28, 30, 32, 34**	**36**	**38, 40, 42, 44, 46, 48, 50**	**52**	**72**	
Visit[d]	**1 (site)**	**2 (site)**	**3 (site)**	**4 (site)**	**5-7 (home/call)**	**8 (site)**	**9-13 (home/call)**	**14 (site)**	**15-19 (home/call)**	**20 (site)**	**21-27 (home/call)**	**28 (site)**	**29 (site)**	
Days[e]	**-28**	**1**	**15**	**29**	**43, 57, 71**	**85**	**99, 113, 127, 141, 155**	**169**	**183, 197, 211, 225, 239**	**253**	**267, 281, 295, 309, 323, 337, 351**	**365**	**505**	
Informed consent[f]	X													
Inclusion and exclusion criteria	X	X												[Recheck clinical status before randomization and/or first dose of investigational intervention.]
Participant demographics	X													
Medical/surgical history[g]	X													Substances: [drugs, alcohol, tobacco, and caffeine]
AERD screening questionnaire[h]	X													
Record planned endoscopic sinus surgery[i]	X	<---------- Every 2 weeks ---------->												
Nasal endoscopy[j]	X	X						X				X	X	Central reading

Procedure	Screening[a]	Intervention Period										EOT/ETD[b]	Follow-up (20 weeks) /EOS[c]	Notes
Week	**-4**	**0**	**2**	**4**	**6, 8, 10**	**12**	**14, 16, 18, 20, 22**	**24**	**26, 28, 30, 32, 34**	**36**	**38, 40, 42, 44, 46, 48, 50**	**52**	**72**	
Visit[d]	**1 (site)**	**2 (site)**	**3 (site)**	**4 (site)**	**5-7 (home/call)**	**8 (site)**	**9-13 (home/call)**	**14 (site)**	**15-19 (home/call)**	**20 (site)**	**21-27 (home/call)**	**28 (site)**	**29 (site)**	
Days[e]	**-28**	**1**	**15**	**29**	**43, 57, 71**	**85**	**99, 113, 127, 141, 155**	**169**	**183, 197, 211, 225, 239**	**253**	**267, 281, 295, 309, 323, 337, 351**	**365**	**505**	
Prior/concomitant/rescue medications	X	<---------- Every 2 weeks ---------->											X	
Smoking status	X	X	X	X		X		X		X		X	X	Smoking history at Visit 1 and smoking status at all other indicated visits
Study intervention administration														
IRT	X	X	X	X		X		X		X		X		
Randomization		X												
IMP administration[k]		<---------- Q2W ---------->												
AxMP dispensation	<----------										---------->			
Efficacy assessments														
CT scan[l]		X						X						
Dispense/collect symptom diary[m]	X												X	

Procedure	Screening[a]	Intervention Period										EOT/ETD[b]	Follow-up (20 weeks) /EOS[c]	Notes
Week	**-4**	**0**	**2**	**4**	**6, 8, 10**	**12**	**14, 16, 18, 20, 22**	**24**	**26, 28, 30, 32, 34**	**36**	**38, 40, 42, 44, 46, 48, 50**	**52**	**72**	
Visit[d]	**1 (site)**	**2 (site)**	**3 (site)**	**4 (site)**	**5-7 (home/call)**	**8 (site)**	**9-13 (home/call)**	**14 (site)**	**15-19 (home/call)**	**20 (site)**	**21-27 (home/call)**	**28 (site)**	**29 (site)**	
Days[e]	**-28**	**1**	**15**	**29**	**43, 57, 71**	**85**	**99, 113, 127, 141, 155**	**169**	**183, 197, 211, 225, 239**	**253**	**267, 281, 295, 309, 323, 337, 351**	**365**	**505**	
Spirometry in participants with asthma only[n]		X		X				X				X	X	
SNOT-22[o]		X		X		X		X		X		X	X	
Symptom Diary[m]	<----------Daily---------->													
UPSIT (in countries where available)		X						X				X		
ACQ-5 in participants with asthma only[o]		X		X		X		X				X	X	
EQ-5D-5L[o]		X				X		X		X		X	X	
PROMIS SD-SF-8b[o]		X				X		X		X		X		
Leicester cough questionnaire[o]		X				X		X				X		
HCRU		X				X		X		X		X	X	
WPAI-SHP[o]		<----------Q4W---------->												
PGIS[o]		X				X		X		X		X	X	
PGIC[o]						X		X		X		X	X	

Procedure	Screening[a]	Intervention Period										EOT/ETD[b]	Follow-up (20 weeks) /EOS[c]	Notes
Week	**-4**	**0**	**2**	**4**	**6, 8, 10**	**12**	**14, 16, 18, 20, 22**	**24**	**26, 28, 30, 32, 34**	**36**	**38, 40, 42, 44, 46, 48, 50**	**52**	**72**	
Visit[d]	**1 (site)**	**2 (site)**	**3 (site)**	**4 (site)**	**5-7 (home/call)**	**8 (site)**	**9-13 (home/call)**	**14 (site)**	**15-19 (home/call)**	**20 (site)**	**21-27 (home/call)**	**28 (site)**	**29 (site)**	
Days[e]	**-28**	**1**	**15**	**29**	**43, 57, 71**	**85**	**99, 113, 127, 141, 155**	**169**	**183, 197, 211, 225, 239**	**253**	**267, 281, 295, 309, 323, 337, 351**	**365**	**505**	
Safety assessments														
Physical examination Full = Mandatory Brief = if clinically indicated	Full	Brief	Brief	Brief		Brief		Brief		Brief		Full	Brief	
Vital signs[p]	X	X	X	X		X		X		X		X		
12-Lead ECG[q]	X											X		
Hematology, clinical chemistry[r]	X					X		X		X		X	X	
Urine analysis[s]	X							X				X		Central urinalysis
TB testing	X													Per local guidelines (local laboratory)
Hepatitis and HIV serology tests[t]	X													
Pregnancy (β-HCG blood) test[u]	X													

Procedure	Screening[a]	Intervention Period										EOT/ETD[b]	Follow-up (20 weeks) /EOS[c]	Notes
Week	**-4**	**0**	**2**	**4**	**6, 8, 10**	**12**	**14, 16, 18, 20, 22**	**24**	**26, 28, 30, 32, 34**	**36**	**38, 40, 42, 44, 46, 48, 50**	**52**	**72**	
Visit[d]	**1 (site)**	**2 (site)**	**3 (site)**	**4 (site)**	**5-7 (home/call)**	**8 (site)**	**9-13 (home/call)**	**14 (site)**	**15-19 (home/call)**	**20 (site)**	**21-27 (home/call)**	**28 (site)**	**29 (site)**	
Days[e]	**-28**	**1**	**15**	**29**	**43, 57, 71**	**85**	**99, 113, 127, 141, 155**	**169**	**183, 197, 211, 225, 239**	**253**	**267, 281, 295, 309, 323, 337, 351**	**365**	**505**	
Urine pregnancy test[u]		<----------									---------->		X	
AEs/SAEs	<----------												---------->	
PK and ADA														
Serum PK samples for itepekimab concentration[v]		X		X		X		X		X		X	X	
Anti-itepekimab antibody[v]		X				X		X				X	X	
Biomarkers														
Blood biomarkers[w]		X		X		X		X				X	X	
Nasal Absorption biomarkers (optional)[x]		X		X		X		X				X		
Urine biomarkers[y]		X		X		X		X				X		
Nasal brushing for RNA and cytology (optional)[z]		X		X				X				X		
Archival Serum/Plasma (optional)[aa]		X		X		X		X				X		

Procedure	Screening[a]	Intervention Period										EOT/ETD[b]	Follow-up (20 weeks) /EOS[c]	Notes
Week	**-4**	**0**	**2**	**4**	**6, 8, 10**	**12**	**14, 16, 18, 20, 22**	**24**	**26, 28, 30, 32, 34**	**36**	**38, 40, 42, 44, 46, 48, 50**	**52**	**72**	
Visit[d]	**1 (site)**	**2 (site)**	**3 (site)**	**4 (site)**	**5-7 (home/call)**	**8 (site)**	**9-13 (home/call)**	**14 (site)**	**15-19 (home/call)**	**20 (site)**	**21-27 (home/call)**	**28 (site)**	**29 (site)**	
Days[e]	**-28**	**1**	**15**	**29**	**43, 57, 71**	**85**	**99, 113, 127, 141, 155**	**169**	**183, 197, 211, 225, 239**	**253**	**267, 281, 295, 309, 323, 337, 351**	**365**	**505**	
Whole blood DNA/ IL-33/ST2 genomic variant analyses (optional)[aa]		X												

Abbreviations: ACQ = asthma control questionnaire; ADA = antidrug antibody; AE = adverse event; AERD = aspirin-exacerbated respiratory disease; AESI = adverse event of special interest; ALT = alanine aminotransferase; AST = aspartate aminotransferase; ATS = American Thoracic Society; AxMP = auxiliary medicinal product; BD = bronchodilator(s); CT = computed tomography; CRSwNP = chronic rhinosinusitis with nasal polyposis; DNA = deoxyribonucleic acid; ECG = electrocardiography; eDiary = electronic diary; eCRF = electronic case report form; ECP = eosinophil cationic protein; CRP = C-reactive protein; CSF = colony stimulating factor; CXCL = chemokine (C-X-C motif) ligand; EOS = end of study; EQ-5D-5L = EuroQol-5 dimension-5 level; EOT = end of treatment; ERS = European Respiratory Society; ETD = early treatment discontinuation; FEF = forced expiratory flow; FEV = forced expiratory volume; FVC = forced vital capacity; GGT = gamma-glutamyl transferase; HBcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCG = human chorionic gonadotropin; HCRU = health care resource utilization; HCV = hepatitis C virus; HCVAb = hepatitis C virus antibodies; HIV = human immunodeficiency virus; IEC = Independent Ethics Committee; IFN-γ = interferon-gamma; Ig = immunoglobulin; IL = interleukin; IMP = investigational medicinal product; INCS = intranasal corticosteroids; IRB = Institutional Review Board; IRT = interactive response technology; ISR = injection site reaction; LABA = long-acting beta-agonists; LAMA = long-acting muscarinic antagonist; LTE4 = Leukotriene E4; LTS = long-term study; MFNS = mometasone furoate nasal spray; NCS = Nasal Congestion Score; NPS = Nasal Polyposis Score; PGIC = Patient Global Impression of Change; PGIS = Patient Global Impression of Severity; PGx = pharmacogenomics; PK = pharmacokinetics; PRO = patient-reported outcome; PROMIS = Patient-Reported Outcomes Measurement Information System; Q2W = every 2 weeks; Q4W = every 4 weeks; RNA = ribonucleic acid; SAE = serious adverse event; SCS = systemic corticosteroids; SD-SF = Sleep Disturbance Short Form; SNOT = Sino-Nasal Outcome Test; SoA = schedule of activities; TARC = thymus and activation-regulated chemokine; TB = tuberculosis; TNF = tumor necrosis factor; TSS = Total Symptom Score; UPSIT = University of Pennsylvania Smell Identification Test; sST2 = soluble suppression of tumorigenicity 2; WOCBP = women of childbearing potential; WPAI-SHP = Work Productivity and Activity Impairment Specific Health Problem.

a The screening period is 28 days +/- 7 days in duration to run in any participant on MFNS, and to collect baseline data. In Japan, participants on INCS (MFNS or other INCS) will continue taking their daily INCS with a stable dose through all periods of the study. In Japan, participants not on INCS prior to screening, will receive MFNS during screening and throughout the study. China participants should be on daily treatment with INCS prior to screening and will continue their daily INCS with a stable dose as background treatment during the screening and throughout the study. Participants receiving rescue medication with SCS or/and surgery during this period will not be randomized. Randomization Visit is defined as Day 1. All subsequent visits will be calculated using this as a reference. Window for subsequent visits is +/-3 days. Assessments/procedures at a site visit are performed in the following order if applicable: PROs and other questionnaires; procedures; safety and laboratory assessments; IMP administration.

b Participants who prematurely discontinue from the study prior to completing the planned treatment period (ie, ETD), will attend the ETD visit and follow the assessments for EOT as shown in this table, and will be requested to attend the remaining follow up visits per the protocol schedule with a +/- 5-day window until the EOS.

c Follow-up period is not applicable for those participants entering a LTS18420 if a LTS18420 for itepekimab is initiated and approved by Health Authorities and country and/or local IRB/IEC. In the absence of a LTS18420 all participants enter the follow-up period.

d Home visits/phone calls will be conducted at the following timepoints: Week 6 (Visit 5), Week 8 (Visit 6), Week 10 (Visit 7), Week 14 (Visit 9), Week 16 (Visit 10), Week 18 (Visit 11), Week 20 (Visit 12), Week 22 (Visit 13), Week 26 (Visit 15), Week 28 (Visit 16), Week 30 (Visit 17), Week 32 (Visit 18), Week 34 (Visit 19), Week 38 (Visit 21), Week 40 (Visit 22), Week 42 (Visit 23), Week 44 (Visit 24), Week 46 (Visit 25), Week 48 (Visit 26), Week 50 (Visit 27).

e Window of +/-3 days applies to all visits during IMP administration. Follow up/EOS has a +/-7 day window.

f Separate consent to be obtained for optional procedures (whole blood DNA, and serum/plasma sampling for archival; nasal brushing for RNA and cytology, blood for genomic variant analyses), and potentially for HIV test, if specific consent is locally required.

g Past medical history including allergic comorbidities (asthma, aspirin sensitivity, allergic rhinitis etc), surgeries will be assessed including type and dates of sinonasal surgeries in the past. SCS use (number of courses, doses, way of administration and duration) in the past 2 years before Visit 1 and/or contraindication/intolerance to SCS, as well as long-term antibiotics use (>2 weeks) in the previous year will be entered in the eCRF.

h See Appendix 14 Section 10.14 for AERD screening questionnaire.

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

j Nasal endoscopy (including use of decongestants before the procedure) will be performed after all other efficacy assessments have been completed for each visit and prior to IMP administration. Standard video sequences will be downloaded by the investigator to the central reader's secured Internet site. For eligibility central reading of Visit 1 will be used. At Visit 2 investigator reviews Visit 1 results from central reader to confirm inclusion criteria. Investigator then reconfirms eligibility based on review of Inclusion/Exclusion Criteria and by investigator's Visit 2 endoscopy local reading. This local read is solely for the purpose of confirming eligibility. The Visit 2 endoscopy will then be centrally read for NPS determination for outcome assessment.

k IMP (itepekimab or placebo) to be administered Q2W at the site. Participants should be monitored by site personnel for at least 30 minutes after administration of the first 3 IMP injections. Monitoring period may be extended as per country-specific requirements. Starting after Visit 4 (Week 4), IMP will be administered by the participant, caregiver, or healthcare professional at the participant's home or in a healthcare facility, depending on what is chosen, according to treatment allocation. If the participant or Investigator decides not to administer IMP at home, the IMP injections can be performed at the site. The last dose will be given 2 weeks prior to the planned EOT visit (Week 50).

l A CT scan should be performed at the Randomization Visit (up to 7 days before first administration of IMP), at Visit 14 (Week 24) +/- 7 days, and central reading will be used for comparison of baseline to Week 24. In countries for which a specific approval procedure for the CT scan is required by a different committee than the IEC/IRB, these countries will be exempted from all the planned study CT scans until approval from these committees is received. It is recommended to avoid the use of SCS as rescue therapy during Week 20 to Week 24. If a participant must use SCS during this period to control CRSwNP worsening/acute sinusitis based on Investigator judgment, the site should make every effort to schedule the Week 24 CT scan prior to SCS rescue therapy.

m An eDiary (ie, CRSwNP sinonasal symptom diary) is used for daily recording of nasal symptoms (from Visit 1 to EOS): 1) nasal congestion/obstruction, 2) anterior rhinorrhea (runny nose), 3) posterior rhinorrhea (post-nasal drip), 4) loss of sense of smell, 5) facial pain/pressure, and 6) headache. This device is dispensed at Visit 1, and information is downloaded from this device on the other indicated days. For endpoints defined using the data collected on the eDiary (such as NCS and TSS), baseline is defined as the average of the scores in the 7 days prior to randomization. Completion of a minimum of 4 out of 7 days is required prior to randomization.

n Spirometry will be performed according to ERS/ATS guidance only in participants with asthma. Pre-BD spirometry will be performed during a washout period of BDs according to their duration of action following the guidance of the ERS/ATS 2019 guideline. For example, withholding the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours, withholding the last dose of ipratropium for at least 12 hours, withholding the last dose of LABA for at least 24 hours, and finally the last dose of ultra long-acting LABA (eg, vilanterol) or the last dose of LAMA should be withheld for at least 36 hours before spirometry is performed. The timing of washout will be verified before performing the measurements.

o During the study participants' responses to the SNOT-22; PGIS, PGIC, EQ-5D-5L, WPAI:SHP, PROMIS SD-SF-8b; ACQ-5 (in participants with asthma), and Leicester cough questionnaire will be recorded in an electronic format.

p Including blood pressure (mmHg), heart rate (beats per minute), respiratory rate (breaths per minute), body temperature (degrees Celsius). Height (cm) will be measured only at Screening. Weight (kg) will be measured at screening and Week 52/EOT.

q ECG will be collected and read locally.

r Hematology will include hemoglobin, hematocrit, platelet count, total red blood cell count, and total white blood cell count with differential. Serum clinical chemistry will include creatinine, blood urea nitrogen, glucose (fasting), lactate dehydrogenase, total cholesterol, total protein, calcium, albumin, total and direct bilirubin, ALT, AST, GGT, alkaline phosphatase, electrolytes (sodium, potassium, bicarbonate), CRP, and creatine phosphokinase. Blood eosinophils and CRP will be blinded after Visit 2.

s Specific gravity pH, glucose, protein, blood, ketones, nitrite, leukocyte esterase Microscopic examination (if blood or protein is abnormal).

t Clinical laboratory testing at Screening (Visit 1) will include a hepatitis screen covering HBsAg, HBsAb, HBcAb IgM and total, HCVAb, HIV screen (anti-HIV-1 and HIV-2 antibodies). In case of results showing HBsAg (negative), and HBcAb total (positive), HBV DNA testing will be performed prior to randomization to rule out a false positivity to clarify the serological status. In case of results showing HCVAb (positive), HCV RNA testing will be performed to rule out a false positivity. In case of results showing positive anti-HIV-1 or anti-HIV-2 antibodies, reflex confirmation testing will be conducted.

u Only for WOCBP: a serum pregnancy test will be performed at Screening (Visit 1); urine pregnancy tests will be performed at the following visits: Visit 2, Visit 4, Visit 6, Visit 8, Visit 10, Visit 12, Visit 14, Visit 16, Visit 18, Visit 20, Visit 22, Visit 24, Visit 26, Visit 28 (the visits listed in the SoA table). A negative result must be obtained at Visit 1 and at Visit 2 prior to randomization. In case of a positive urine test, the study intervention will be withheld and a serum pregnancy test performed as soon as possible to confirm the pregnancy. Pregnancy will lead to definitive treatment discontinuation in all cases. Sufficient amount of urine pregnancy test kits will be provided to WOCBP for visits that can be performed with a phone call. The outcome of monthly home urine pregnancy tests will be recorded and communicated to the site during the phone visits. See Section 8.3.5 of the Protocol – Pregnancy testing for instruction on timepoints.

v Systemic drug concentration and ADA samples are to be collected prior to dosing. If an SAE and/or AESI occurs related to anaphylaxis, systemic hypersensitivity reaction, and/or severe ISR lasting more than 24 hours, additional blood samples may be collected for determination of functional itepekimab concentration (PK), and/or ADA assessment at or near the onset of the event.

w Blood biomarkers may include but are not limited to: total IgE, TARC, eotaxin-3, periostin, ECP, IL-5, IL-13, IFN-y, IL-17A, IL-33, sST2. All biomarkers (except for blood neutrophil and eosinophil count) can be considered optional in China.

x Nasal absorption biomarkers may include but are not limited to: IFN-y, IL-5, IL-17A, IL-33, TNF-α, IL-17F, IL-22, IL-13, CXCL8 (IL-8), IL-4, IL-6, IL-1β, tryptase, CXCL9, CXCL10, CSF3. All biomarkers (except for blood neutrophil and eosinophil count) can be considered optional in China.

y Urine biomarkers: LTE4 and creatinine. All biomarkers (except for blood neutrophil and eosinophil count) can be considered optional in China.

z Optional at participating sites and requires additional informed consent. The nasal brushing should be performed after the NPS central video and nasal secretion collection. Nasal brushings are optional for participants enrolled in China.

aa Optional serum/plasma samples may be used for research purposes related to respiratory diseases such as CRS or inflammatory diseases (eg, exploratory biomarkers of disease or drug effect), pathway biology, additional drug safety assessments, or development and validation of bioassay methods beyond those defined in the present protocol. Optional DNA sample may be collected once during the study. Pharmacogenetics informed consent is required. Genetic analyses will be optional for participants enrolled in China.

2 INTRODUCTION

Itepekimab (also referred to as REGN3500/SAR440340), is a human IgG 4P mAb that binds IL-33 with subnanomolar affinity and thereby inhibits IL-33 signaling. This antibody is currently being investigated as a potential innovative therapy for COPD, and in a POC study in noncystic fibrosis bronchiectasis.

2.1 STUDY RATIONALE

CRS is an inflammatory disease of the mucosa of the nasal cavity and paranasal sinuses characterized by 12 weeks or more of the following cardinal symptoms: nasal obstruction, anterior or posterior nasal discharge, reduction or loss of sense of smell, and facial pain/pressure/fullness. In the US and Europe it is estimated that CRS affects approximately 10% of the population (1, 2). The etiology and pathophysiology of CRS are incompletely understood with data supporting the role of environmental and host factors in the development of disease (14). Phenotypically, CRS is divided mainly into 2 types based on the presence or absence of NP: CRS with NP (CRSwNP) and CRS without NP (CRSsNP).

In CRSwNP, there is a predominant type 2 inflammatory endotype (eosinophilic), however some patients present with non-type 2 inflammation (macrophages, neutrophils) (3). In the US 87% of patients with CRSwNP have type 2 endotype (4) with relatively similar percentages in Europe (85%) and Australia (75%) (5). In Asia, while the contribution of type 2 inflammation has increased overtime, the percentage of non-type 2 inflammation varies between 17% and 58% (5). However, recent studies show that the proportion of eosinophilic CRSwNP in China is as high as 73.7%, which is comparable to the data from Western countries (6, 7). Currently approved biologics for CRSwNP target type 2 inflammation (eg, anti-IL-5, anti-IL4-Rα, anti-IgE). These therapies are associated with incomplete responses, eg, in the SINUS trials of dupilumab in CRSwNP, ~65% of participants had an improvement of at least 1 point in the NPS, and ~46% had an improvement of at least 2 points in the NPS (8). The partial response to therapy and the lack of targeting of non-type 2 inflammation highlight the critical unmet medical need and the importance of developing novel therapies that could target type 2 and non-type 2 inflammatory pathways.

IL-33 is a pro-inflammatory cytokine that triggers and amplifies inflammatory responses in both innate and adaptive immune systems when epithelial cells are stressed or damaged due to exposure to inflammatory triggers. Multiple lines of evidence support the important role of IL-33 in CRSwNP. In a murine model of CRS, there was an increase in IL-33 expression in epithelial cells and in infiltrating immune cells, IL-33 blockade resulted in decreased polypoid lesions, mucosal edema and thickness, subepithelial collagen layer and numbers of goblet cells (9). Moreover, in an animal model of AERD, one of the most recalcitrant forms of CRSwNP, levels of IL-33 are increased, and IL-33 blockade resulted in improved lung resistance after aspirin exposure (10). Additionally, these preclinical data are supported by translational data showing elevated IL-33 expression in both eosinophilic and noneosinophilic CRSwNP, and by single cell RNA sequencing data showing elevated IL-33 expression in basal and endothelial cells from CRSwNP tissues (11).

Lastly and importantly, data from the Regeneron Genetics Center using a new 5-variant IL-33 signaling GPS showed that NP (ICD10 code J33, 9061 cases and 422 513 allergy-free controls) was among the most significant associations with the IL-33 GPS. Specifically, data showed that individuals in the top 20% of the GPS, who are predicted to have higher IL-33 signaling, had 49% higher risk of NP ($p = 8 \times 10^{-62}$) and, for comparison, 22% higher risk of asthma ($p = 3 \times 10^{-115}$). When considering the rare IL-33 LoF variant separately, heterozygote carriers had 52% lower risk of NP ($p = 3 \times 10^{-7}$). These novel associations establish NP as a novel indication for IL-33 blockade.

In a mouse model of chronic airway inflammation, blocking IL-33 with itepekimab-normalized persistent and exacerbating inflammatory markers, including eosinophilic, neutrophilic, and $ST2^+$ $CD4^+$ T-cell infiltration (12). Moreover, in PoC studies, itepekimab showed efficacy in both the rates of loss of asthma control in patients with moderate-to-severe asthma and the rates of COPD exacerbation in former smokers with COPD, highlighting the broad (type 2 and non-type 2) anti-inflammatory potential of IL-33 blockade with itepekimab (13).

To develop itepekimab as a potential treatment for CRSwNP, a randomized, double-blind, placebo-controlled study is planned. The study aims to assess the effect of itepekimab in addition to INCS. This Phase 3 study will evaluate the efficacy and safety profile of 2 different dosage regimens of itepekimab compared to placebo over a period of 52 weeks. The study will enroll participants with CRSwNP with significant symptoms despite use of INCS, previous surgery and/or treatment with SCS. The key objective of this study will be to evaluate the clinical efficacy and safety profile of itepekimab administered as add-on therapy to CRSwNP participants with difficult-to-treat disease.

A detailed description of the chemistry, pharmacology, efficacy, and safety of itepekimab is provided in the IB.

2.2 BACKGROUND

CRSwNP is a clinical condition characterized by the presence of multiple polyps in the upper nasal cavity, originating from the osteomeatal complex and the spheno-ethmoid recess and characterized by mucosal inflammation of the nasal cavity and paranasal sinuses with symptoms lasting more than 12 weeks. Clinically, CRSwNP is defined by long-term symptoms (>12 weeks) of nasal obstruction and congestion, reduction in or loss of sense of smell, anterior and posterior rhinorrhea. These symptoms can impact greatly upon a patient's QoL.

Beyond the sinonasal symptoms, patients with CRS suffer from fatigue (approximately 54%) (15). Poor sleep quality is reported in approximately 75% of patients (16). Further, a case-control study found that patients with CRS have worse cognitive scores on a standardized questionnaire than healthy controls (17). Importantly, cognitive function improves with medical or surgical treatment of CRS. In addition, rates of depression in patients with CRS exceed those of the general population, with recent data showing an estimated HR of 1.56 (95% CI 1.43-1.79) (18, 19).

The presence or absence of polyps is confirmed by performing endoscopy. Coronal CT scans can confirm the presence and extent of sinus and polyp involvement. With an estimated prevalence of 2% to 4% across multiple populations (20, 21, 22, 23), CRSwNP has a high burden of symptoms and associated co-morbidities, and a high relapse rate after treatment. Treatment options for patients with CRSwNP range from local or systemic CS to functional endoscopic sinus surgery, and biologics targeting type 2 inflammation.

NPs are most commonly thought to be caused by allergy, although a significant number is associated with no respiratory or allergic trigger that can be demonstrated. Risk factors include genetic susceptibility, anatomic abnormalities, infection, local immunologic imbalance and eicosanoid dysmetabolism (manifested as aspirin intolerance), some or most of which may play a role in its pathogenesis (24, 25, 26).

Asthma is an important co-morbid condition in patients with CRSwNP. The prevalence of asthma in general populations of patients with CRSwNP varies widely from 2% to 66% (15), however, this percentage increases from 68% to 91% in patients with refractory CRSwNP (27, 28). In Phase 3 trials of CRSwNP, the percentage of patients with asthma varied from 59% to 71% (8, 29). This study will recruit a minimum of approximately 65% participants with asthma.

Another subgroup of patients with CRSwNP that presents with difficult-to-treat disease, are those patients with AERD (or NSAID-exacerbated respiratory disease), with the Samter triad of aspirin sensitivity, asthma and NP (30). In clinical trials of biologics in difficult-to-treat CRSwNP, the percentage of AERD participants varied from 17% to 39% (31). This is a subpopulation of patients with high unmet need, not previously selectively targeted in CRSwNP trials with biologics. This study is anticipated to enroll approximately a minimum of 25% of participants with AERD (8, 29).

CRS is also associated with increased societal burden, with significant increase in health care expenditures in patients with CRS compared to controls. In the US, the indirect societal cost linked to absenteeism and decreased productivity is estimated at 61.2 million potential workdays missed (15), which results in a total decreased productivity cost of approximately 13 billion dollars annually (32).

Current available therapies include nasal and oral CS, type 2 targeting biologics, and in recalcitrant cases - sinonasal surgery. There remains, however, an unmet medical need to treat patients with non-type 2 inflammation and those who are non-responders to existing biologics, with significant impact on patient well-being and societal burden. Itepekimab with its novel mechanism of action targeting both type 2 and non-type 2 inflammation may become a novel effective treatment option for CRSwNP patients.

A detailed description of the chemistry, pharmacology, efficacy, and safety of itepekimab is provided in the IB.

2.3 BENEFIT/RISK ASSESSMENT

To date, no risks with itepekimab have been regarded as identified important risks. More detailed information about the known and expected benefits and risks and reasonably expected AEs of itepekimab may be found in the IB.

2.3.1 Risk assessment

Based on our completed clinical studies, the AE profile indicates that itepekimab is generally well tolerated in participants with COPD and asthma. Like other mAbs, there is a potential risk of systemic hypersensitivity reactions (including immunogenicity) associated with itepekimab administration. Due to its mechanism of action as an IL-33 antagonist, which inhibits downstream inflammatory pathways in damaged epithelial tissue, serious infections, including opportunistic infections, are considered important potential risks specific to itepekimab. To manage these risks, careful participant selection, close monitoring, and prompt identification and treatment of AE are implemented in the clinical study. Risk minimization, monitoring, and management plans are outlined in the IB. The IB also addresses all pertinent safety data collected during clinical development thus far, including observed adverse reactions from completed clinical trials.

To assess the effects on fertility, surrogate parameters were evaluated in a 26-week SC toxicology study conducted in monkeys, followed by a 13-week recovery period. No itepekimab-related effects were observed on menstrual cycle length in females or on sperm motility, morphology, concentration, or volume in males. There were no microscopic effects on reproductive organs. Therefore, there is no evidence suggesting that itepekimab affects surrogate parameters of fertility. Additionally, an extended pre and postnatal development (ePPND) toxicity study in cynomolgus monkeys revealed no embryo-fetal lethality, developmental toxicity, or growth retardation up to postnatal Day 180. The no-observed AE level (NOAEL) was determined to be 100 mg/kg/week SC. After the 18th dose, the maternal area under the concentration-time curve (AUC_{tau}) at a dose of 100 mg/kg/week SC was measured to be 22 900 day*µg/mL.

It is important to note that mAbs can cross the placenta and potentially harm the fetus. Therefore, risk minimization measures have been implemented in the study, excluding females who are lactating, breastfeeding, or pregnant. WOCBP (premenopausal females capable of becoming pregnant) are only eligible if they use one of the specified highly effective contraception methods outlined in the protocol's inclusion criterion I 06. Male contraception is not required for the study. It is expected that extremely low levels of itepekimab will reach the fetus through seminal fluid. Monoclonal antibodies have specific physicochemical characteristics that limit their passive transmission through biological membranes. For therapeutic antibodies to reach the fetus through seminal transfer, they would need to undergo vaginal absorption, which poses a significant barrier. Based on conservative assumptions and using the highest dose of itepekimab tested in Study R3500 HV-1551 (10 mg/kg IV), and assuming 100% transfer from maternal exposure to the fetus, the highest potential exposure of itepekimab to a fetus through seminal transfer would be approximately 0.00025 µg/mL. This value is approximately 17 times lower than the pharmacologically active concentration measured in vitro (33, 34).

During early human clinical studies, itepekimab demonstrated good tolerability in healthy adult subjects in the completed first-in-human single ascending dose study, where single 4 doses of 0.3, 1, 3, 10 mg/kg, and 150 mg SC itepekimab or placebo were administered (Study R3500 HV-1551). It was also well tolerated by participants with moderate asthma in the completed first-in-patient multiple ascending dose study, which assessed 75 mg or 150 mg SC itepekimab or placebo once every week (QW) for 4 weeks (R3500-AS-1619). No deaths or SAE were reported.

In Study ACT15102, itepekimab monotherapy or co-administered with dupilumab for a period of 12 weeks, both at a dose of 300 mg Q2W, was well tolerated by patients with moderate-to-severe asthma. The percentage of participants experiencing at least one TEAE was well balanced across treatment groups.

In Study ACT15104, the percentage of participants with at least one treatment-emergent SAE (TESAE) was similar between the itepekimab group (14.0%) and the placebo group (15.2%). There were no treatment-emergent ADA observed in Studies ACT15102 and ACT15104, or any of the clinical studies completed to date.

The full safety data and other potential risks for itepekimab are summarized in the IB.

Ongoing Phase 3 studies (EFC16750, EFC16819, and LTS18133), and a Phase 2 mechanistic study (PDY16967) in COPD and a Phase 2 study (ACT18018) in non-cystic fibrosis bronchiectasis are actively monitoring safety. An independent DMC has access to unblinded safety information, and, at the time of this protocol finalization, all studies could be continued without amendments to the ongoing studies. The current EFC18418 study will also fall within the purview of a DMC, which will regularly evaluate the balance of benefits and risks.

Table 1 presents a summary of potential risks of study participation and mitigation strategies.

Table 1 - Risk assessment

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
Systemic hypersensitivity reactions, including events associated with immunogenicity	There were no preclinical findings suggestive of systemic hypersensitivity reactions. In the GLP toxicology studies, the occurrence of immunogenicity to itepekimab was low, with anti-itepekimab antibodies detected in 5% and 2% of itepekimab-treated animals in the single-dose (REGN3500-PK-15053) and repeat-dose (REGN3500-TX-15034) studies, respectively. In the repeat-dose toxicology study in cynomolgus monkeys (REGN3500-TX-15034), 1 monkey (out of 48 monkeys receiving itepekimab) receiving the 100 mg/kg IV dose had a positive ADA assay during the recovery period that was 8.6-fold greater than the baseline sample, which is suggestive of a moderate response. In the ACT15102 study, the incidence of systemic hypersensitivity AESIs was slightly higher in the itepekimab and itepekimab + dupilumab groups compared to placebo and dupilumab groups (3 [4.1%] participants each in the itepekimab and itepekimab + dupilumab groups, and 1 [1.4%] participant each in the dupilumab and placebo groups). All cases of systemic hypersensitivity were mild or moderate in intensity and none was serious. All participants with systemic hypersensitivity recovered. In the ACT15104 study, incidence of systemic hypersensitivity AESIs was similar between itepekimab and	Protocol exclusion criteria: • Known allergy to itepekimab or to excipients. Monitoring: • Participants should be monitored for any signs or symptoms of a hypersensitivity reaction for at least 30 minutes for the first 3 IMP injections that are administered. The monitoring period may be extended as per country-specific or local site requirements. Management of hypersensitivity: • The study protocols provide detailed instructions on how to manage reactions following injection including rules on definitive discontinuation in case of anaphylaxis or systemic hypersensitivity and the recommendation to determine ADA level

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
	placebo (1 [0.6%] in placebo and 2 [1.2%] participants in the itepekimab arm). All cases of systemic hypersensitivity were moderate in intensity, and none was serious. All participants with systemic hypersensitivity recovered. No treatment-emergent ADA response was observed against itepekimab in any of the clinical studies completed to date.	measurements using a validated assay (see Section 8.9). • Analysis of correlation of ADA status with safety data.
Serious infections, including opportunistic infections	There were no preclinical findings suggestive of infections. In ACT15102, 3 participants with an event of infection SAEs were reported among a total of 11 participants: infection SAE were similar between the 4 groups: 0 event in placebo, 1 event in itepekimab 300 mg Q2W,1 event in itepekimab 300 mg Q2W + dupilumab 300 mg Q2W, and 1 event in dupilumab 300 mg Q2W. There were no reported cases of opportunistic infections. In ACT15104, 19 participants with events of infection SAE were reported among a total of 65 participants: 10 in placebo and 9 in itepekimab. One participant each in the placebo groups and 2 participants in the itepekimab group experienced an opportunistic infection: herpes zoster. All cases were of mild-moderate intensity and led to protocol predefined permanent treatment discontinuation. Neither was considered serious or related to IMP by the Investigator. Both events were resolved at the time of data cut-off. For the overall susceptibility for serious and/or opportunistic infection, refer to the relevant section in this table.	Protocol exclusion criteria: • Participant with known or suspected immunodeficiency disorder, including history of systemic/invasive opportunistic infections. • Participant with TB. • Participant with HIV infection or HIV seropositivity at screening (Visit 1). • Participants with a positive (or indeterminate) HBsAg or positive IgM HBcAb or positive total HBcAb confirmed by positive HBV DNA or positive HCV Ab confirmed by positive HCV RNA. Management of infections: • Monitoring of participants for events related to/suggestive of serious infections or opportunistic infections. • The protocol contains rules on definitive discontinuation in case of opportunistic infections.

Abbreviations: Ab = antibody(ies); ADA = antidrug antibody(ies); AESI = adverse event of special interest; DNA = deoxyribonucleic acid; GLP = Good Laboratory Practice; HBV = hepatitis B virus; HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HIV = human immunodeficiency virus; Ig = immunoglobulin(s); IMP = investigational medicinal product; IV = intravenous; NTM = nontuberculous mycobacteria; Q2W = every 2 weeks; RNA = ribonucleic acid; SAE = serious adverse event; TB = tuberculosis.

2.3.2 Benefit assessment

IL-33 is a pro-inflammatory cytokine that triggers and amplifies inflammatory responses in both innate and adaptive immune systems when epithelial cells are stressed or damaged due to exposure to inflammatory triggers. Multiple lines of evidence support the important role of IL-33 in CRSwNP. In a murine model of CRS, there was an increase in IL-33 expression in epithelial cells and in infiltrating immune cells, and IL-33 blockade resulted in decreased polypoid lesions, mucosal edema and thickness, subepithelial collagen layer and numbers of goblet cells (9). Moreover, in an animal model of AERD, one of the most recalcitrant forms of CRSwNP, levels of

IL-33 are increased, IL-33 blockade resulted in improved lung resistance after aspirin exposure (10). Additionally, these preclinical data are supported by translational data showing elevated IL-33 expression in both eosinophilic and noneosinophilic CRSwNP, and by single cell RNA sequencing data showing elevated IL-33 expression in basal and endothelial cells from CRSwNP tissues (11). Genetic evidence also supports the association between IL-33 GPS and the presence of NPs. Itepekimab, a mAb, binds to IL-33 and inhibits its signaling with potential effects in type 2 and non-type 2 disease. Taken together these data support the potential benefits of treatment with itepekimab in CRSwNP.

In the PoC study involving patients with moderate-to-severe asthma who were not well controlled on ICS + LABA therapy (ACT15102), itepekimab administered as monotherapy (300 mg Q2W) or in combination with dupilumab (300 mg Q2W) significantly decreased the likelihood of experiencing LOAC and improved pre-BD FEV1 compared to placebo in patients gradually withdrawn from their baseline controller therapy (35).

In a PoC study conducted in patients with moderate-to-severe COPD (ACT15104), itepekimab demonstrated a 19.2% reduction in the risk of experiencing moderate-to-severe AECOPD compared to placebo over a treatment period of up to 52 weeks. However, this difference did not reach statistical significance (RR: 0.808, 95% CI 0.613 to 1.065; p = 0.1296). Subgroup analysis based on smoking status revealed a significant effect in former smokers. Specifically, in former smokers, itepekimab showed a 42.5% risk reduction in moderate-to-severe AECOPD compared to placebo (RR: 0.575, 95% CI 0.388 to 0.853, nominal p = 0.0061). However, in the current smoker population, itepekimab did not demonstrate a reduction in the annualized rate of moderate-to-severe AECOPD (-9.4%, RR 1.094, 95% CI 0.743 to 1.612, nominal p = 0.6472), and no benefits were observed in other evaluated endpoints indicating that active smoking may diminish the efficacy of itepekimab. The effects of itepekimab on the reduction in AECOPD were similar between the subgroups of patients with baseline blood eosinophils of at least 250 cells/mm^3 and those with levels less than 250 cells/mm^3. These data highlight the benefits of treatment with itepekimab in patients with type 2 and non-type 2 inflammation (13).

Currently approved biologics for CRSwNP all target type 2 inflammation, with a significant percentage of patients with uncontrolled symptoms. This highlights the significant unmet medical need for novel therapies that target both type 2 and non-type 2 inflammation.

Considering itepekimab's potential effect on both type 2 and non-type 2 inflammation, it is hypothesized that administering itepekimab in addition to INCS (such as MFNS) may have beneficial effects on patients with CRSwNP. These effects may include improvement in symptoms and reduction of inflammation, and decreased use of rescue therapy such as systemic corticosteroids and/or surgery with improvement in QoL.

2.3.3 Overall benefit/risk conclusion

Considering the measures taken to minimize risk to participants participating in this study, the potential risks identified in association with itepekimab are justified by the anticipated benefits that may be afforded to participants with CRSwNP.

3 OBJECTIVES, ENDPOINTS, AND ESTIMANDS

Table 2 - Objectives and endpoints

Objectives	Endpoints
Primary	
• To evaluate the efficacy of itepekimab compared with placebo on NP size and nasal congestion.	• Change from baseline to Week 24 in the endoscopic NPS. • Change from baseline to Week 24 in the NCS (co-primary).
Secondary	
• To evaluate the long-term efficacy of itepekimab compared with placebo on NP size.	• Change from baseline to Week 52 in endoscopic NPS (key secondary).
• To evaluate the long-term efficacy of itepekimab compared to placebo on nasal congestion.	• Change from baseline to Week 52 in NCS (key secondary).
• To evaluate the efficacy of itepekimab compared with placebo on sinus opacification.	• Change from baseline to Week 24 in opacification of sinuses assessed by CT scan using the LMK score.
• To evaluate the efficacy of itepekimab compared to placebo on symptoms of CRSwNP.	• Change from baseline to Weeks 24 and 52 in the TSS (nasal congestion/obstruction, anterior/posterior rhinorrhea, and loss of sense of smell).
• To evaluate the efficacy of itepekimab compared to placebo on sense of smell.	• Change from baseline to Weeks 24 and 52: - Loss of smell severity score using the daily CRSwNP sinonasal symptom eDiary. - UPSIT score.
• To evaluate the efficacy of itepekimab compared to placebo on health-related quality of life.	• Change from baseline to Weeks 24 and 52 in SNOT-22 total score.
• To evaluate the efficacy of itepekimab compared to placebo on sleep disturbance.	• Change from baseline to Weeks 24 and 52 in PROMIS SD-SF-8b scores.
• To evaluate the ability of itepekimab compared to placebo to reduce the risk of worsening/acute sinusitis requiring treatment with SCS or sinus surgery.	• Proportion of participants with CRSwNP requiring SCS or surgery for CRS. • Annualized rate of SCS course[a] or surgery for CRS during the planned study intervention period. • Time to first either SCS or surgery for CRS.
• To evaluate the effect of itepekimab compared to placebo on asthma in the subgroup of participants with comorbid asthma.	• Change from baseline to Weeks 24 and 52 in pre-BD FEV1 (in mL) in participants with co-morbid asthma. • Change from baseline to Weeks 24 and 52 in ACQ-5 score in participants with co-morbid asthma.
• To evaluate the effect of itepekimab compared to placebo in the subgroup of participants with AERD.	• Change from the baseline to Week 24 and 52 in NPS and NCS in the subgroup of participants with AERD. • Proportion of participants with AERD requiring SCS or surgery for CRS during the planned study intervention period.

Objectives	Endpoints
	• Annualized rate of SCS course or surgery for CRS during the planned study intervention period in participants with AERD. • Time to first either SCS or surgery for CRS in participants with AERD. • Change from baseline to Weeks 24 and 52 in pre-BD FEV1 (in mL) in participants with AERD.
• To evaluate the efficacy of itepekimab compared to placebo.	• Proportion of NPS responders at Weeks 24 and 52 (defined as participants with improvement by at least 1 point in NPS). • Proportion of NPS responders at Weeks 24 and 52 (defined as participants with improvement by at least 2 points in NPS).
• To evaluate the safety and tolerability of itepekimab compared to placebo in participants with CRSwNP.	• Incidence of TEAEs, TESAEs, TEAESIs and TEAEs leading to treatment discontinuation.
• To evaluate the PK of itepekimab.	• Itepekimab concentration in serum.
• Assessment of immunogenicity to itepekimab over time compared to placebo.	• Incidence of treatment-emergent anti-itepekimab antibody (ADA) responses throughout the study.
Tertiary/Exploratory	
• To evaluate the effect of itepekimab on overall health status, cough, PGIS and PGIC.	• Change from baseline to Weeks 24 and 52 in the EQ-5D index and VAS. • Change from baseline to Weeks 24 and 52 in PGIS score for each symptom and for symptoms overall. • PGIC score at Weeks 24 and 52 for each symptom and for symptoms overall. • Change from baseline to Weeks 24 and 52 in Leicester Cough Questionnaire total score.
• To evaluate the efficacy of itepekimab compared to placebo in CRSwNP quality of life.	• Proportion of SNOT-22 responders at Weeks 24 and 52 (defined as participants with improvement of at least 8.9 points in SNOT-22).
• To evaluate the effects of itepekimab compared to placebo on total sinus opacification.	• Change from baseline to Week 24 in sinus (all sinuses) percent opacification volume assessed by CT scan.
• To evaluate the effect of itepekimab on health care resource use/productivity compared to placebo.	• Cumulative number of health care resource utilization by visit type. • Change from baseline to Weeks 24 and 52 in WPAI-SHP on overall work impairment and daily activity impairment.
• To evaluate the early effect of itepekimab compared to placebo on lung function and asthma in the subgroup of participants with co-morbid asthma.	• Change from baseline to Weeks 4 in pre-BD FEV1.

Objectives	Endpoints
• To evaluate the effect of itepekimab on PROs overtime.	• Change from baseline to Weeks 4, 12, 24, 36, and 52 in SNOT-22 domain scores: Nasal, Ear/Facial, Sleep, Function, and Emotion. • Change from baseline to Weeks 4, 12 and 36 in SNOT-22 total scores. • Change from baseline to Weeks 12, 24, 36, 52 in EQ-5D index and EQ-VAS. • Change from baseline to Weeks 12, 24, 36, and 52 in PGIS for each symptom. • PGIC score for each symptom at Weeks 12, 24, 36, and 52. • Change from baseline to Weeks 4, 12, 24, and 52 in ACQ-5 in participants with asthma.
• To characterize the effects of itepekimab in CRSwNP participants by evaluating blood, urine and nasal biomarkers compared to placebo.	• Pharmacodynamic biomarkers in blood, nasal absorption and urine.
• To evaluate the transcriptome in participants treated with itepekimab.	• Change from baseline in the NES for itepekimab and IL-33 gene signatures at Weeks 4, 24, and 52 in nasal brushings.
• To investigate genetic factors that may predict itepekimab efficacy and safety.	• Genomic analysis in consenting adults.

Abbreviations: ACQ = asthma control questionnaire; ADA = anti-drug antibody; AERD = aspirin-exacerbated respiratory disease; BD = bronchodilator; CRS = chronic rhinosinusitis; CRSwNP = chronic rhinosinusitis with nasal polyposis; CT = computed tomography; EQ-5D = EuroQol-5 dimension; FEV = forced expiratory volume; IL = interleukin; LMK = Lund Mackay Score; NCS = Nasal Congestion Score; NES = Normalized Enrichment Score; NP = nasal polyp; NPS = Nasal Polyposis Score; PGIC = Patients' Global Impression of Change; PGIS = Patients' Global Impression of Severity; PK = pharmacokinetic(s); PRO = patient reported outcomes; PROMIS = Patient-Reported Outcomes Measurement Information System; SCS = systemic corticosteroids; SD-SF = sleep disturbance short form; SNOT = Sino-Nasal Outcome Test; TEAE = treatment-emergent adverse event; TESAE = treatment-emergent serious adverse event; TEAESI = treatment-emergent adverse events of special interest; TSS = total symptoms score; UPSIT = University of Pennsylvania Smell Identification Test; VAS = visual analogue scale; WPAI-SHP = Work Productivity and Activity Impairment-Specific Health Problem.

a Initiation of rescue therapy as defined in Section 6.9.1. A course of SCS is considered continuous if intervention is separated by less than 7 days.

For China, please see Section 10.8.1 for details.

Primary estimands defined for primary and key secondary efficacy endpoints are summarized in Table 3 below. More details are provided in Section 9.2.

Table 3 - Summary of primary estimands for main endpoints

Endpoint	Estimands			
Category (estimand)	**Endpoint**	**Population**	**Intercurrent event(s) handling strategy**	**Population-level summary (Analysis and missing data handling)**
Primary objective: To evaluate the efficacy of itepekimab compared with placebo on NP size and nasal congestion at Week 24.				
Co-primary endpoint (co-primary estimand 1)	Change from baseline to Week 24 in the endoscopic NPS	ITT	1) For selected prohibited/rescue medications (eg, prohibited biologic therapy) or nasal/sinus surgery prior to Week 24 will be handled with a composite variable strategy: data after the IE will be assigned to the worst possible score. 2) The following IEs will be handled with a treatment policy strategy. All assessments after starting such IE and before or at Week 24 will be included: a) Study intervention discontinuation. b) Use of SCS for any reason. c) Use of other prohibited/rescue medications prior to Week 24.	Difference in LS means between itepekimab and placebo from ANCOVA model with change from baseline to Week 24 in the endoscopic NPS as response variable, intervention group, asthma/AERD strata and regions as fixed effects and the baseline value as covariate. For participants who discontinue IMP before Week 24 without use of selected prohibited/rescue medications or nasal/sinus surgery prior to Week 24: multiple imputation approach will be used to impute missing endpoint value at Week 24, and this multiple imputation will use all participants from the same randomized arm, excluding participants who use selected prohibited/rescue medications or nasal/sinus surgery prior to Week 24. Each of the imputed complete datasets will be analyzed by fitting the ANCOVA model. Statistical inference obtained from all imputed data will be combined using Rubin's rule.
Co-primary endpoint (co-primary estimand 2)	Change from baseline to Week 24 in the NCS	ITT	Same as first co-primary estimand	Same as first co-primary estimand
Key secondary objective: To evaluate the efficacy of itepekimab compared with placebo on NP size and nasal congestion at Week 52**.**				
Key secondary endpoint (estimand 3)	Change from baseline to Week 52 in the NPS	ITT	Same as first co-primary estimand.	Same as first co-primary estimand.
Key secondary endpoint (estimand 4)	Change from baseline to Week 52 in the NCS	ITT	Same as first co-primary estimand.	Same as first co-primary estimand.

Abbreviations: AERD = aspirin-exacerbated respiratory disease; ANCOVA = analysis of covariance; IE = intercurrent event; ITT = intent-to-treat; LS = least squares; NCS = nasal congestion score; NP = nasal polyp; NPS = nasal polyp score; SCS = systemic corticosteroid(s).

3.1 APPROPRIATENESS OF MEASUREMENTS

The primary and secondary efficacy assessments as well as the safety assessments used in this study are standard for the evaluation of therapy in participants with CRSwNP, which have been used or are being used in similar designed Phase 2 and Phase 3 studies such as dupilumab (SINUS-24 and SINUS-52, Phase 3, NCT02912468 and NCT02898454), mepolizumab (SYNAPSE, Phase 3, NCT03085797) and tezepelumab (WAYPOINT, Phase 3, NCT04851964).

4 STUDY DESIGN

4.1 OVERALL DESIGN

This is a Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group, 3-arm study to assess the efficacy, safety, and tolerability of 2 different dosing regimens of SC itepekimab in adult participants with inadequately-controlled CRSwNP on background of INCS.

This study will include adult participants (≥18 years of age) with bilateral nasal polyposis and chronic symptoms of sinusitis despite previous surgery and/or treatment with SCS. Participants are required to have a bilateral endoscopic NPS of at least 5 out of a maximum of 8, with a score of at least 2 for each nostril; manifest symptoms of nasal blockade/obstruction/congestion with a NCS at Screening of at least 2 (0-3 scale); and manifest at least 1 out of the following 2 symptoms at screening: (1) anterior or posterior rhinorrhea; (2) reduction or lost sense of smell.

All eligible participants will be randomized in 1:1:1 ratio (approximately 210 participants in total) and treated for 52 weeks, receiving SC administrations of itepekimab or placebo according to the following dosing schedules:

- Itepekimab 300 mg, administered as a single SC injection Q2W.
- Itepekimab 300 mg, administered as a single SC injection Q4W with alternating SC injection of matching placebo at the 2-week interval between active IMP.
- Placebo, administered as a single SC injection of matching placebo to itepekimab Q2W.

Itepekimab will be administered as an add-on therapy to MFNS. In Japan, participants on INCS (MFNS or other INCS) will continue taking their daily INCS with a stable dose through all periods of the study. In Japan, participants not on INCS prior to screening, will receive MFNS during screening and throughout the study. In China, participants will continue their stable daily dose of INCS which may include MFNS during the screening period and throughout the study.

The co-primary endpoints are changes from baseline to Week 24 in NPS and NCS in the itepekimab-treated participants compared to placebo. NPS is assessed based on nasal endoscopy performed locally by the Investigator and centrally read for scoring.

Randomization will be stratified by asthma/AERD status (no asthma, asthma only, asthma & AERD), and region (Asia or rest of the world). This study will aim to enroll approximately 65% of participants with co-morbid asthma, and approximately 25% participants with AERD.

This study consists of three periods with a study duration of approximately 76 weeks for all participants:

- Screening run in on MFNS for 4 weeks.
- Randomized itepekimab/placebo intervention period (52 weeks).
- Post-IMP treatment safety follow-up (20 weeks).

Eligible participants who complete the treatment period will be offered the opportunity to participate in an open-label LTS18420 study with itepekimab if approved by Health Authority & Ethical Committees.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

A randomized, placebo-controlled study design where the effect of the IMP is assessed on top of standard of care background therapy (MFNS or other INCS) is considered to be the most appropriate design to examine the efficacy and safety of a novel biologic therapy in CRSwNP. Change in bilateral NPS, and in nasal congestion/obstruction symptom assessment are considered to be standard co-primary efficacy assessment based on guidance from the FDA (Docket number FDA-2021-D-1096) and extensive precedent from Phase 3 trials (Dupilumab SINUS-24 and SINUS-52, Mepolizumab SYNAPSE) and other studies underway at the time of protocol development (NCT05274750, NCT05281523, NCT04851964). This combination of endpoints provides an objective anatomic assessment of efficacy along with an assessment of the most common symptom associated with CRSwNP. Imaging assessment with CT scan will also be performed to calculate LMK score, an important secondary endpoint. The 52-week duration of this study allows for assessment of the broad range of short-term, mid- and long-term effects itepekimab may have on NPS, CRSwNP symptom control, HRQoL, and lung function in those participants with concomitant asthma.

Based on the inclusion criteria for this study, all study participants will have inadequately-controlled CRSwNP, with a high burden of NP size and significant accompanying symptoms. MFNS represents a standard therapy described in the European EPOS 2020 guidelines, and therefore participants are maintained on this treatment throughout the study. In countries where MFNS is not an approved therapy, participants will be maintained on background standard of care (SoC) therapy which may include other INCS drugs or no therapy.

This study will include non-smokers and former smokers. Former smoking status in this study is defined as smoking cessation of ≥6 months prior to screening. At least 6 months was chosen because while it is generally believed that a majority of reversible alteration in the lung has a recovery period of a few weeks after smoking cessation(36, 37). The risk of resuming smoking is the highest shortly after cessation and reduces over time. Six months of abstinence is generally considered to be a reasonable estimate of life-long abstinence (38).

Itepekimab has demonstrated efficacy in asthma (35) and in former smokers with COPD (13) in Phase 2 studies. Covering both Type 2 and non-Type 2 inflammation, pathways thought to play significant roles in CRSwNP. The relative contribution of these pathways to the development of CRSwNP may vary according to genetic backgrounds, environmental triggers or both, highlighting the importance of a therapy that could target diverse inflammatory pathways. Further, asthma and AERD commonly co-exists with inadequately-controlled CRSwNP. Measures of lung function and asthma control will be assessed throughout the study in this subgroup.

4.2.1 Participant input into design

As the design of this trial is very similar to previous trials which were conducted with dupilumab in CRSwNP (EFC14146 and EFC14280), no feedback from participants was requested specifically for this study.

4.3 JUSTIFICATION FOR DOSE

The dose regimen of itepekimab 300 mg SC Q2W was well tolerated in Phase 2 clinical studies when administered for 12 weeks in participants with moderate-to-severe asthma (Study ACT15102; itepekimab 300 mg Q2W [N = 73], itepekimab Q2W + dupilumab Q2W [N = 74]) and for 24 to 52 weeks in participants with moderate-to-severe COPD (Study ACT15104; n = 172). In participants with moderate-to-severe asthma, itepekimab 300 mg Q2W monotherapy demonstrated a significant reduction in LOAC (primary endpoint) and a significant improvement in pre-BD FEV1 (secondary endpoint) compared with that for placebo at Week 12 in the overall population (Study ACT15102). In former smokers with moderate-to-severe COPD but not in current smokers with COPD, itepekimab 300 mg Q2W demonstrated a substantial and nominally significant reduction in the risk of experiencing a moderate-or-severe AECOPD and a meaningful and nominally significant improvement in pre-BD FEV1 compared with that for placebo (Study ACT15104).

The itepekimab PK profile in healthy subjects, participants with asthma, and participants with COPD is described by a 2-compartment population PK (Pop PK) model with first order absorption and linear elimination. Body weight was the primary factor responsible for itepekimab PK variability in which higher body weight was associated with faster clearance of drug.
In a preclinical pharmacology study, a concentration of 17 mg/L was shown to be associated with maximum in vivo efficacy in a chronic exposure to House Dust Mite (HDM) asthma model in mice.

Based on the totality of clinical data and the PK and PK-PD analysis results, 2 dosing regimens of itepekimab 300 mg Q2W and itepekimab 300 mg Q4W for the Phase 3 program in participants with CRSwNP were selected. Both dose regimens of 300 mg SC Q2W and Q4W are expected to achieve a mean C_{trough} at steady state higher than the concentration associated with 90% target occupancy (target engagement threshold) and 17 mg/L (preclinical threshold), respectively. Based on this information, the less frequent dosing regimen (Q4W) may provide a similar benefit/risk ratio in the former smoker participants with COPD.

Therefore, these 2 dosage regimens used in the Phase 3 program in COPD will be used in this CRSwNP study as well, due to the types of inflammatory response similarities (both type-2 and non-type-2) between CRSwNP, asthma and COPD.

4.4 END-OF-STUDY DEFINITION

The end of the study is defined as the date of EOS visit of the last participant in the study, except for participants who enter LTS18420 study. For participants who enter LTS18420 study, the last visit in this study will be the EOT Visit.

A participant is considered to have completed the study if the participant has completed all periods of the study including the last visit, except for those participants who wish to enroll in the LTS18420, for whom the last visit in this study will be the EOT Visit.

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. Participants must be 18 years of age or older, at the time of signing the informed consent.

Type of participant and disease characteristics

I 02. Participants with a history of CRSwNP for at least 1 year prior to screening.

I 03. Participants must have at least one of the following features:

- Prior sinonasal surgery for NP.
- Worsening symptoms of CRS requiring treatment with SCS within the prior 2 years before screening (Visit 1).
- Worsening symptoms of CRS in the past 2 years which would have required treatment with SCS, however participant is intolerant or has a contraindication to SCS.

I 04. An endoscopic bilateral NPS of at least 5 out of maximum score of 8 (with a minimum score of 2 in each nasal cavity) at screening and randomization.

I 05. Ongoing symptoms (for at least 12 weeks before Visit 1) of:

1. Nasal congestion/blockade/obstruction with moderate or severe (symptom severity score 2 or 3) at Visit 1 and a weekly average severity of greater than 1 in the week before randomization (Visit 2),

   AND

2. At least one of the following two symptoms: loss of smell or rhinorrhea (anterior/posterior).

Weight

Not applicable.

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

I 06. All

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

a) Male participants:

- No contraceptive measures required for this study.

b) 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 WOCBP

    OR
  - Is a WOCBP and agrees to use a contraceptive method that is highly effective, with a failure rate of <1%, as described in Appendix 4 (Section 10.4) during the study (at a minimum until 20 weeks after the last dose of study intervention).
  - A WOCBP must have a negative highly sensitive pregnancy test (urine or serum as required by local regulations) on Day 1 before the first dose of study intervention.
  - If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.
- Additional details can be found in Appendix 4 (Section 10.4).
- The Investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

Informed Consent

I 07. Capable of giving signed informed consent as described in Appendix 1 (Section 10.1) of the protocol which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

Other inclusion criteria

Not applicable.

5.2 EXCLUSION CRITERIA

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

Medical conditions

E 01. Participants with a history of clinically significant renal, hepatic, metabolic, neurologic, hematologic, ophthalmologic, respiratory (excluding those with asthma and AERD which may be included in the study), gastrointestinal, cardiovascular, cerebrovascular, or other significant medical illness or disorder, which, in the judgment of the Investigator, could interfere with the study or require treatment that might interfere with the study.

E 02. Participants who are currently smoking tobacco and/or vaping, or participants in whom smoking/vaping cessation has occurred <6 months prior to Screening (Visit 1). Nicotine replacement therapy and/or noninhaled tobacco product use are not considered current smoking of tobacco.

E 03. Participants meet any contraindications for MFNS such as hypersensitivity to MFNS or any of its components; or participants with uncontrolled opportunistic infections.

E 04. Active TB or history of latent untreated TB, history of incompletely treated TB, or non-TB mycobacterial infection will be excluded from the study unless it is well documented by a specialist that the participant has been adequately treated and can now start intervention with a biologic agent, in the medical judgment of the Investigator and/or infectious disease specialist. TB testing would be performed on a country-by-country basis according to local guidelines if required by regulatory authorities or ethic committees.

E 05. Known or suspected immunodeficiency disorder, including history of invasive/systemic opportunistic infections (Appendix 12 Section 10.12).

E 06. Evidence of severe infection requiring systemic treatment with antibacterial, antiviral, antifungal, antiparasitic, or antiprotozoal medications within 4 weeks before Screening (Visit 1) or during the screening period.

E 07. Participants with active autoimmune disease or participants using immunosuppressive therapy for autoimmune disease (eg, allergic granulomatous angiitis [Churg-Strauss syndrome], granulomatosis with polyangiitis [Wegener's granulomatosis], rheumatoid arthritis, inflammatory bowel disease, primary biliary cirrhosis, systemic lupus erythematosus, multiple sclerosis), participants with Young's syndrome, Kartagener's syndrome or other dyskinetic ciliary syndromes, or with concomitant cystic fibrosis.

E 08. History of malignancy within 5 years before Screening (Visit 1), or during the screening period, except completely treated in situ carcinoma of the cervix, completely treated and resolved nonmetastatic squamous or basal cell carcinoma of the skin, and precancerous lesions or disorders.

E 09. Participants with a history of a severe systemic hypersensitivity reaction to a mAb.

E 10. Participants with conditions/concomitant diseases making them non-evaluable at Visit 1 or for the primary efficacy endpoint such as:

- Antrochoanal polyps.
- Nasal septal deviation that would occlude at least one nostril.
- Acute sinusitis, nasal infection, or upper respiratory infection.
- Ongoing rhinitis medicamentosa.
- Allergic granulomatous angiitis (Churg-Strauss syndrome), granulomatosis with polyangiitis (Wegener's granulomatosis), Young's syndrome, Kartagener's syndrome or other dyskinetic ciliary syndromes, concomitant cystic fibrosis.
- Radiologic suspicion or confirmed invasive or expansive fungal rhinosinusitis.

E 11. Participants with nasal cavity malignant tumor and benign tumors (eg, papilloma, blood boil etc).

E 12. Participants with severe uncontrolled asthma with history of 2 and/or more exacerbations, requiring SCS or 1 hospitalization requiring SCS in the past year.

E 13. History of concomitant lung disease (other than asthma, eg, COPD, interstitial lung disease) which in the opinion of the Investigator could interfere with performance and interpretation of spirometry.

Prior/concomitant therapy

E 14. Initiation of allergen immunotherapy within 3 months prior to Visit 1 or a plan to begin therapy or change its composition during the screening period or the randomized treatment period.

E 15. Participant who has taken: anti-IgE therapy (eg, omalizumab) within 130 days (4 months) prior to Screening (Visit 1) or any other immune-directed biologic therapy (eg, anti-IL5, anti-IL5R, anti-TSLP, anti-IL6, anti-IL17, anti-IL23, anti-IL12/23, anti-IL4ra, etc) or systemic immunosuppressant (eg, methotrexate, any anti-TNF mAbs, B and/or T-cell targeted immunosuppressive therapies, JAK inhibitors) within 2 months or 5 half-lives prior to Screening (Visit 1), whichever is longer.

E 16. Participants who have received live attenuated vaccine(s) within 4 weeks before Screening (Visit 1) or plans to receive such vaccines during the study are excluded.

E 17. Participants treated with INCS (MFNS is permitted), intranasal emitting devices/stents, nasal spray using exhalation delivery system such as Xhance™ during the screening period. In Japan and China INCS other than MFNS are permitted.

E 18. Participants receiving leukotriene antagonists/modifiers unless a participant is on a stable dose for at least 30 days prior to Visit 1.

E 19. Exposure to another investigative drug (mAb as well as small molecules) prior to Screening (Visit 1), within the period specified as follows: an interval of less than 6 months or <5 PK half-lives for investigative mAb, and an interval of less than 30 days or <5 PK half-lives, whichever is longer, for investigative small molecules.

E 20. Participants who have undergone any sinus intranasal surgery (including polypectomy) within 6 months before Visit 1.

E 21. Participants who have had a sinonasal surgery changing the lateral wall structure of the nose making impossible the evaluation of NPS.

E 22. Participants who received SCS 1 month prior to Screening (Visit 1) or during the screening period (between Visit 1 and Visit 2).

Prior/concurrent clinical study experience

E 23. Participant who has previously participated in itepekimab clinical trials.

E 24. Known allergy to itepekimab or its excipients, or any drug or other allergy that, in the opinion of the Investigator, contraindicates participation in this study.

Diagnostic assessments

E 25. Clinically significant laboratory tests at Screening (Visit 1):

- ALT or AST >2 times ULN.
- Hemoglobin <10 g/100 mL for male and <9 g/100 mL for female.
- Neutrophils <1500/mm^3 (<1000/mm^3 for those of African descent).
- Platelets <100 000/mm^3.
- Creatinine >150 µmol/L.

E 26. Participants with any of the following result at Screening (Visit 1): positive (or indeterminate) hepatitis B surface antigen (HBsAg) or positive IgM HBcAb or positive total HBcAb confirmed by positive HBV DNA or positive HCV Ab confirmed by positive HCV RNA.

E 27. History of HIV infection or positive HIV 1/2 serology at Screening (Visit 1).

Noncompliance to completion of the e-diary

E 28. Participants must demonstrate at least the following for acceptable compliance: completing the eDiary for any 4 in the 7 days immediately preceding the Baseline Visit (Visit 2).

Other exclusion criteria

E 29. Individuals accommodated in an institution because of regulatory or legal order; prisoners or participants who are legally institutionalized.

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

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

For any country-related specific regulation that would prevent the participant from entering the study see Appendix 8 Section 10.8 (country-specific/region requirements).

5.3 LIFESTYLE CONSIDERATIONS

5.3.1 Meals and dietary restrictions

Not applicable.

5.3.2 Caffeine, alcohol, and tobacco

Use of inhaled tobacco products (eg, smoking tobacco, vaping, heated tobacco, etc) and marijuana products will not be allowed from 6 months prior to Screening (Visit 1) until after the final follow-up visit. If abstinence is difficult for the participant, the participants may seek medical help and receive supportive treatment with Nicotine Replacement Therapy (NRT), by oral, or transdermal administration (but not inhalation or intranasal). Use of non-pharmaceutical products intranasally is prohibited.

5.3.3 Activity

Not applicable.

5.3.4 Other restrictions

Not applicable.

5.4 SCREEN FAILURES

A screen failure occurs when a participant who consents to participate in the clinical study is not subsequently randomized. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure reasons, eligibility criteria, and any SAE.

If certain dynamic laboratory tests do not meet the inclusion criteria at Screening (Visit 1), these laboratory assessments may be repeated, at the discretion of the Investigator, if the parameter result is judged to be likely to return to acceptable range for study inclusion within the Screening period prior to Baseline (Visit 2). There is no need to screen fail such participants if the test finally meets the inclusion criteria.

Individuals who do not meet the criteria for participation in this study (screen failure) may be re-screened. Re-screened participants should be assigned a new participant number for every re-screening event. In this situation, the re-screened participant should sign a new ICF.

5.5 CRITERIA FOR TEMPORARILY DELAYING

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 9: (Section 10.9: Contingency measures for a regional or national emergency that is declared by a governmental agency) should be considered for screening/enrollment/randomization/administration of study intervention.

6 STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

Study interventions are all pre-specified, IMPs and AxMPs, medical devices and other interventions (eg, surgical and behavioral) intended to be administered to the study participants during the study conduct.

6.1 STUDY INTERVENTION(S) ADMINISTERED

6.1.1 Investigational medicinal product(s)

The IMP is to be administered every 14 +/- 3 days (Q2W; itepekimab or placebo) (up to 26 doses) or 28 +/- 3 days (Q4W; itepekimab) (up to 13 doses) with placebo injection in between during the treatment period (Table 4). Each PFS contains a deliverable volume of 2 mL with an itepekimab concentration of 150 mg/mL or 0 mg/mL.

The IMP will be administered by the Investigator/designee, participants/caregivers (under the supervision of the Investigator/delegate or after sufficient training), or health care professional (in case of exceptional circumstances) following clinic procedures and blood collection (if applicable). Participants should be monitored for at least 30 minutes after administration of the first 3 IMP injections at the site by the site staff. The monitoring period may be extended as per country-specific or local site specific requirements.

The SC injection sites should alternate between the left or right upper thighs, 4 quadrants of the abdomen, or the left or right upper arms, so that the same site is not injected twice during consecutive visits.

To train participants or their caregivers how to prepare and inject IMP, the Investigator will first train the participant at an onsite visit during the treatment period. At this visit, the participant will perform the injection under the supervision of the Investigator or delegate. At subsequent study visits, participants will be trained to self-inject IMP or caregivers will be trained to inject IMP to the participant, and they are allowed to inject IMP at home after a minimum of 3 self-administered injections at investigational site from Visit 4 (Week 6) onwards. All trainings shall be documented in the participant's study file as well as the determination and clearance for the participant's and/or caregiver's to complete an injection at home. Prior to Visit 4 (Week 6) injections cannot be administered at home by a participant or caregiver, but in exceptional circumstances this will be allowed by a health care professional. The participant should only perform the injection in the abdomen, or left or right upper thighs. The caregiver can perform the injection in left or right upper thighs, the abdomen, or left or right upper arms. The site of administration during the previous site visit should be taken into consideration (the same site should not be injected twice during consecutive visits). The participant or caregiver should also be instructed to monitor for any reaction following injection per country-specific or local site specific requirements. The start date for home administration by participant or caregiver can be postponed temporarily or indefinitely if this is considered necessary by the Investigator or preferred by the participant or caregiver. In that case, the participant will be asked to return to the investigational site for their IMP injections or have IMP administered by a home nurse (if appropriate).

Table 4 - Investigational medicinal product(s) administered

Intervention label	SAR440340/RGN3500	SAR440340/RGN3500	Placebo
Intervention name	Itepekimab	Itepekimab	Placebo matching Itepekimab
Intervention description	SC injection, 300 mg Q2W	SC injection, 300 mg Q4W	SC injection, placebo Q2W
Type	Biological/Vaccine	Biological/Vaccine	Biological/Vaccine
Dose formulation	Prefilled syringe	Prefilled syringe	Prefilled syringe
Unit dose strength(s)	150 mg/mL	150 mg/mL	0 mg/mL
Dosage level(s)	300 mg Q2W	300 mg Q4W with alternating placebo administration at the 2-week interval between IMP.	0 mg/mL Q2W
Route of administration	SC injection	SC injection	SC injection
Use	Experimental	Experimental	Experimental
Packaging and labeling	Study intervention will be provided in PFS. Each PFS will be labelled as required per country requirement.	Study intervention will be provided in PFS. Each PFS will be labelled as required per country requirement.	Study intervention will be provided in PFS. Each PFS will be labelled as required per country requirement.
[Current/former name(s) or alias(es)]	Itepekimab	Itepekimab	Not applicable

Abbreviations: IMP = investigational medicinal product; PFS = prefilled syringe; Q2W = every 2 weeks; Q4W = every 4 weeks; SC = subcutaneous.

6.1.2 Auxiliary medicinal product(s)

Table 5 - Auxiliary medicinal product administered

Intervention label	MFNS
Intervention name	Mometasone furoate nasal spray; ATC code R01AD
Intervention description	MFNS 50 µg/actuation administered 2 actuations per nostril twice daily (400 µg total dose per day) or once daily for participants who cannot tolerate twice daily (200 µg total dose).
Type	Drug
Dose formulation	Solution for administration via spray pump.
Unit dose strength(s)	50 µg/actuation
Dosage level(s)	100 µg/nostril (2 actuations) bilaterally twice daily.
Route of administration	Intranasal spray
Use	Background treatment
Packaging and labeling	Varies and depends on pharmaceutical presentation and countries
Current/ former name(s) or alias(es)	Mometasone furoate

Abbreviations: ATC = Anatomical Therapeutic Chemical; MFNS = mometasone furoate nasal spray.

6.1.3 Study arms

Table 6 - Study arm(s)

Arm title	300 mg Q2W	300 mg Q4W	Placebo
Arm type	Experimental	Experimental	Placebo
Arm description	Participants will receive itepekimab 300 mg Q2W as SC injection for up to 52 weeks.	Participants will receive itepekimab 300 mg Q4W with alternating placebo administration at the 2-week interval between active IMP as SC injection for up to 52 weeks.	Participants will receive placebo Q2W as SC injection for up to 52 weeks.
Associated intervention labels	NA	NA	NA

Abbreviations: IMP = investigational medicinal product; Q2W = every 2 weeks, Q4W = every 4 weeks, SC = subcutaneous.

The IMP and AxMP may be supplied at the site or in case of regional/national emergency from the Investigator/site/Sponsor to the participant via a Sponsor-approved courier company where allowed by local regulations and agreed upon by the participant.

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 9: (Section 10.9: Contingency measures for a regional or national emergency that is declared by a governmental agency).

6.1.4 Devices

The itepekimab PFS is classified as a combination product with an integral medical device where the principal mechanism of action is that of the itepekimab (See Section 8.4.9 Guidelines for Reporting Product Complaints for product complaints). Medical devices for diagnostic interventions (eg, ECG) are not considered as “investigational device” in the context of this study.

6.2 PREPARATION, HANDLING, STORAGE, AND ACCOUNTABILITY

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

Any quality issue noticed with the receipt or use of an IMP/AxMP (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 8.4.9).

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, allow the IMP to be used other than as directed by this clinical trial protocol, or dispose of IMP in any other manner.

6.3 ASSIGNMENT TO STUDY INTERVENTION

All participants will be centrally assigned to randomized study intervention using an IRT. Before the study is initiated, the telephone number and call-in direction for the Interactive Voice Response System (IVRS) and/or the log in information and direction for the Interactive Web Response System (IWRS) will be provided to each site.

Definition of a randomized participant is a participant from screened population who has been allocated to a randomized intervention regardless of whether the intervention was received or not. A participant cannot be randomized more than once in the study. The randomized intervention kit number list is generated centrally by Sanofi. The IMPs are packaged in accordance with this list. Study intervention will be dispensed at the study visits as summarized in the SoA (Section 1.3).

During the randomization process, participants will be stratified by asthma/AERD status (no asthma, asthma only, asthma & AERD), and region (Asia or rest of the world).

6.4 BLINDING

This is a double-blind study in which participants/care providers/Investigators/outcomes assessors are blinded to study intervention. The IRT will be programmed with blind-breaking instructions. In case of an emergency, the Investigator has the sole responsibility for determining if unblinding of a participant's intervention assignment is warranted (eg, in case of available antidote). Participant safety must always be the first consideration in making such a determination. If the Investigator decides that unblinding is warranted, he/she may, at the Investigator's discretion, contact the Sponsor to discuss the situation prior to unblinding a participant's intervention assignment unless this could delay emergency treatment for the participant. If a participant's intervention assignment is unblinded, the Sponsor must be notified within 24 hours of this occurrence. The date and reason for the unblinding must be recorded.

The bioanalyst and pharmacokineticist responsible for the sample analysis and PK evaluation will be unblinded. They will, however, agree not to disclose the randomization schedule or the individual unblinded analytical results before the database lock.

Sponsor safety staff may unblind the intervention assignment for any participant with an SAE for the purpose of expedited regulatory reporting (see Section 8.4.4). Sponsor staff involved in the conduct of the study will remain blinded to the participant intervention assignment.

Methods of blinding

Itepekimab and placebo will be provided in identically matched 2-mL PFS. To protect the blind, each treatment kit of 2-mL (itepekimab/placebo) glass PFS will be prepared such that the treatments (itepekimab and its matching placebo) are identical and indistinguishable and will be labeled with a treatment kit number.

In accordance with the double-blind design, study participants, Investigators, and study site personnel will remain blinded to study treatment and will not have access to the randomization scheme or to the IMP content (itepekimab or placebo) except under circumstances described above in this section.

6.5 STUDY INTERVENTION COMPLIANCE

When participants are dosed at the site, they will receive study intervention directly from the Investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the eCRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention. During scheduled telephone contacts as per SoA, the site should verify the IMP compliance/ administrations with the participants and at next visit check the completion of the paper administration form(s).

When participants self-administer study intervention(s) at home, compliance with study intervention will be assessed at each subsequent phone or site visit. Compliance will be assessed by direct questioning, and counting returned empty labelled cartons during the site visits and documented in the source documents and relevant form. Deviations from the prescribed dosage regimen have to be recorded.

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.

Compliance with AxMP will be checked and recorded at each visit by site staff.

6.6 DOSE MODIFICATION

Dose interruption of MFNS is permitted at the site Investigator’s discretion to manage side effects. Participants may continue in the study if MFNS dosing is interrupted or permanently discontinued.

6.6.1 Retreatment criteria

Not applicable.

6.7 CONTINUED ACCESS TO INTERVENTION AFTER THE END OF THE STUDY

After the end of the study, a separate LTS18420 may be offered to participants who completed the study and are still taking the IMP. This LTS18420 will allow to assess long-term safety and efficacy of the itepekimab and will be described in a separate protocol.

If the LTS18420 is not conducted, and depending on the participant's unmet medical need, the non-availability of suitable alternative therapies, and an assessment of what is known about the benefits and risks of itepekimab, participants who have successfully completed their participation in this clinical trial (completed EOS Visit) will be eligible for post-trial access to itepekimab.

The Investigator/treating physician will determine if access to itepekimab is the best medical option for the participant and will then submit a request to the Sponsor, if allowed by local regulations.

Provision of itepekimab will be in compliance with all applicable national and local laws and regulations, including safety reporting obligations.

A participant will not be eligible for post-trial provision of itepekimab if his/her participation in the trial is terminated prematurely.

The Sponsor's post-trial access responsibilities will need to be periodically re-evaluated. Based on new information about the IMP (including adverse reactions), the continued health benefit to the individual and market availability of the product or alternative therapies, post-trial access may be terminated. This includes situations where the trial may be stopped due to safety concerns or other issues.

6.8 TREATMENT OF OVERDOSE

Symptomatic overdose is an AESI (defined in Section 8.4.7). No antidote is available for itepekimab.

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 <8 days.

In the event of an overdose (symptomatic or asymptomatic), the Investigator/treating physician should:

1. Contact the Sponsor or Sponsor representative(s) immediately.
2. Closely monitor the participant for any AE/SAE and laboratory abnormalities.

3. Obtain a serum sample for PK analysis as soon as possible from the date of the last dose of study intervention if requested by the Sponsor or Sponsor representative(s) (determined on a case-by-case basis).
4. Document appropriately in the eCRF.

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

6.9 PRIOR AND CONCOMITANT THERAPY

Any medication or vaccine (including over-the-counter or prescription medicines, recreational drugs, vitamins, and/or herbal supplements) 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 route and frequency.

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

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

- Anti-IL5 or IL5R mAb (eg, benralizumab, mepolizumab, reslizumab, depemokimab).
- Anti-TSLP (tezepelumab).
- Anti-IgE therapy (eg, omalizumab).
- Anti-IL4 receptor mAb (eg, dupilumab).
- Other mAbs including anti-IL6, anti-IL17, anti-IL23, anti-IL12/23, anti-IL13, etc.
- Systemic immunosuppressants (eg, methotrexate, any anti-TNF mAbs, B and/or T-cell targeted immunosuppressive therapies, JAK inhibitors).
- Other investigational drugs.
- Live-attenuated vaccines (Appendix 15 Section 10.15).
- Allergen immunotherapy (except if initiated more than 3 months prior to Visit 1 and dose stable 1 month prior to Visit 1).
- INCS drops or sprays other than MFNS (except in Japan and China).
- Long-term courses (>2 weeks) of SCS.
- Initiation of maintenance antibiotic therapy is prohibited.
- Xhance, device.

- Intranasal emitting devices/ stents.
- Initiation of leukotriene antagonists/modifiers unless on stable dose for ≥30 days prior to Screening (Visit 1).
- Oral or intranasal decongestants other than single use during endoscopy as below.

Participants who between Visit 1 and Visit 2 receive any of the prohibited treatments, or treatment with SCS (oral, IV, IM, SC) or undergo surgery will not be randomized. They may however be re-screened following the procedures described in Section 10.1.

The following is a list of concomitant medications that are permitted during the study:

- Nasal normal saline.
- Single intranasal decongestants administration eg, oxymetazoline hydrochloride (to reduce the swelling and widen the path for the endoscope), as well as a topical anesthetic, eg, lidocaine are allowed before endoscopy.
- Short-acting beta-agonist (SABA), LABA, and LAMA.
- Methylxanthines (eg, theophylline, aminophyllines).
- Inhaled CSs.
- Systemic antihistamines.
- Rescue medication including short courses of SCS for treatment of NP as described in Section 6.9.1 of the Protocol or short courses of SCS to treat other serious co-existing diseases (such as asthma exacerbation) are allowed.

6.9.1 Rescue therapy

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

- Systemic antibiotics (up to 2 weeks) in case of acute infection.
- Short course SCS (prednisone or equivalent prednisolone up to 7 days; avoid use 4 weeks before Week 24 or Week 52, if possible).
- Sinonasal surgery for CRSwNP (8 weeks of IMP treatment is recommended prior to surgery to allow onset of treatment effect).

Participants receiving rescue treatment other than surgery during the study should continue on study drug unless the Investigator decides to withdraw the study treatment. Before starting treatment with SCS participants should come to the study site for the clinical assessments. It is recommended to avoid use of SCS as rescue therapy during the Week 20 to Week 24. If a participant must use SCS during this period to control worsening of symptoms based on Investigator judgment the site should make every effort to schedule the Week 24 CT scan prior to SCS rescue therapy. For participants who undergo or are planned for surgery for CRSwNP, 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 visit. In any case participants who prematurely discontinued the intervention will be encouraged to return to the study site for the efficacy and safety assessments planned at EOT visit and for additional visits. Additional appropriate medical/therapy per local guideline or per Investigators decision may be considered to use as rescue medicine.

The date and time of rescue medication administration as well as the name and dosage regimen of the rescue medication must be recorded in the eCRF.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

Discontinuation of specific sites or of the study as a whole are detailed in Appendix 1 (Section 10.1.9).

7.1 DISCONTINUATION OF STUDY INTERVENTION

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 have an ETD visit with all assessments planned for the EOT Visit. If study intervention is permanently discontinued, the participant should, if at all possible, remain in the study to be evaluated for safety and efficacy. See the SoA 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.

Definitive (permanent) discontinuation is any treatment discontinuation associated with the definitive decision from the Investigator not to re-expose the participant to the IMP at any time during the study, or from the participant not to be re-exposed to the IMP whatever the reason.

The participants may withdraw from treatment with the IMP at any time, irrespective of the reason, or participants may be withdrawn by the Investigator's decision. All efforts should be made to document the reason(s) for treatment discontinuation, and this should be documented in the eCRF.

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

- At their own request or at the request of their legally authorized representative (legally authorized representative means an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective participant to the participant's participation in the procedure(s) involved in the research).
- If, in the Investigator's opinion, continuation in the study would be detrimental to the participant's well-being.
- At the specific request of the Sponsor.
- In the event of a protocol deviation, at the discretion of the Investigator or the Sponsor.
- Pregnancy.
- Anaphylactic reactions or systemic allergic reactions that are related to IMP and require treatment (see Appendix 13 [Section 10.13]).
- Diagnosis of a malignancy during study, excluding squamous or basal cell carcinoma of the skin.

- Any situation that meets permanent discontinuation rule as outlined in Appendix 6 (Section 10.6).
- Any opportunistic infection, such as TB or other infections whose nature or course may suggest an immunocompromised status (Appendix 12 [Section 10.12]).
- Serum ALT>3 × ULN and total bilirubin>2 × ULN (see Appendix 6 [Section 10.6]).
- Serum ALT>5 × ULN if baseline ALT≤2 × ULN or ALT>8 × ULN if baseline ALT>2 × ULN (see Appendix 6 [Section 10.6]).

Any abnormal laboratory value or ECG parameter will be immediately rechecked for confirmation (within 48 hours) before making a decision of permanent discontinuation of the IMP for the concerned participant.

In case of exposure to prohibited concomitant medication such as, but not limited to immunomodulating mAb or immunosuppressants as listed in the prohibited medications from Section 6.9, a decision should be made on the need for temporary or permanent discontinuation of IMP. The decision to resume the treatment with IMP will be made by the Investigator based on the clinical judgment and potential risks of drug interactions.

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 using the procedure normally planned for ETD Visit.

In addition, and to allow assessment of participant outcomes over the stipulated study period, participants will be asked and encouraged to complete all remaining study treatment visits and participate in all safety follow-up assessments according to the visit schedule with a +/- 5-day window.

For such participants the assessment schedule may be reduced. For site visits, under exceptional circumstances when a participant cannot or does not want to come to the site for a scheduled visit, a phone contact can be made. During the phone contact, at least information about AEs, concomitant medications, and exacerbation events should be collected.

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

7.1.2 Liver chemistry stopping criteria

Discontinuation of study intervention for abnormal liver tests is required by the Investigator when a participant meets one of the conditions outlined in Appendix 6 (Section 10.6) 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 decided by the Investigator corresponds to 1 or more dose not administered to the participant. Temporary intervention discontinuation may be considered by the Investigator because of suspected AEs, use of prohibited medication (see Section 7.1.1) or disruption of the clinical trial due to a regional or national emergency declared by a governmental agency (Appendix 9 [Section 10.9: Contingency measures for a regional or national emergency that is declared by a governmental agency]). For all temporary intervention discontinuations, duration should be recorded by the Investigator in the appropriate pages of the eCRF.

7.1.4 Rechallenge

Re-initiation of intervention with the IMP will be done under close and appropriate clinical and/or laboratory monitoring once the Investigator will have considered according to his/her best medical judgment that the responsibility of the IMP(s) in the occurrence of the concerned adverse event was unlikely and if the selection criteria for the study are still met (refer to Section 5.1 and Section 5.2).

For a regional or national emergency declared by a governmental agency, contingency measures are included in Appendix 9 (Section 10.9: Contingency measures for a regional or national emergency that is declared by a governmental agency).

Study intervention restart or rechallenge after liver chemistry stopping criteria are met by any participant in this study is not allowed.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

- A participant may withdraw from the study at any time at the participant's own request for any reason (or without providing any reason).
- A participant may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, or compliance reasons.
- At the time of discontinuing from the study, if possible, an ETD Visit should be conducted, as shown in the SoA (Section 1.3). See SoA (Section 1.3) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- If the participant withdraws consent from the study, the Sponsor will retain and continue to use any data collected before such a withdrawal of consent, as per applicable clinical regulation(s).
- If a participant withdraws from the study, the participant 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 eCRF and in the participant's medical records. In the medical record, at least the date of the withdrawal and the reason should be documented.
- In addition, a participant may withdraw his/her consent to stop participating in the study. 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 rerandomized/reallocated (treated) in the study. Their inclusion and intervention numbers must not be reused.

7.3 LOST TO FOLLOW UP

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

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule, and ascertain whether the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls, and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, the participant 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 randomized, 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.

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA (Section 1.3). Protocol waivers or exemptions are not allowed.
- Adherence to the study design requirements, including those specified in the SoA (Section 1.3), is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- In the event of a significant study-continuity issue (eg, caused by a pandemic), alternate strategies for participant visits, assessments, medication distribution and monitoring may be implemented by the Sponsor or the Investigator, as per local Health Authority/ethics requirements (see Appendix 9 [Section 10.9]).
- Safety/laboratory/analyte results that could unblind the study (eosinophil count, itepekimab levels, and ADA titers) will not be reported to investigative sites or other blinded personnel until the study has been unblinded, unless these are considered critical.
- The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will be within a safe limit for human clinical trials as recommended by the local IRB and IEC.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.
- It is recommended that assessments/procedures at a site visit are performed in the following order if applicable and possible:
  - PROs and other questionnaires.
  - UPSIT.
  - 12-lead ECG.
  - Procedures:
    - Spirometry for participants with asthma only.
    - eDiary download.
    - Safety, laboratory, and biomarker assessments.
    - Nasal secretion sample collection followed by nasal brushing collection.
    - Pre-treatment medications for nasal endoscopy.
    - Nasal endoscopy.
    - Administration of IMP should be performed after blood sampling on visits where sampling for PK is obtained.

For a regional or national emergency declared by a governmental agency, contingency measures are included in Appendix 9 (Section 10.9: Contingency measures for a regional or national emergency that is declared by a governmental agency).

8.1 ADMINISTRATIVE PROCEDURES

Participant demography, previous medical/surgical history, and prior/concomitant medications will be collected at Screening Visit (Visit 1).

8.1.1 Smoking History and Status

The smoking history and status for each participant will be obtained at each study visit as indicated in the SoA.

Participant smoking history will be evaluated and grouped into three categories based on their response to the following; Current Smoker, Former Smoker, and Never Smoker (39).

Participants who report smoking at least 100 cigarettes in their lifetime and who, at the time of the survey, smoke either every day or occasionally are defined as a Current Smoker. Participants who reported smoking at least 100 cigarettes in their lifetime and who, at the time of the survey, do not smoke at all are defined as a Former Smoker. Participants who report never having smoked 100 cigarettes are defined as Never Smoker. Participants who are determined to be Current Smokers at Visit 1 (Screening) are not eligible for participation in the study and will be added into the eCRF as a screen failure.

For participants who are Former Smokers, their smoking history will be assessed using the number of pack-year criteria.

The pack-year is calculated by multiplying the average number of packs of cigarettes smoked per day (1 pack = 20 cigarettes) by the number of years the person has smoked. For example, 1 pack year is equal to smoking 1 pack per day for 1 year, or 2 packs per day for half a year. Participant smoking history will be documented into the study source document and the eCRF.

Current smokers are not eligible for the study. Former smokers are only eligible in whom smoking cessation has occurred ≥6 months prior to Screening (Section 5.2; E 02). Former smokers who resume smoking during the study do not need to be withdrawn from study participation.

8.2 EFFICACY ASSESSMENTS

Planned timepoints for all efficacy assessments are provided in the SoA.

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

The CRSwNP sinonasal symptom diary is designed to assess the severity of CRS sinonasal symptoms on daily basis. These symptoms include nasal congestion/obstruction, anterior rhinorrhea and posterior rhinorrhea, facial pain/pressure, loss of smell, and headache (40). Each of the individual items of the diary are scored from 0 ("No symptoms") to 3 ("Severe symptoms - symptoms that are hard to tolerate, cause interference with activities of daily living"). Higher scores on the items of the individual symptoms denote greater symptom severity.

The CRSwNP Total symptom Score (TSS) is a composite score derived from the following individual items: NC/obstruction, anterior/posterior rhinorrhea, and loss of smell. The total score ranges from 0 to 9 and consists of the sum of NC, the averaged rhinorrhea item scores, and loss of smell. Higher scores on TSS indicate greater overall symptom severity.

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

The CRSwNP Symptom Diary is provided in Appendix 10 (Section 10.10.1) Participants will complete the CRSwNP sinonasal symptom diary as described in the SoA (Section 1.3).

8.2.2 Nasal polyp score

The NPS is the sum of the right and left nostril scores, as evaluated by means of nasal endoscopy. NP is graded based on polyp size as follows:

Table 7 - 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 assessments, prior to administration of IMP, and preceded by local administration of anaesthetic drugs in combination with a decongestant based on local protocols.

Standard video sequences will be uploaded and sent to centralized reader. Centralized imaging data assessments and scoring by independent physician reviewers for the imaging data will be performed for all endoscopies. To confirm eligibility at Visit 2, the Visit 1 central reading will be made available to the site. Local reading of nasal endoscopy is done at Visit 2 to confirm eligibility. Visit 2 endoscopy will be uploaded for later central review.

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

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

8.2.3 Nasal congestion/obstruction score

The NCS is scored using a 0-3 categorical scale where 0 = no symptoms, 1 = mild symptoms, 2 = moderate symptoms and 3 = severe symptoms.

- Outcome value is defined as the preceding 28-day average of morning scores recorded in eDiary.

8.2.4 Computed tomography

The CT scans should be performed anytime before first administration of IMP at Visit 2 (baseline CT data) and Visit 14 (Week 24). Whenever possible a cone beam CT scan should be utilized. If a participant needs to be re-screened or is terminated early from the study intervention, a repeat CT scan may be performed if local regulations allow. If a Participant discontinues the study intervention prematurely, the CT scan will be performed as soon as possible, with all other assessments normally planned in EOT Visit.

It is recommended to avoid use of SCS as rescue therapy during the Week 20 to Week 24 period. If a participant must use SCS during these periods to control CRSwNP worsening/acute sinusitis based on Investigator judgment the site should make every effort to schedule the Week 24 CT scan prior to SCS rescue therapy.

The CT scan will be performed locally and reviewed centrally by independent blinded reviewer(s). For the analysis, central reading of baseline CT will be used for comparison with EOT central reading. For both LMK scores and 3D volumetric measurement of the sinuses, the same acquisitions (sequences) will be used for centralized imaging data assessments and scoring by an independent physician reviewer for the imaging data. Central reading of Visit 1 will be used for comparison with Week 24 CT scan. The final results of central reading will be made available after the study. Details on CT will be available in a separate operational manual provided to the sites.

8.2.4.1 Lund-Mackay score

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, frontal sinus on each side. The osteomeatal complex is graded as 0 = not occluded, or 2 = occluded, deriving a maximum score of 12 per side (41). This scoring system has been validated in several studies (42, 40).

8.2.4.2 Three-Dimensional volumetric measurement of the maxillary sinus

For the analysis, central reading of baseline CT will be used for comparison with Week 24 central reading. The sites will remove participant-identifying information from the imaging data header prior to uploading the imaging data to the central reader. The % change in opacification from baseline to Week 24 will be calculated.

8.2.5 Smell test: University of Pennsylvania Smell Identification Test

The UPSIT test is a rapid and easy-to-administer method to quantitatively assess human olfactory function. The UPSIT shows a high test-retest reliability and scores on this test are strongly correlated with the detection threshold for phenyl ethyl alcohol in the same individuals. When the UPSIT is administered in the standardized manner, clinical subjects show a high degree of uniformity in UPSIT performance when tested in different laboratories.

The test consists of 4 booklets, each containing 10 odorants with one odorant per page. The test-time is about 15 min. The stimuli are embedded in 10-50 (mu) diameter plastic microcapsules on brown strips at the bottom of each page. Above each odorant strip is a multiple-choice question with 4 alternative words to describe the odour. The subject is asked to release the odorant by rubbing the brown-strip with the tip of a pencil and to indicate which of 4 words best describes the odour. Thus, each subject receives a score out of 40 possible correct answers. The final score will be recorded in the eCRF.

The 40-odorant UPSIT is used in over 1500 clinics and laboratories throughout the US, Canada, South America, and Europe, and has been administered to nearly 200 000 people since its development in the early 1980s. A particular strength of this test is that it provides an olfactory diagnosis based on comparing the participant's test score with normative data, providing a percentile score of an individual relative to his or her age-matched normal group. Furthermore, a clinician can distinguish participants with a normal sense of smell (normosmia) from those with different levels of reduction (mild, moderate and severe microsmia) or loss (anosmia) (43). The UPSIT will be developed and used to match to each culture easing participants identifications of the odorant depending on degree of loss of sense of smell.

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

8.2.6 Spirometry

Participants with co-morbid asthma, will undergo spirometry in accordance with the ATS/ERS guidelines (44, 45) and prior to administration of IMP at the planned time points (SoA, Section 1.3). For participants with co morbid asthma who are prescribed BD, pre-BD spirometry will be performed after a wash out period of BD according to their action duration, following the guidance of the ATS/ERS 2019 guidance. For example, withholding the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours, withholding the last dose of LABA for at least 24 hours, and finally the last dose of ultralong-acting LABA (like vilanterol) or the last dose of LAMA should be withheld for at least 36 hours. This will be verified before performing the measurements. In addition, participants will be asked to avoid consuming alcohol 8 hours prior to spirometry, and to avoid engaging in strenuous exertion for at least 30 minutes prior to all lung function assessments.

At all site visits, spirometry should be performed preferably in the morning – afternoon is allowable when morning spirometry cannot be performed. Spirometry should be done at approximately the same time at each visit throughout the study. The same spirometer and standard spirometric techniques, including calibration, will be used to perform spirometry at all visits, and whenever possible, the same person should perform the measurements. Three measurements fulfilling the ATS/ERS guidelines acceptability and repeatability criteria should be obtained at every site visit, if possible.

Spirometry will be centrally read.

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

8.2.7 Sino-nasal outcome test

The SNOT-22 is a PRO questionnaire designed to assess the impact of CRS on patient's HRQoL (46). SNOT-22 has 22 items covering five domains: Nasal, Ear/Facial, Sleep, Function, and Emotion. The recall period is past 2 weeks. Each item is rated on a 6-point Likert scale response option, ranging from 0 (No problem) to 5 (Problem as bad as it can be). A global score ranging from 0 to 110 is calculated by summing the responses to all items; higher score indicates greater rhinosinusitis-related health burden. The questionnaire is an easy, valid and reliable tool (46). The minimally important difference that is the smallest change in SNOT-22 score that can be detected by a participant was found to be 8.9 points (46). The SNOT-22 is provided in Appendix 10 of the Section 10.10.

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

8.2.8 Asthma Control Questionnaire, 5-question version, in participants with comorbid asthma

The ACQ is a questionnaire that measures the adequacy of asthma control and any changes in asthma control that may occur spontaneously or as a result of treatment. The ACQ-5 has 5 questions on the asthma symptoms and participants are asked to recall how their asthma has been during the previous week. Only participants with co-morbid asthma will be asked to complete the questionnaire in the eDiary during clinic visits. Participants should complete the questionnaire before the spirometry test.

The ACQ-5 has 5 questions which assess the most common asthma symptoms:

- Frequency in past week awoken by asthma during the night.
- Severity of asthma symptoms in the morning.
- Limitation of daily activities due to asthma.
- Shortness of breath due to asthma.
- Frequency of wheezing.

Participants are asked to recall how their asthma has been during the previous week and to respond to the symptom questions on a 7-point scale (0 = no impairment, 6 = maximum impairment). The ACQ score is the mean of the item responses and ranges from 0 (totally controlled) and 6 (severely uncontrolled).

A global score is calculated: the questions are equally weighted, and the ACQ-5 score is the mean of the 5 questions. Higher score indicates lower asthma control. Participants with a score below 1.0 reflect adequately-controlled asthma and participants with scores above 1.0 reflect inadequately-controlled asthma. On the 7-point scale of the ACQ-5, a change or difference in score of 0.5 is the smallest change that can be considered clinically important, corresponding to the Minimal Clinically Important Difference (MCID) defined by the developer. Measurement properties such as reliability, ability to detect change have been documented in the literature (47).

The ACQ-5 is provided in Appendix 10 (Section 10.10).

8.2.9 EuroQol-5 questionnaire

The EQ-5D is a standardized PRO measure of health status developed by the EuroQol Group in order to provide a simple, generic measure of health for clinical and economic appraisal (48, 49). The adult version of the questionnaire is adapted to participants age 16 and older. The EQ-5D consists of 2 parts: the descriptive system and the EuroQoL-VAS. The EQ-5D-5L descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 levels of perceived problems: “no problem”, “slight problems”, “moderate problems”, “severe problems”, and “extreme problems” (50). The respondent is asked to indicate his/her health state by ticking (or placing a cross) in the box against the most appropriate statement in each of the 5 dimensions; this results in a 1-digit number expressing the level for that dimension. The digits for 5 dimensions can be combined in

a 5-digit number describing the respondent's health state. The health state will be converted into a single utility index value. The EQ-VAS records the respondent's self-related health on a vertical VAS where the endpoints are labeled "best imaginable health state (100)" and "worst imaginable health state (0)". This information can be used as a quantitative measure of health outcome as judged by the individual respondents. The recall period of the questionnaire is "today".

The EQ-5D-5L is provided in Appendix 10 (Section 10.10).

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

8.2.10 Patient Global Impression of Change and Patient Global Impression of Severity

The PGIC is a 7-item questionnaire that asks the participant to provide a self-assessment of change in individual CRSwNP symptoms (ie, nasal congestion/obstruction, anterior rhinorrhea, posterior rhinorrhea, facial pain/pressure, loss of smell, and headache) and in their CRSwNP overall on a 5-point scale compared to just before the participant started taking the study treatment. The response choices are: 1 = "Much better", 2 = "A little better", 3 = "No change", 4 = "A little worse", 5 = "Much worse".

The PGIS is a 7-item questionnaire that asks participants to provide a self-assessment of the severity of individual CRSwNP symptoms and in their CRSwNP overall on a 4-point scale for the past week. Response choices are: 1 = "None", 2 = "Mild", 3 = "Moderate", and 4 = "Severe".

The PGIC and PGIS are provided in Appendix 10 (Section 10.10).

Participants will complete the PGIC and PGIS as described in the SoA (Section 1.3).

8.2.11 Work Productivity and Activity Impairment - Specific Health Problem (WPAI-SHP)

The WPAI-SHP Questionnaire (51) is a 6-item instrument that measures absenteeism, presenteeism, and impairments over the past 7 days in both paid work and daily activities due to one's health. Four scores are generated: "Percent work time missed due to problem", "Percent impairment while working due to problem", "Percent overall work impairment due to problem", and "Percent activity impairment due to problem". Each score ranges from 0% to 100%, with higher scores indicating grater impairment and less productivity.

The WPAI-SHP is provided in Appendix 10 (Section 10.10).

8.2.12 Leicester Cough Questionnaire

The Leicester Cough Questionnaire is validated PRO questionnaire evaluating cough on quality of life in subjects with CRS (52) (See Appendix 10, Section 10.10).

The questionnaire comprises 19 items and takes 5 to 10 minutes to complete. Each item assesses symptoms or the impact of symptoms over the last 2 weeks on a 7-point Likert scale ranging from 1: "all of the time" to 7: "none of the time". Scores in 3 domains (Physical, Physiological, and Social) are calculated as a mean for each domain (range 1 to 7). A total score (range 3 to 21) is also calculated by adding the domain scores together. Higher scores indicate better QoL.

8.2.13 Patient-Reported Outcomes Measurement Information System Sleep Disturbance - Short Form 8b

The PROMIS V1.0 SD-SF-8b is a generic 8-item sleep disturbance assessment that evaluates difficulties with falling asleep, staying asleep, and getting enough sleep; and perceptions on the quality and satisfaction of sleep (53). Five-point Likert scales are used for response options (ie, not at all to very much; never to always; and very poor to very good). Scores are calculated with a conversion of the raw score (score range 8 to 40) into a standardized T-score for which the reference population has a mean of 50 and SD of 10. Higher scores indicate more disturbed sleep.

The PROMIS SD-SF-8b is provided in Appendix 10 (Section 10.10).

8.3 SAFETY ASSESSMENTS

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

8.3.1 Physical examinations

- A complete physical examination will include, at a minimum, assessments of the skin, nasal cavities, eyes, ears, respiratory, cardiovascular, gastrointestinal, neurological, lymphatic and musculoskeletal systems. Height and weight will also be measured and recorded at screening. Weight will also be measured and recorded at Week 52/EOT and ETD.
- A brief physical examination will include, at a minimum, assessments of the nasal cavities, respiratory and cardiovascular systems. Additional systems may be examined as per clinical judgment of the Investigator.
- Investigators should pay special attention to clinical signs related to previous serious illnesses and intercurrent infections.

8.3.2 Vital signs

- Oral/Tympanic/Rectal/Axillary/Skin/Temporal artery temperature (°C), heart rate (beat per minute), respiratory rate (breaths per minute), and systolic and diastolic blood pressure (mmHg) will be recorded (if possible before blood collection for laboratory tests).
- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (eg, television, cell phones).

8.3.3 Electrocardiograms

- Single 12-lead ECG(s) will be obtained as outlined in the SoA (see Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and corrected QT (QTc) intervals.

- The ECGs will be obtained prior to laboratory assessments. A qualified Investigator or appropriate designee (qualified physician) should review the ECGs in a timely manner to determine if there are any safety concerns and for clinical management of the participant. In case of abnormal findings identified by the qualified Investigator or appropriate designee (qualified physician), the ECG should be provided to the cardiologist if deemed necessary for further confirmation and description of the findings. The Investigator must always date and sign the ECG and comment on the assessment before filing this in the medical records. In the event of any clinically significant abnormal finding that meet the definition of an AE (Section 8.4) the Investigator will continue to monitor the participant with additional ECGs until the ECG findings return to baseline ECG findings or the Investigator determines that follow-up is no longer necessary.
- Any clinically significant ECG related to a preexisting condition at Screening (Visit 1) that does not affect the conduct of the study per the Investigator's judgment will need to be well documented in the source documentation.

8.3.4 Clinical safety laboratory tests

- See Appendix 2 (Section 10.2) for the list of clinical laboratory tests to be performed and to the SoA (Section 1.3) for the timing and frequency.
- The Investigator must review the laboratory results, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory results must be retained with source documents. See Appendix 3 (Section 10.3) for abnormal laboratory results reporting. All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 20 weeks after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator.
  - If clinically significant 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 eCRF.
  - Critical values alerts are linked to extremely high or low laboratory test values which are considered to be potentially life-threatening. In case of abnormal lab value, the Central Laboratory will contact the site.
  - Special procedures for collection, storage, and shipping of serum are described in the Central Laboratory Manual.
  - At Screening, hepatitis serology testing is performed in order to rule out active or chronic infection. Guidance on hepatitis serology eligibility interpretation is provided in Table 8.

Table 8 - Hepatitis serology testing

Hepatitis serology result	Protocol action
HBsAg: positive or indeterminate	Excluded
HBsAb positive, HBsAg negative, HBcAb: negative	Eligible
HBcAb IgM: positive	Excluded
HBcAb Total: positive (with or without HBsAb positive)	Test for HBV DNA If HBV DNA Positive: Excluded If HBV DNA Indeterminate: Eligible
HCV antibody: positive	Test for HCV RNA If HCV RNA Positive: Excluded If HCV RNA Indeterminate: Eligible

Abbreviations: DNA = deoxyribonucleic acid; HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HBsAb = hepatitis B surface antibody; HCV = hepatitis C virus; Ig = immunoglobulin; RNA = ribonucleic acid.
See Section 10.8.5 for country-specific requirements for Czechia.

8.3.5 Pregnancy testing

Pregnancy testing will be performed in all WOCBP at screening with a blood test using a central laboratory, and at subsequent visits using Sponsor-provided urine tests, or locally provided urine test (China only) (see SoA, Section 1.3). Participant will be instructed to not administer next IMP in case of suspected/confirmed pregnancy and contact the site.

8.4 ADVERSE EVENTS (AES), SERIOUS ADVERSE EVENTS (SAES) AND OTHER SAFETY REPORTING

The definitions of AE and SAE can be found in Appendix 3 (Section 10.3). The definition of AESI is provided in Section 8.4.7

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

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative) that meet the definition of an AE or SAE and remain responsible for following up AE that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the IMP (see Section 7). This includes events reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

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

8.4.1 Time period and frequency for collecting AE and SAE information

All AE (serious or nonserious) will be collected from the signing of the ICF until EOS visit at the timepoints specified in the SoA (Section 1.3).

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

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

8.4.2 Method of detecting AE and SAE

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

8.4.3 Follow-up of AE and SAE

After the initial AE/AESI/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. At the pre-specified study end-date, all SAE and AESI (as defined in Section 8.4.7), 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).

8.4.4 Regulatory reporting requirements for SAE and other safety reporting

- Prompt notification by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and Investigators.
- SAE that are considered expected will be specified in the reference safety information (specify IB or label).
- Investigator safety reports must be prepared for SUSAR 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 SAE) from the Sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements. It is the responsibility of the Sponsor to assess whether an event meets the criteria for a SUSAR, and therefore, is expedited to regulatory authorities.
- For the European Union, safety reporting to the agency is described in Section 10.8.6.1.

8.4.5 Pregnancy

- Details of all pregnancies in female participants and, if indicated, female partners of male participants will be collected after the start of study intervention and until 20 weeks after the last administration of study intervention. Refer to Section 5.1.
- 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 or female partner of male participant (after obtaining the necessary signed informed consent from the female partner) pregnancy.
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAE and will be reported as such.
- The participant/pregnant female partner will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant/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 8.4.4. While the Investigator is not obligated to actively seek this information in former (study participant/pregnant female partner), he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study intervention or be withdrawn from the study.

8.4.6 Disease-related events and/or disease-related outcomes not qualifying as AE or SAE

Worsening of the underlying CRSwNP disease may occur during the study, including worsening of symptoms such as nasal congestion/obstruction, loss of smell, facial pain, and rhinorrhea. These events are associated with the disease under study, and thus will not be considered unexpected. Specifically, worsening of underlying condition is not considered an AE unless it meets the criteria of seriousness as indicated in Section 10.3.2.

NOTE: However, if either of the following conditions applies, then the event must be recorded and reported as an AE/SAE (instead of a disease-related event [DRE]):

- The event is, in the Investigator's opinion, of greater intensity, frequency, or duration than expected for the individual participant,

  OR

- The Investigator considers that there is a reasonable possibility that the event was related to study intervention.

8.4.7 Adverse events of special interest

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

- Pregnancy of a female participant entered in a study as well as pregnancy occurring in a female partner of a male participant entered in a study with IMP/AxMP;
  - Pregnancy occurring in a female participant entered in the clinical trial or in a female partner of a male participant entered in the clinical trial. It will be qualified as an SAE only if it fulfills one of the seriousness criteria (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 Section 8.4.5).
- Symptomatic overdose (serious or nonserious) with IMP/AxMP (see definition of an overdose in Section 6.8). 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 <8 days.
- Drug abuse with IMP: An abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects, ie, intentional non-therapeutic use of a medicinal product by a participant for a perceived reward or desired non-therapeutic effect including, but not limited to, "getting high"(euphoria).
- Increase in alanine transaminase (ALT)
  - ALT>3 × the ULN associated with total bilirubin>2 × ULN,

    OR
  - ALT>5 × the ULN if baseline ALT≤2 × ULN,
  - ALT>8 × ULN if baseline ALT>2 × ULN.

- Other project specific AESI(s)
  - Anaphylactic reactions or systemic allergic reactions that require treatment (see Appendix 12 [Section 10.12]).
  - Severe ISR that last longer than 24 hours.

  Note: A severe ISR (for AE reporting) is any event that meets one of the following criteria:
  - With a diameter of at least 10 cm.
  - Impacting daily activities.
  - With ulceration or necrosis.
  - For which operative intervention is required.

  Note: adverse event intensity should be reported as 'severe' if ISR is reported as 'severe ISR AESI'.
  - Any infection meeting at least one of the following criteria:
    - Any serious infection (SAE).
    - Requires parenteral (IV, IM, SC) antimicrobial therapy. Note: antimicrobial therapy refers to antibiotic, antiviral, and antifungal agents.
    - Requires oral antimicrobial therapy for longer than 2 weeks.
    - Is a parasitic infection.
    - Is an opportunistic infection (see Appendix 12 [Section 10.12]).
  - Malignancy.

The definitions of an AE or SAE can be found in Appendix 3 (Section 10.3).

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

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study intervention or study (see Section 8.4).

8.4.8 Medication errors or misuses of medicinal product

All reports of medication error or misuse in relation to the IMP with or without an AE must be recorded on the corresponding page(s) of the CRF and transmitted to the Sponsor’s representative following standard processes.

A medication error is an unintended failure in the drug treatment process (ie, mistake in the process of prescribing, storing, dispensing, preparing, or administering medicinal products in clinical practice) that leads to, or has the potential to lead to harm to the participant. This includes situations in which a participant was involved or not (eg, even if the error was recognized and intercepted before the participant received or used the product), and whether it resulted in harm to the participant or not.

A misuse refers to situations where the medicinal product is intentionally and inappropriately used, ie, not in accordance with the terms of the marketing authorization or outside what is foreseen in the protocol, by the participant for a therapeutic purpose.

Of note, if a medication error or misuse meets the protocol definition of an overdose, it will be recorded in the overdose page of the eCRF.

8.4.9 Guidelines for reporting product complaints

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

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

8.5 PHARMACOKINETICS

Blood samples will be collected for determination of functional itepekimab concentrations in serum as specified in the SoA (Section 1.3). Samples may be collected at additional time points during the study if warranted (see Appendix 6, Section 10.6). Special procedures for collection, storage, and shipping of serum are described in separate operational manuals. The actual date and time (24-hour clock time) of each sample will be recorded. The sample types for PK samples are described in Table 9.

Table 9 - Summary of handling procedures for PK samples

Sample type	PK (itepekimab)
Matrix	Serum
Blood sample volume	5 mL
Blood handling procedures	See Operational Manual
Serum aliquot split	2 aliquots
Serum shipment condition	In dry ice

Abbreviations: PK = pharmacokinetic(s).

The bioanalytical methods for PK are summarized in Table 10.

Table 10 - Summary of bioanalytical methods for PK samples

Analyte	PK (itepekimab)
Matrix	Serum
Analytical technique	ELISA
Site of bioanalysis	Regeneron

Abbreviations: ELISA = enzyme-linked immunosorbent assay; PK = pharmacokinetic(s).

Drug concentration information that may unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

Note: If an SAE or AESI (anaphylaxis, systemic hypersensitivity reaction, and severe ISR lasting 24 hours) occurs in a participant, additional blood samples may be collected for determination of functional itepekimab concentration at or near the onset of the occurrence of the event.
An unscheduled systemic drug concentration page in the eCRF must be completed as such a case as well.

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

- Pharmacokinetic samples could be used for testing analytical method performance such as comparability and incurred sample reproducibility and for possible exploratory analysis of drug metabolites. The exploratory data will not be included in the study report but will be kept on file.

For China, please see Section 10.8.1 for details.

8.6 PHARMACODYNAMICS

See Section 8.8

8.7 GENETICS

A whole blood sample for exploratory DNA analysis will be collected from participants eligible for enrollment, who have consented to participate in the optional genetic analysis component of the study. Participation is optional in this blood-based DNA analysis. Participants who do not wish to participate in the genetic research may still participate in the study. Whole blood samples for DNA analysis will be collected at pre-dose baseline. In the event of DNA extraction failure, a replacement genetic blood sample may be requested from the participant. Signed informed consent will be required to obtain a replacement sample unless it was included in the original consent.

A nasal brushing sample taken from the inferior turbinate of each nostril will be collected for exploratory RNA analysis from participants eligible for enrollment. Participants have the option to opt out from participation in providing nasal brushing samples.

Samples collection is indicated in the SoA (Section 1.3).

Whole blood DNA samples and nasal brushing RNA samples may be used to determine a possible relationship between gene expression levels and/or genetic variation and

- Response to treatment with itepekimab (which may include aspects such as biologic effects and clinical efficacy).
- How the body processes itepekimab.
- Possible side effects of itepekimab.
- Features of CRSwNP and related diseases.

Analysis of nasal brushing RNA will also be performed to identify changes in gene expression from baseline and identify potentially predictive and response-associated gene signatures.

Details on handling, shipping, and destruction of samples for genetic analysis is described in a separate document except where not applicable due to country-specific requirements.

Results of these exploratory analyses may be presented in reports separate from the CSR.

More information regarding genetic research can be found in Appendix 5 (Section 10.5).

For China, please see Section 10.8.1 for details.

8.8 BIOMARKERS

- Blood samples will be collected to perform analysis of markers associated with CRSwNP and/or itepekimab activity to determine the effect of itepekimab on the biomarkers. Biomarkers may include and are not limited to total IgE, TARC, eotaxin3, periostin, ECP, IL5, IL13, IFNg, IL17A, IL33, sST2. Samples will be collected according to the schedule described in the SoA and as detailed in the laboratory manual provided separately to the sites. Analysis will be stepwise and depending upon outcome some analyses may be skipped.
- Blood eosinophils, neutrophils, and monocytes will be assessed pre-dose and at time points described in the SoA (see Section 1.3).
- Samples for analysis of nasal absorption biomarkers will be collected, which may include and are not limited IFNg, IL5, IL17A, IL33, TNFα, IL17F, IL22, IL13, CXCL8 (IL8), IL4, IL6, IL1β, tryptase, CXCL9, CXCL10, colony stimulating factor (CSF)3. Analysis will be stepwise and depending upon outcome some analyses may be skipped.
- Nasal brushing for analysis on gene expression changes will be assessed at selected time points described in the SoA.
- Urine biomarkers: leukotriene E4 (LTE4) and creatinine.

For China, please see Section 10.8.1 for details.

8.9 IMMUNOGENICITY ASSESSMENTS

Antibodies to itepekimab will be evaluated in serum samples collected from all participants according to the SoA (Section 1.3). Additionally, serum samples should also be collected at the final visit from participants who discontinued study intervention or were withdrawn from the study.

Instructions for the collection and handling of these samples will be provided by the Sponsor. These samples will be tested by the Sponsor or Sponsor's designee using a validated assay method.

Samples for immunogenicity analyses and their derivatives may be stored for up to 5 years after last patient last visit (LPLV) for potential re-analyses.

A 3-tiered approach will be employed to assess the immunogenicity of itepekimab when applicable: samples will be screened and then confirmed for antibodies binding to itepekimab and the titer of confirmed positive samples will be reported. Other analyses may be performed to further characterize the immunogenicity of itepekimab.

All samples collected for detection of antibodies to itepekimab may also be evaluated for itepekimab serum concentration to enable interpretation of the antibody data.

For China, please see Section 10.8.1 for details.

8.10 HEALTH ECONOMICS OR MEDICAL RESOURCE UTILIZATION AND HEALTH ECONOMICS

For all participants throughout the study, the Investigator and study site personnel will collect data about health care resource utilization associated with medical encounters that are related to CRSwNP and asthma for participants with asthma co-morbidity. Protocol-mandated procedures, tests, and encounters are excluded.

The data collected will include the number of outpatient/specialist encounters and emergency room/urgent care clinic visits.

The Sponsor may use the collected data to conduct economic analyses. Hospitalization and CRS-related surgery data are collected per protocol in other sections and thus will not be collected again but can inform economic analyses.

8.11 USE OF BIOLOGICAL SAMPLES AND DATA FOR FUTURE RESEARCH

Future research may help further the understanding of disease and the development of new medicines. Reuse of coded data and biological samples (leftover and additional) collected as part of the study will be limited to future scientific research conducted under a research plan for the purpose of diagnosing, preventing or treating diseases. The future research projects will be conducted under the Sponsor's and/or its affiliates' and/or, if applicable, the partner of

the Sponsor which has licensed the study drug to the Sponsor or which is co-developing the study drug with the Sponsor's control, acting alone or in collaboration with research partners such as universities, research institutions or industrial partners with whom the coded study data may be shared.

Coded study data and biological samples will be stored and used for future research only when consented to by participants (see Section 10.1.3) and, when applicable, further information on the future research has been provided to the study participant unless prohibited by local laws or IRBs/IECs (in such case, consent for future use of data/sample will not be included in the local ICF). The conditions for reuse will be adapted locally with the appropriate language in the ICF.

In any case, a specific consent will be collected for the performance of genetic analyses on leftover and/or additional samples.

For China, please see Section 10.8.1 for details.

Data protection – Processing of coded study data

The study participant will be provided will all mandatory details of the data processing in Part 2 of the core ICF.

The Sponsor adopts safeguards for protecting participant confidentiality and personal data (see Section 10.1.4).

Use of leftover samples and additional samples for future research

Remaining leftover samples will be used only after the study ends, ie, EOS as defined in the study protocol. Additional/extra samples can be collected and used during the study conduct at a given timepoint (eg, at randomization Visit) as defined in the study protocol.

The study participant will be provided with all mandatory details of the use of the human biological samples (leftover and additional) in Part 2 of the core ICF.

Study participant data will be stored for up to 25 years for regulatory purposes. Biological samples for future use will be stored for up to 25 years after the EOS unless local regulations require a different retention period. Any samples remaining at the end of retention period will be destroyed. If a participant requests destruction of his/her samples before the end of the retention period, the Investigator must notify the Sponsor (or its contract organization) in writing. In such case, samples will be destroyed and related coded data will be anonymized unless otherwise required by applicable laws.

9 STATISTICAL CONSIDERATIONS

The statistical analysis plan will be finalized prior to interim analysis and database lock and it 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.

9.1 POPULATIONS FOR ANALYSES

The following populations for analyses are defined.

Table 11 - Populations for analyses

Population	Description
Screened	All participants who signed the ICF.
Randomized	All participants from screened population who have been allocated to a randomized intervention by IRT regardless of whether the intervention was received.
Exposed	All screened participants who have taken at least 1 dose of study intervention regardless of the amount of study intervention administered.
ITT/Efficacy	All randomized participants. Participants will be analyzed according to the intervention allocated by randomization.
Safety	All randomized participants who have taken at least 1 dose of study intervention, regardless of the amount of intervention administered. Participants will be analyzed according to the intervention they actually received.
PK	All participants from the safety population with at least one post-baseline PK result. Participants will be analyzed according to the intervention they actually received.
ADA	All participants from the safety population treated with itepekimab with at least one post-baseline ADA result (positive, negative or inconclusive). Participants will be analyzed according to the intervention they actually received.

Abbreviations: ADA = antidrug antibody; ICF = informed consent form; IRT = interactive response technology; ITT = intent-to-treat; PK = pharmacokinetics.

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

9.2 STATISTICAL ANALYSES

9.2.1 General considerations

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

For endpoints defined using the data collected on the eDiary (such as NCS and TSS), baseline is defined as the average of the scores in the 7 days prior to randomization; for the baseline to EOT analysis, the average of the scores from the preceding 28 days to the corresponding timepoint will be defined as the analysis score for that timepoint.

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

The observation period will be divided into 4 segments:

- The **pre-treatment** period is defined as the period up to first IMP administration.
- The **TE period** is defined as the period from the first IMP administration to the last IMP administration + 154 days (ie, to the end of 20-week safety follow-up period).
  The TE period includes the following 2 periods:
  - The **on-treatment period** defined as the period from the first IMP administration to the last administration of the IMP + 14 days.
  - The **residual treatment period** defined as the period from the end of the on-treatment period to the end of the TE period.
- The **post-treatment period** defined as the period from the end of the TE period.

9.2.2 Primary endpoint(s) analyses

9.2.2.1 Definition of endpoint(s)

The two co-primary endpoints are the change from baseline to Week 24 in bilateral endoscopic NPS and in NCS.

9.2.2.2 Main analytical approach

The 2 co-primary endpoints will be analyzed with the primary estimand defined according to the following attributes:

- Endpoint: change from baseline to Week 24 in NPS and NCS.
- Intervention condition: itepekimab 300 mg Q2W and itepekimab 300 mg Q4W will be compared to placebo, on top of background therapy.
- Analysis population: intent-to-treat (ITT) population.
- Intercurrent events:
  - The following IEs will be handled with a composite variable strategy. Data after the IE will be assigned to the worst possible score:
    a) Use of selected prohibited/rescue medication (eg, prohibited biologic therapy) prior to Week 24.
    b) Nasal/sinus surgery prior to Week 24.

- The following IEs will be handled with a treatment policy strategy. All assessments after starting such IE and before or at Week 24 will be included:
  a) Use of SCS for any reason.
  b) Study intervention discontinuation.
  c) Use of other prohibited/rescue medications prior to Week 24.

- Population-level summary: difference in LS means between itepekimab and placebo from ANCOVA model with change from baseline to Week 24 in NPS and NCS as response variables, intervention group (itepekimab 300 mg SC Q2W, itepekimab 300 mg Q4W, or placebo) and randomization stratification factors (asthma/AERD status and regions) as fixed effects, and the baseline value as covariates. The corresponding 95% CI will be provided along with the p-value. In addition, descriptive statistics including number of participants, mean, SEM, and LS means will be provided for each intervention group.
- Missing data handling.

After applying the rules for IEs, if there is still missing data, then the missing data will be handled as follows:

- For participants who discontinue IMP before Week 24 without use of selected prohibited/rescue medication (eg, prohibited biologic therapy) or nasal/sinus surgery prior to Week 24: MI approach will be used to impute missing endpoint value at Week 24, and this MI will use all participants from the same randomized arm, excluding participants who use selected prohibited/rescue medication (eg, prohibited biologic therapy) or nasal/sinus surgery prior to Week 24.

  Each of the imputed complete data will be analyzed by fitting the ANCOVA model. Statistical inference obtained from all imputed data will be combined using Rubin's rule.

9.2.2.3 Sensitivity analyses

The reason and pattern of missing data will be carefully examined. Sensitivity analyses will be performed to confirm robustness of the results with respect to the missing data handling strategy in addition to the primary estimand. In particular, a sensitivity analysis will be performed using a control-based (ie, jump to reference) pattern mixture model by multiple imputation (PMM-MI) for missing data. Details of the sensitivity analyses will be provided in the SAP.

9.2.2.4 Supplementary analyses

Supplementary analyses will be performed, eg, to confirm robustness of the results with respect to the IE handling strategy in addition to the primary estimand. In particular, a supplementary analysis will be performed considering a composite strategy for handling the use of SCS for any reason, the use of selected prohibited/rescue medication (eg, prohibited biologic therapy) and nasal/sinus surgery prior to Week 24 (data after the IE will be assigned to the worst observation carried forward [WOCF]). In addition, a supplementary analysis will be performed considering a treatment policy strategy to handle all the IEs. Details of the supplementary analyses will be provided in the SAP.

9.2.3 Secondary endpoint(s) analyses

The secondary endpoints detailed in this section are as follows:

- **Continuous efficacy endpoints** including change from baseline in NPS and in NCS at Week 52, change from baseline in LMK score at Week 24, change from baseline in TSS, in Loss of Smell Symptom Severity score, in UPSIT score, in SNOT-22 total score and PROMIS SD-SF-8b score at Week 24 and Week 52: these endpoints will be analyzed in the same fashion as the co-primary endpoints described in Section 9.2.2.2.
- **Proportion endpoints,** including proportion of participants with CRSwNP requiring SCS or surgery for CRS during the planned study intervention period and proportions of NPS responders, will be analyzed using an MH method stratified by asthma/AERD strata and region. The estimate of the MH weighted risk difference and corresponding Wald 95% confidence interval and Wald test using Sato variance will be provided. All data collected after study intervention discontinuation will be used in the analysis. Participants who discontinue the study without an event will be considered as no event.
- **Time to first SCS use or surgery for CRS** will be analyzed using a Cox regression model. The time to the first event will be included as the dependent variable while intervention group, asthma/AERD strata and region will be used as covariates. The HR will be estimated for comparison of each Itepekimab regimen to placebo.
  The Kaplan-Meier method will be used to derive the probabilities that a participant would experience an event up to specific time points for each intervention group.
- **The annualized number of SCS course or surgery for CRS** during the planned study treatment will be analyzed using a negative binomial regression model. The model will include the number of SCS course or surgery for CRS during the planned study treatment period as the response variable, with intervention group, asthma/AERD strata and regions. Log transformed treatment duration will be the offset variable. The estimated annualized number of SCS courses or surgery for CRS for each treatment group and its 95% CI will be derived from the negative binominal model. The event rate ratio of each Itepekimab regimen versus placebo and the corresponding 95% CI and p-values will be provided.
- **Changes from baseline to Week 24 and 52 in pre-BD FEV1 and in ACQ-5 score** will be analyzed in participants with comorbid-asthma. These endpoints will be analyzed in the same fashion as for the coprimary endpoints without the asthma/AERD strata as a covariate in the model.
- **The following efficacy endpoints will be analyzed in participants with AERD,** in the same fashion as the one considered on the entire population without the asthma/AERD strata as a covariate in the model.
  - Change from baseline to Week 24 and 52 in NPS, NCS, pre-BD FEV1 and ACQ-5 score.
  - The proportion of participants requiring SCS or surgery for CRS during the planned study intervention period.
  - Annualized rate of SCS or surgery for CRS during the planned study intervention period.

- Time to first either SCS or surgery for CRS.

Other secondary endpoints analyses are defined in Section 9.2.6.1 (AE, SAE), Section 9.2.6.2 (laboratory abnormalities), Section 9.2.7 (PK, immunogenicity).

9.2.4 Tertiary/exploratory endpoint(s) analyses

Unless otherwise noted, tertiary and exploratory endpoints will be summarized through appropriate descriptive methods, according to the type of endpoint.

9.2.4.1 Analysis of biomarkers

For exploratory parameters that include biomarkers, summarized description by intervention group and timepoint, if applicable will be provided. Absolute and percent change from baseline will be calculated for selected parameters. Time profile plots (mean +/- SEM, SD) will be presented for selected parameters by intervention group.

9.2.5 Multiplicity adjustment

Multiplicity is considered for the significance testing of multiple efficacy endpoints. The overall Type-I error rate will be controlled at the 2-sided 0.05 level.

As a nonbinding futility IA is planned for the study (see Section 9.3), an administrative penalty of $\alpha = 0.001$ will be taken from the significance level used at final analysis; that is, a 2-sided $\alpha = 0.049$ will be used for the final primary efficacy analysis. No further multiplicity adjustment will be performed for the IA.

At the final analysis, the family-wise Type I error rate for testing multiple hypotheses pertaining to the primary endpoint and secondary endpoints will be strongly controlled using a gate-keeping procedure. The procedure starts with testing the co-primary endpoints between 300 mg Q2W and placebo at the 2-sided 0.049 significance level. If both co-primary endpoints are significant, then the co-primary endpoints for 300 mg Q4W, the key secondary endpoints and a selective set of secondary endpoints including the efficacy endpoints on asthma and AERD sub-populations for both doses will be tested using a prespecified multiplicity testing procedure with the overall Type I error rate being controlled at 0.049 level among the multiple endpoints and the comparisons between each dose (300 mg Q2W or 300 mg Q4W) and placebo. The complete list of the endpoints and the multiplicity testing procedure will be specified in the SAP.

9.2.6 Safety analyses

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

9.2.6.1 Adverse events

General common rules for adverse events

The AEs will be analyzed in the following 3 categories:

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

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

Analysis of all adverse events

Adverse event incidence table will be provided by treatment group for all types of TEAEs: all TEAEs, all treatment emergent AESI (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 number (%) of participants experiencing at least 1 event.

Deaths will also be analyzed.

9.2.6.2 Laboratory variables, vital signs and electrocardiograms

Quantitative analyses

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

Analyses according to Potentially Clinically Significant Abnormality

PCSA analyses will be performed based on the PCSA list currently in effect at Sanofi at the time of the database lock.

Analyses according to PCSA will be performed based on the worst value during the TE period, using all measurements, either scheduled, nonscheduled or repeated.

For laboratory variables, vital signs and ECG variables, the incidence of participants with at least 1 PCSA during the TE period will be summarized regardless of the baseline level and according to the following baseline status categories:

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

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

- Normal/missing.
- Abnormal.

9.2.6.3 Product complaints

Product complaints will be summarized in the safety population.

9.2.7 Other analyses

Analyses of PK and immunogenicity will be described in the SAP.

For a regional or national emergency declared by a governmental agency, contingency measures are included in Appendix 9 (Section 10.9: Contingency measures for a regional or national emergency that is declared by a governmental agency).

9.3 INTERIM ANALYSES

A non-binding futility interim analysis (IA) will be planned after a minimum of approximately 90 pooled participants in the Phase 3 studies (EFC18418 and EFC18419) have completed at least a minimum of 24 weeks. There is no plan to change the conduct of this trial except to possibly stop the trial due to unfavorable benefit-risk. The unblinded interim look will be performed by an independent group separated from personnel involved in the trial conduct, data collection and management, and final statistical analysis.

A detailed IA plan will be finalized, including the decision rules, analyses to be included, methods to be used, and the processes and procedure intended to control access to comparative interim results to preserve trial integrity, prior to any interim administrative look.

An administrative penalty of 0.001 will be taken from the significance level used at final analysis, if applicable.

Data Monitoring Committee

This study will use an independent DMC. Details on DMC structure and role are presented in Section 10.1.5.

During the course of the study, an external statistician (independent from the Sponsor) will perform the unblinded safety and efficacy analyses for the purpose of the DMC data review and formal non-binding futility IA. Access to the data and analyses will be restricted to the DMC members. In addition, following the formal non-binding futility IA, DMC will make recommendations on continuation of the study, and will communicate unblinded results to limited personnel from the Sponsor, only if criteria pre-specified by the Sponsor are met. Access to the data and analyses will be provided to limited personnel from the Sponsor involved in the conduct of the study, if applicable. There is no plan to change the conduct of this trial except to possibly stop the trial due to unfavorable benefit-risk.

9.4 SAMPLE SIZE DETERMINATION

Approximately 210 participants will be randomized in 1:1:1 ratio to investigational intervention groups.

The sample size calculations are based on the co-primary endpoints NPS and NCS. The planned sample size is approximately 70 participants per study intervention group. With a two-sample t-test at a two-sided significance level of $\alpha = 0.049$, this sample size will provide:

- 95% power to detect a -1.10 difference for change from baseline in NPS at Week 24 between itepekimab and placebo and a common SD of 1.79. The minimal detectable difference is around -0.60.
- 95% power to detect a -0.55 difference for change from baseline in NCS at Week 24 between itepekimab and placebo and a common SD of 0.9. The minimal detectable difference is around -0.30.

The combined power of the 2 co-primary efficacy endpoints is at least 90% assuming no negative correlation between the 2 endpoints.

Differences of -1.10 and -0.55 in NPS and NCS from placebo are considered clinically relevant (54). The common SDs were estimated from LIBERTY NP SINUS-24 and SINUS-52 trials with dupilumab (NCT02912468; NCT02898454).

For the key secondary endpoints of change from baseline in NPS and NCS at Week 52, the study will have a 95% power to detect the same treatment differences as for the co-primary endpoints with the same assumed common SDs based on a two-sided α level of 0.049.

Note that as the primary analyses will be performed based on the ITT population with the dropouts (ie, one of the intercurrent events) handled using the treatment policy strategy and missing data imputed using the MI method, the sample size calculations were performed on all randomized participants. In other words, the detectable treatment differences stated above are for ITT population including early dropouts. Very low dropout rates (<5%) were observed from LIBERTY NP SINUS-24 and SINUS-52 studies (NCT02912468; NCT02898454), therefore the impact on the treatment effects is expected to be minimal.

Calculations were made based on two-sample t-test using nQuery Advisor 9.2.1.0.

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.
  - The Regulation No 536/2014 of the European Parliament and the Council of 16 April 2014 on clinical trials on medicinal products for human use, as applicable.
  - The General Data Protection Regulation (GDPR) and any other applicable data protection laws.
  - Any other applicable laws and regulations.
- The protocol, protocol amendments, ICF, Investigator's brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- 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, as applicable:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, Regulation No 536/2014 of the European Parliament and the Council of the European Union for clinical studies, European Medical Device Regulation 2017/745 for clinical device research, and all other applicable local regulations.

- 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 concerned 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.

As applicable, according to requirements of the Regulation No 536/2014 of the European Parliament and the Council of the EU, the Sponsor will be responsible for obtaining approval from the Competent Authorities of the EU Member States and/or Ethics Committees, as appropriate, for any amendments to the clinical trial that are deemed as “substantial” (ie, changes which are likely to have a significant impact on the safety or physical or mental integrity of the clinical trial participants or on the scientific value of the trial) prior to their implementation.

According to the Regulation No 536/2014 of the European Parliament and the Council of the EU and as specified by the applicable regulatory requirements in non-EU/EEA countries, Sanofi, as the clinical trial Sponsor, needs to report to the concerned regulatory agency(ies) serious breaches without undue delay but not later than 7 calendar days of becoming aware of that breach.
A serious breach is defined as a deviation of the version of the protocol applicable at the time of the breach or the applicable clinical trial regulation that is likely to affect to a significant degree the safety and rights of a subject or the reliability and robustness of the data generated in the clinical trial.

The Sponsor shall ensure that all parties involved in the conduct of the clinical trial promptly report any events that might meet the definition of a serious breach.

Therefore, Investigators shall within 48 hours after being aware of a deviation that might meet the definition of a serious breach, report to the Sponsor any suspected serious breach to enable the Sponsor to carry out the required assessment and notify the regulatory agency/ies in the event of a confirmed serious breach. To that extent, the principal Investigator must have a process in place to ensure that the site staff or service providers engaged by the principal Investigator/institution are able to identify the occurrence of a (suspected) serious breach and that a (suspected) serious breach is promptly reported to the Sponsor through the contacts (e-mail address or telephone number) provided by the Sponsor.

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 ICF will be provided to the study participant in paper version. When feasible, an e-Consent process may be used at global level and/or locally if permitted by country regulations.

- The Investigator or the Investigator's representative will explain the nature of the study, including the risks and benefits, to the potential participants, and answer all questions regarding the study, including what happens to the participants when their participation ends (post-trial access strategy for the study).
- Potential participants must be informed that their participation is voluntary. They 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, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- In case of ICF amendment while the participants are still included in the study, they must be re-consented 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 re-consent or be informed of the amendment (eg, if the processing of personal data is modified, if the Sponsor changes, etc.).
- A copy of the ICF(s) must be provided to the participants.

Participants who are re-screened are required to sign a new ICF.

The ICF contains 2 separate sections that address the use for future research of participants' data and/or samples (remaining mandatory ones or new extra samples collected for optional research). Optional exploratory research must be detailed in the section "Optional tests/procedures" and future research is to be defined in core study ICF Part 2. Each option is subject to an independent consent and must be confirmed by ticking checkboxes in core study ICF Part 3, each checkbox corresponding to a specific use: consent for the performance of an optional exploratory research; consent for storage and use of coded data for future research; consent for use of leftover samples and associated coded data for future research; consent for collection of additional biological samples for storage and use for future research, and consent for performance of genetic analyses on biological samples. The Investigator or authorized designee will explain to each participant the objectives of the exploratory research and why data and samples are important for future research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period.

For a regional or national emergency declared by a governmental agency, contingency measures are included in Appendix 9 (Section 10.9: Contingency measures for a regional or national emergency that is declared by a governmental agency).

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 trial participants, 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 personal 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 ethnicity will be collected in this study because it is expected to modify the drug response/because it is required by regulatory agencies (eg, on African American population for the FDA or on Japanese population for the Pharmaceuticals and Medical Devices Agency in Japan). They will not be collected in the countries where this is prohibited by local regulation.

- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor or its service providers, when applicable, 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.
- Participants must be informed that their 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.
- Participants must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- The contract between Sponsor, Investigators, and study sites specifies responsibilities of the parties related data protection, including handling of data security breaches and respective communication and cooperation of the parties. Accordingly, the Investigator and the institution will promptly notify the Sponsor about any data security breaches and detail in the notification the nature of the breach, the categories (eg, Sponsor’s personnel, study participants or their relatives, healthcare professionals, etc.), the approximate number of subjects concerned, the type and approximate number of data records concerned and the likely consequences of the breach. The institution and/or Investigator

will investigate the causes of the data security breach and take actions to minimize the effects of said breach. The institution and/or Investigator will record all information relating to the breach, including the results of their own investigations and investigations by authorities, as applicable, and will take all measures as necessary to prevent future data security breaches.

- Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.
- Participants must be informed that their study-related data will be used for the whole "drug development program", ie, for this trial as well as for the following steps necessary for the development of the investigational product, including to support negotiations with payers and publication of results.

Protection of personal data related to professionals involved in the study

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

- Professionals have the possibility to lodge a complaint with Sanofi leading Supervisory Authority, the "Commission Nationale de l'Informatique et des Libertés" (CNIL) or with any competent local regulatory authority.
- Personal data of professionals will be retained by Sanofi for up to 25 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 at once 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 DPO: Sanofi DPO - 46 avenue de la Grande Armée - 75017 PARIS - France (to contact Sanofi by e-mail, visit https://www.sanofi.com/en/our-responsibility/sanofi-global-privacy-policy/contact).

10.1.5 Committees structure

10.1.5.1 Data Monitoring Committee

A DMC, independent from the Sponsor, will be monitoring this study. This committee is governed by a DMC Charter. The DMC will comprise externally based individuals with expertise in the diseases under study, biostatistics, or clinical research. The composition of the committee is dependent upon the scientific skills and knowledge required for monitoring the particular study.

The primary responsibilities of the DMC are to review safety data, and efficacy where needed, during the course of the trial for evaluation of benefit/risk, review results, and make appropriate recommendations to the Sponsor regarding the stopping of a study for efficacy, for safety, or for futility. DMC recommendation may also include modifications of the study or discontinuing individual participants or specific subgroups of participants. In the above-mentioned capacities, the DMC is advisory to the Sponsor. The Sponsor is responsible for promptly reviewing and for taking into account in a timely manner the recommendations of the DMC in terms of study continuation with or without alterations, or of potential termination of a dose or study.

- Case unblinding may be performed for above reviews if necessary.

10.1.6 Dissemination of clinical study data and results

Study participants

At the end of the clinical study, the Sponsor may publish the study results in scientific journal(s). As part of the review for publication, independent scientists may need to use "coded" data of all the study participants to independently verify the study's results.

Sanofi shares information about clinical trials and results on publicly accessible websites, based on company commitments, international and local legal and regulatory requirements, and other clinical trial disclosure commitments established by pharmaceutical industry associations. These websites include ClinicalTrials.gov, euclinicaltrials.eu, and sanofi.com, as well as some national registries. For pediatric and adult trials, the results will generally be submitted/released 6 and 12 months respectively, after the end of the clinical trial worldwide (ie, the last active, participating country).

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

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

Professionals involved in the study or in the drug development program

Sanofi undertakes the legal obligation to disclose the full name of the Investigator and his/her affiliated institute/ hospital's name and location on the China Trial Disclosure website as required by the National Medical Products Administration in its guidance "Drug Clinical Trial Registration and Information Disclosure Management Practice (Trial Implementation)", requesting name disclosure of Chinese and foreign investigational sites and Investigators in any eligible clinical trial.

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

10.1.7 Data quality assurance

- All participant data relating to the study will be recorded on printed or eCRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data).
  The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.
- Guidance on completion of eCRFs will be provided in eCRF Completion Instructions.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- QTL will be pre-defined to identify systematic issues that can impact participant safety and/or reliability of study results. These pre-defined parameters will be monitored during the study and important deviations from the QTL and remedial actions taken will be summarized in the CSR.
- Monitoring details describing strategy, including definition of study critical data items and processes (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 different retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.8 Source documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator’s site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in monitoring guidelines.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.

- The Sponsor or designee will perform monitoring to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.9 Study and site start and closure

First act of recruitment

The first act of recruitment is the first participant screened 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:

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

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

10.1.10 Publication policy

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

10.2 APPENDIX 2: CLINICAL LABORATORY TESTS

- The tests detailed in Table 12 will be performed by the central laboratory (inclusive of central laboratory in China).
- Local laboratory results are only required in the event that the central laboratory results are not available in time for either study intervention administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study intervention decision or response evaluation, the results must be recorded.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.
- Pregnancy testing will be performed at screening with a blood test using a central laboratory, and at subsequent visits using Sponsor-provided urine tests, or locally-provided urine test (China only).

Table 12 - Protocol-required laboratory tests

Laboratory tests	Parameters
Hematology	Platelet count
	Erythrocyte count (Red blood cells)
	Red blood cell indices:
	MCV
	MCH
	%Reticulocytes
	White blood cell count with differential:
	Neutrophils
	Lymphocytes
	Monocytes
	Eosinophils
	Basophils
	Hemoglobin
	Hematocrit

Laboratory tests	Parameters
Clinical chemistry[a]	Urea nitrogen
	Potassium
	Creatinine/Creatinine clearance/eGFR
	Glucose (fasting)
	Sodium
	Bicarbonate
	Calcium/Total calcium/Corrected calcium
	Albumin
	AST/SGOT
	ALT/SGPT[a]
	Alkaline phosphatase[a]
	Lactate dehydrogenase
	Creatine phosphokinase
	Total cholesterol
	Total and direct bilirubin
	Total protein
	CRP
	GGT
Routine urinalysis	Specific gravity
	pH, glucose, protein, blood, ketones, nitrite, leukocyte esterase
	Microscopic examination (if blood or protein is abnormal)
Pregnancy testing	Highly sensitive hCG pregnancy test (as needed for women of childbearing potential)[b]
Other screening tests	A serum pregnancy test will be performed at Screening (Visit 1); urine pregnancy tests will be performed at the visits listed in the SoA table (Section 1.3)[b]. A negative result must be obtained at Visit 1 and at Visit 2 prior to randomization. In case of a positive urine test, the study intervention will be withheld and a serum pregnancy test performed as soon as possible to confirm the pregnancy. Pregnancy will lead to definitive treatment discontinuation in all cases. Sufficient amount of urine pregnancy test kits will be provided to WOCBP for visits that can be performed with a phone call. The outcome of monthly home urine pregnancy tests will be recorded and communicated to the site during the phone visits. The result will be recorded. Participant will be instructed to not administer next IMP in case of suspected/confirmed pregnancy and contact the site. Clinical laboratory testing at Screening (Visit 1) will include a hepatitis screen covering HBsAg, HBsAb, HBcAb IgM and total, HCVAb, HIV screen (anti-HIV-1 and HIV-2 antibodies). In case of results showing HBsAg (negative), and HBcAb total (positive), HBV DNA testing will be performed prior to randomization to rule out a false positivity to clarify the serological status. In case of results showing HCVAb (positive), HCV RNA testing will be performed to rule out a false positivity. In case of results showing positive anti-HIV-1 or anti-HIV-2 antibodies, reflex confirmation testing will be conducted. HIV serologic testing at Screening (Visit 1): HIV screen (anti-HIV-1 and HIV-2 antibodies). Tuberculosis testing will be done according to local guidelines (local laboratory) or if not available, in central laboratory (Quantiferon test) at Screening (Visit 1).

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; DNA = deoxyribonucleic acid; eGFR = estimated glomerular filtration rate; GGT = gamma-glutamyl transferase; HBcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; hCG = human chorionic gonadotropin; HCVAb = hepatitis C virus antibodies; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; IgM = immunoglobulin m; IMP = investigational medicinal product; MCH = mean corpuscular hemoglobin; MCV = mean corpuscular volume; SGOT = serum glutamic-oxaloacetic transaminase; SGPT = serum glutamic-pyruvic transaminase.

a Details of liver chemistry stopping criteria and required actions and follow-up are given in Section 7.1.2 Liver Chemistry Stopping Criteria and Appendix 6 (Section 10.6) (Liver and other safety. Suggested actions and follow-up assessments).

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

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 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 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 a hospitalization, emergency room visit, or visit to/by a health care provider). The participants 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 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 the participant will be collected during an interview with the participants and by review of available medical records at the next visit.
- Solicited AEs are predefined local at the injection site and systemic events for which the participant is specifically questioned, and which are noted by the participants in their diary.

Events meeting the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis that is:
  - 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.
- Any abnormal other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (ie, not related to

progression of underlying disease, or more severe than expected for the participant's condition), 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 condition 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.
- Signs, symptoms, or the clinical sequelae of any medication errors, misuse and abuse with the IMP.
- 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 an AE or SAE if they fulfill the definition of an AE or SAE. Lack of efficacy or failure of expected pharmacological action also constitutes an AE or SAE.

Events NOT meeting the AE definition

- Any abnormal laboratory findings or other abnormal safety assessments that 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 untoward medical occurrence that, at any dose, meets 1 or more of the criteria listed:

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 important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
    - 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.

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: A type of adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- Moderate: A type of adverse event that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
- Severe: A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

Assessment of causality

- The Investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. The Investigator will use clinical judgment to determine the relationship.
- *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.
- 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.
- For causality assessment, the Investigator will also consult the IB and/or product information, for marketed products.
- The Investigator must review and provide an assessment of causality for each AE/SAE and document this in the medical notes. There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report to the Sponsor's representative. However, **it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to** the Sponsor's representative.
- The Investigator may change his/her opinion of causality in light of follow-up information and send 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 or during a recognized follow-up period, the Investigator will provide the Sponsor with a copy of any postmortem findings including histopathology, if available.
- 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

SAE reporting to the Sponsor via an electronic data collection tool

- The primary mechanism for reporting an SAE to the Sponsor's representative will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) 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 offline 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 offline, then the site can report this information on a paper SAE form (see next section) or to the Sponsor's representative by telephone.
- Contacts for SAE reporting can be found in the ISF.

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 timeframes.
- Contacts for SAE reporting can be found in contact list in the ISF.

10.4 APPENDIX 4: CONTRACEPTIVE AND BARRIER GUIDANCE

10.4.1 Definitions

Woman of childbearing potential

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

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

Women in the following categories are not considered WOCBP.

1. Premenarchal.

2. Premenopausal female with 1 of the following:
   - Documented hysterectomy.
   - Documented bilateral salpingectomy.
   - Documented bilateral oophorectomy.
   - For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, Mullerian agenesis, androgen insensitivity), Investigator discretion should be applied to determining study entry.

   Note: Documentation can come from the site personnel's: review of the participant's medical records, medical examination, or medical history interview.
3. Postmenopausal female.
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
4. A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
5. Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.4.2 Contraception guidance

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

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
Highly Effective Methods[b] That Have Low User Dependency
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c] • IUD • IUS[c] • Bilateral tubal occlusion. • Vasectomized partner. *(Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.)*
Highly Effective Methods[b] That Are User Dependent
• 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.)

Abbreviations: CTFG = clinical trial facilitation group; IUD = intrauterine device; IUS = intrauterine hormone-releasing system; LAM = lactational amenorrhea method.

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. If locally required, in accordance with CTFG guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action.

Note: Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and LAM are not acceptable methods of contraception for this study. Male condom and female condom should not be used together (due to risk of failure with friction).

10.5 APPENDIX 5: GENETICS

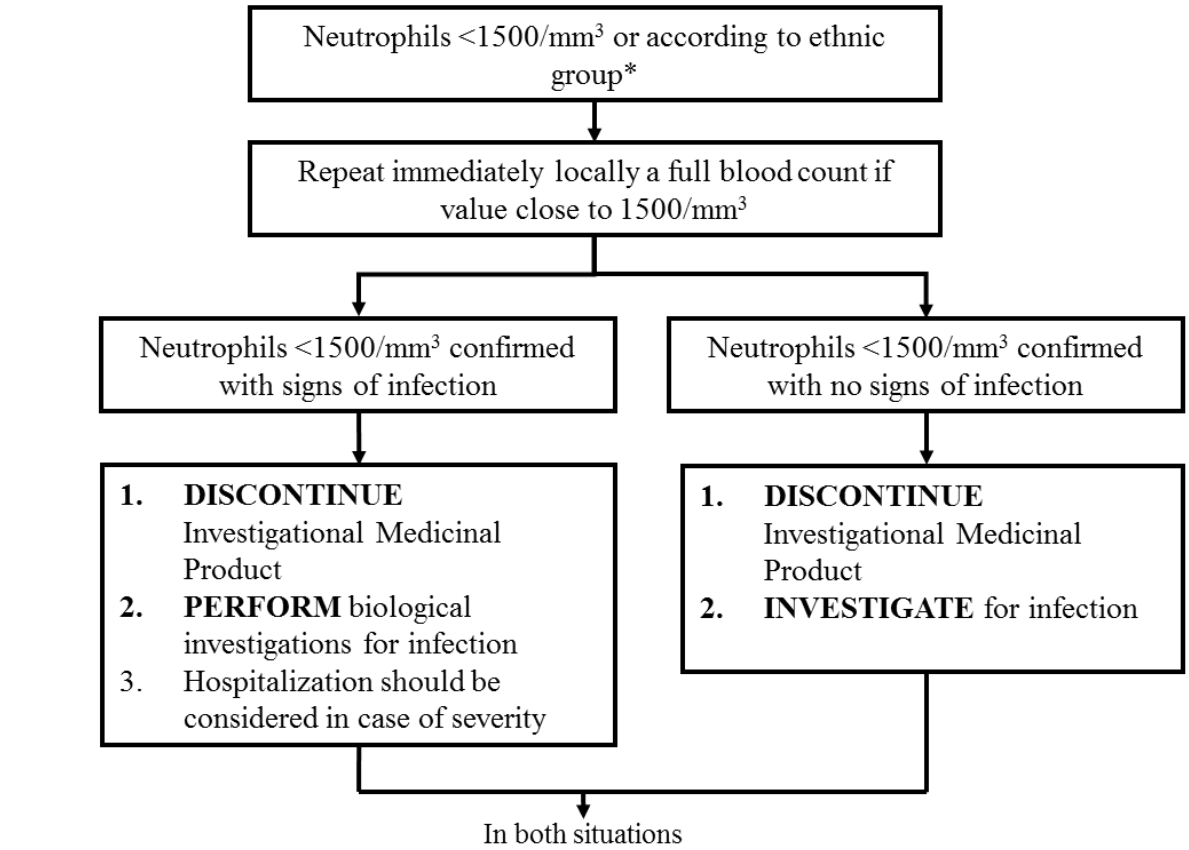
Use/Analysis of RNA and/or DNA

- Genetic variation may impact a participant's response to study intervention, susceptibility to, and severity and progression of disease. Variable response to study intervention may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis from consenting participants.
- RNA and DNA samples will be used for research related to itepekimab or CRSwNP and related diseases. They may also be used to develop tests/assays including diagnostic tests related to itepekimab and/or interventions of this drug class and CRSwNP. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome, and/or RNA sequencing to determine expression levels of gene(s) of interest.
- RNA and DNA samples will be used for research related to itepekimab or CRSwNP and related diseases. They may be used to determine a possible relationship between gene expression levels (RNA) or gene variants (DNA) and response to treatment with itepekimab, how the body processes itepekimab and possible side effects of itepekimab. Additional analyses may be conducted if it is hypothesized that this may help further understand the clinical data.
- The DNA and RNA samples may be analyzed as part of a multi-study assessment of genetic or transcriptomic factors involved in the response to itepekimab or study interventions of this class to understand the study disease or related conditions.
- The results of genetic analyses may be reported in the CSR or in a separate study summary.

- The Sponsor will store the RNA and DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on itepekimab and/or study interventions of this class or CRSwNP continues but no longer than 25 years or other period as per local requirements.

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

NEUTROPENIA

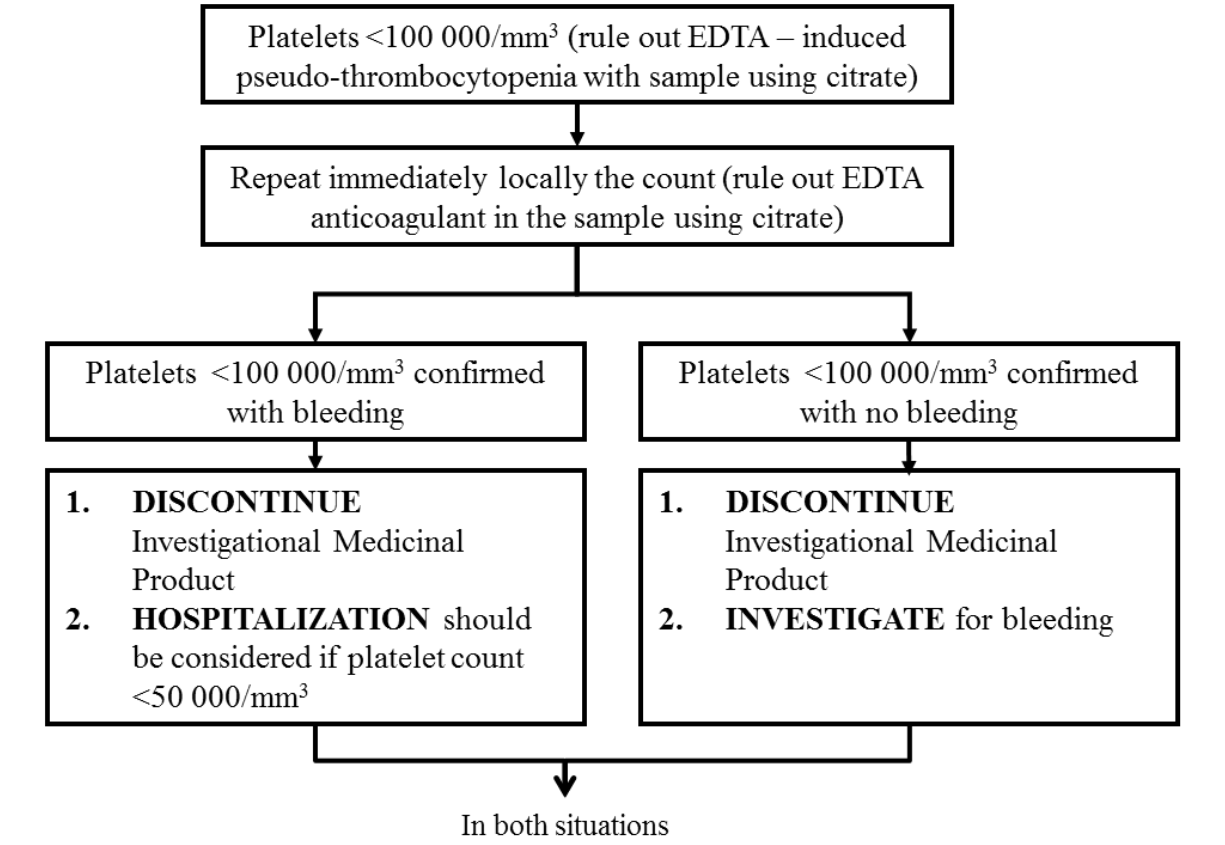


3. **INFORM** the local monitor
4. **INVESTIGATE** previous treatments particularly long-term, even a long time ago, exposure to toxic agents, e.g., benzene, X-rays, etc.
5. **PERFORM** and collect the following investigations (results):
   - RBC and platelet counts, Absolute Neutrophil Count (ANC)
   - 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

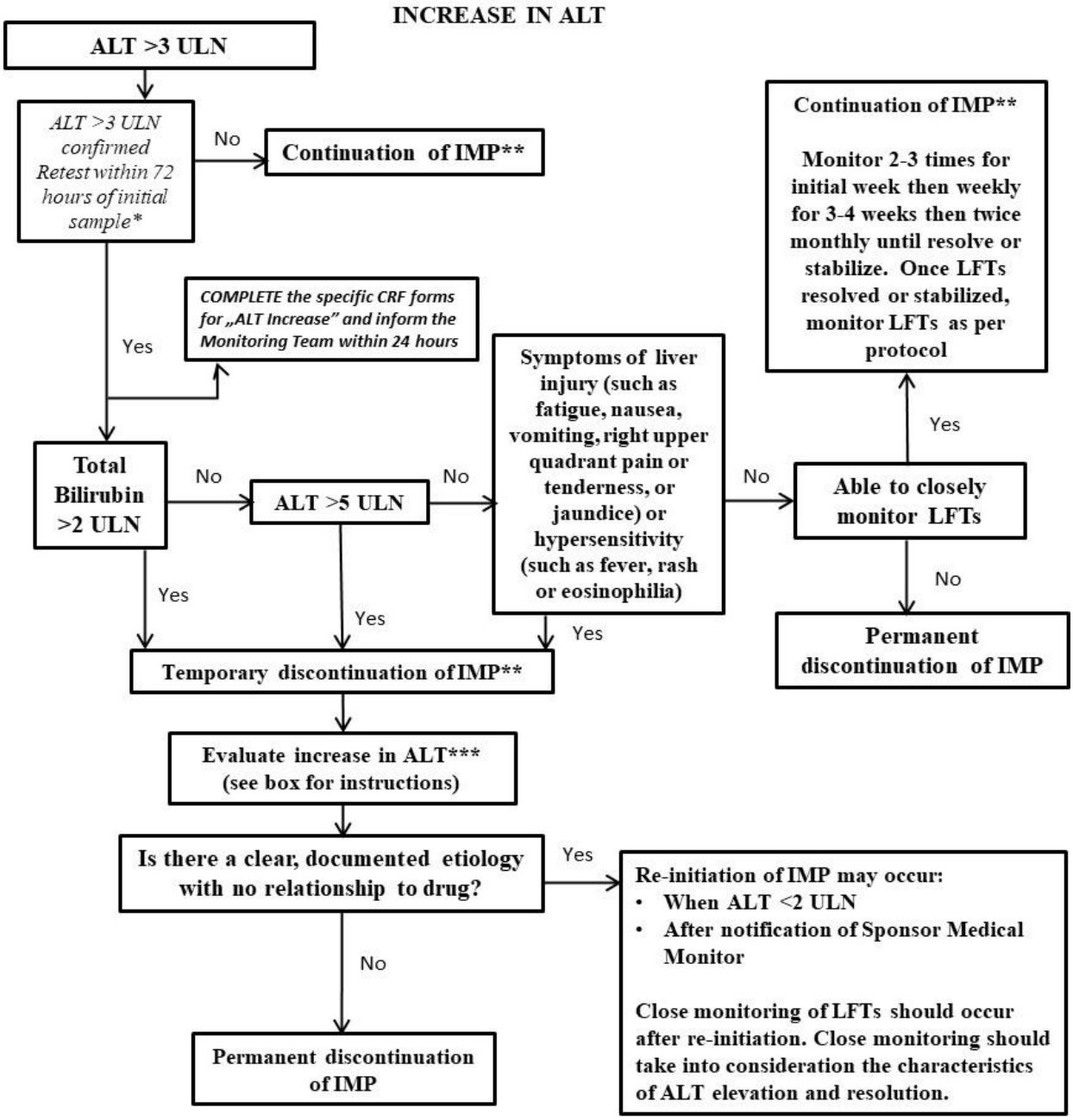
***** For individuals of African descent, the relevant value of concern is <1000/mm³

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

THROMBOCYTOPENIA



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



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

** Unless a protocol-defined criterion for permanent discontinuation is met.

*** See box below.

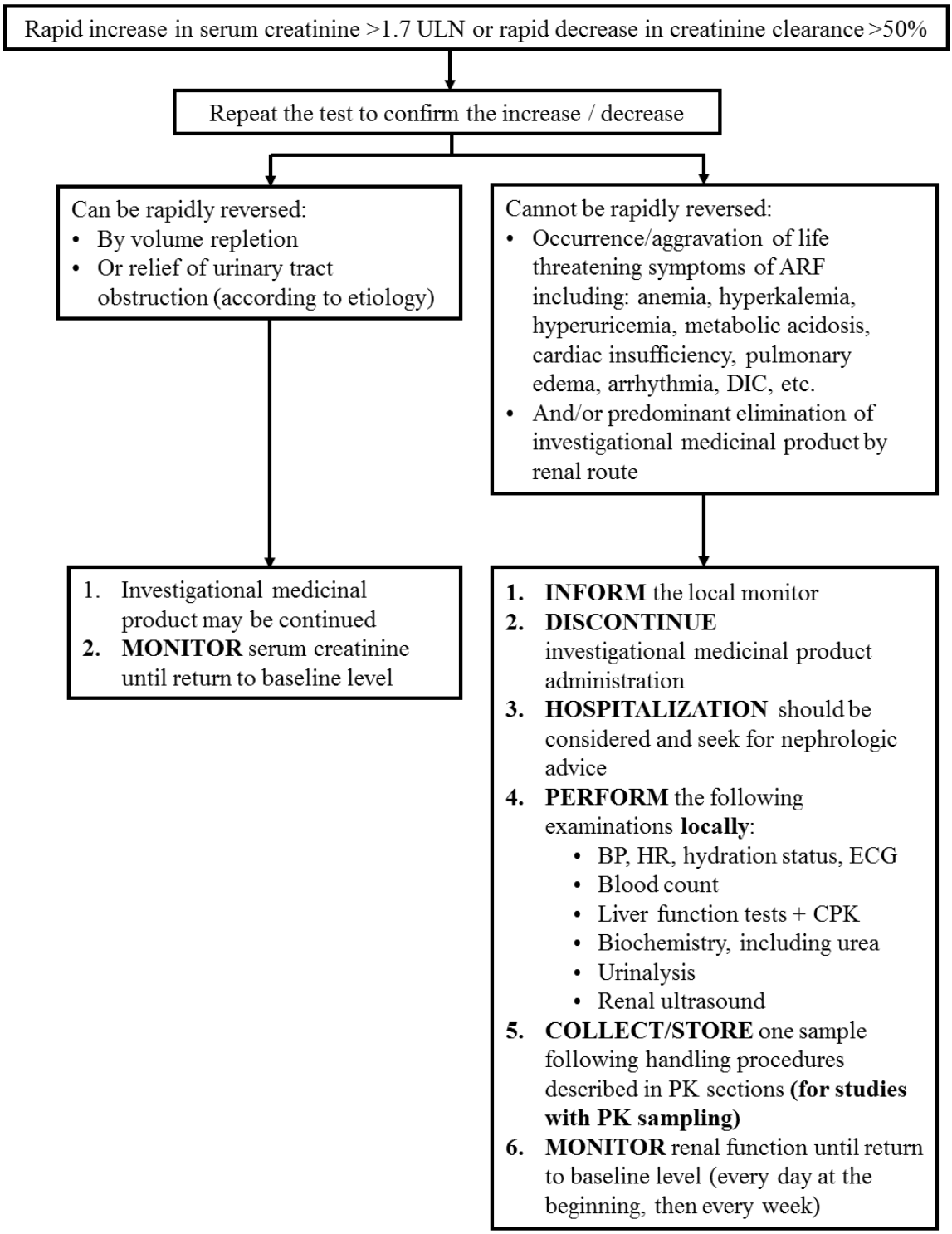
Note:

- "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.

Evaluate Increase in ALT***

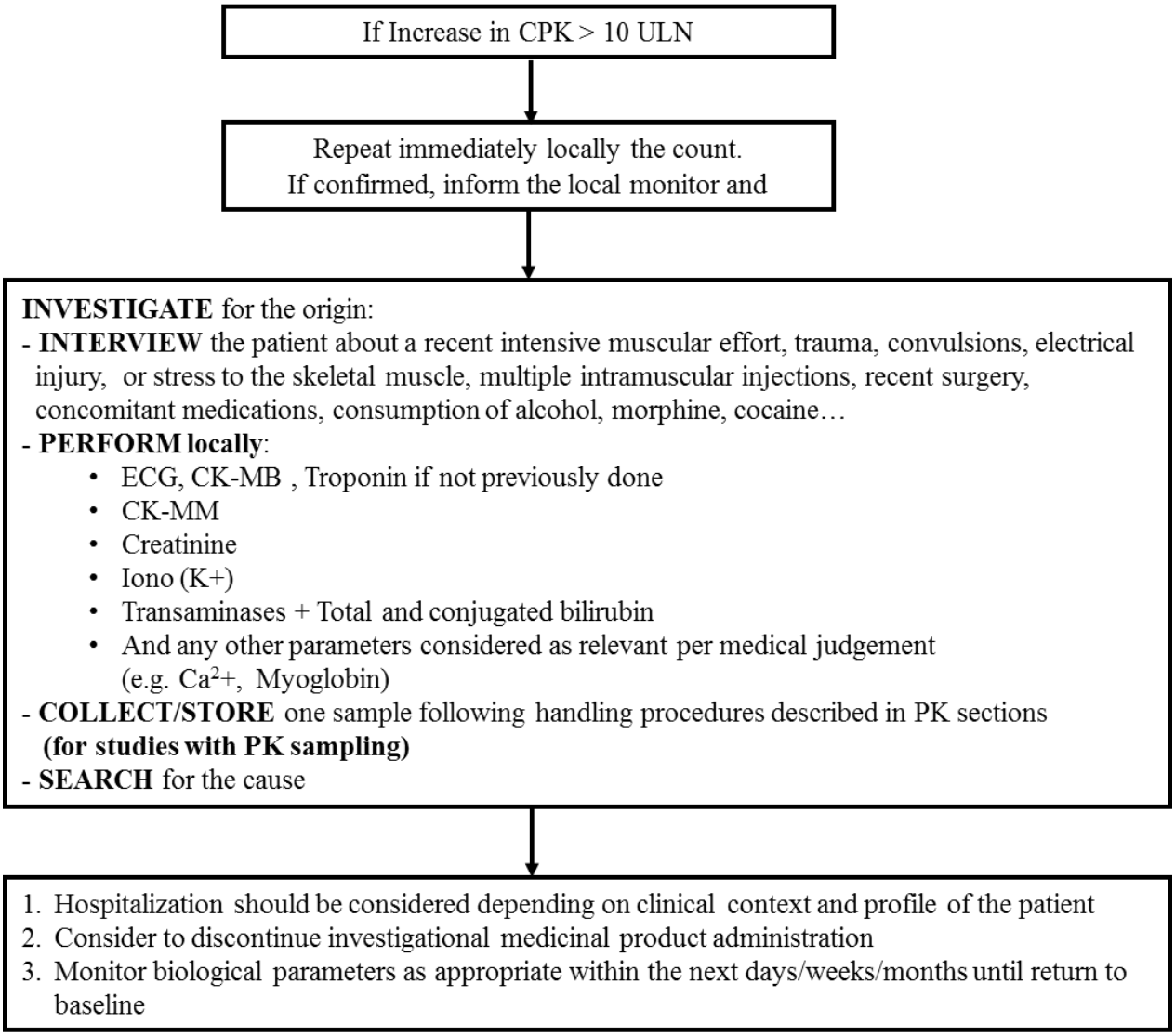
1. **INFORM** the Site Monitor who will forward the information to the Study Manager
2. **INVESTIGATE** specifically for malaise with or without loss of consciousness, dizziness, and/or hypotension and/or episode of arrhythmia in the previous 72 hours; rule out muscular injury
3. **INVESTIGATE** if any recent alcohol use or travel
4. **INVESTIGATE** if any use of non-prescription medications including herbal or dietary supplements
5. **PERFORM** the following tests:
   - LFTs: AST, ALT, alkaline phosphatase, GGT, 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)
6. **CONSIDER** Auto-antibodies: antinuclear, anti-DNA, anti-smooth muscle, anti-LKM
7. **CONSIDER** iron, ferritin and transferrin
8. **CONSIDER** biomarkers for alcohol use (eg, urine ethyl glucuronide (EtG)]
9. **CONSIDER** consulting with hepatologist
10. **CONSIDER** patient hospitalization if INR>2 (or PT<50%) and/or central nervous system disturbances suggesting hepatic encephalopathy
11. **MONITOR LFTs after discontinuation of IMP:**
    - As *closely as possible* (or **every 48 hours)** until stabilization, then every 2 weeks until return to ≤ULN, baseline value (if baseline >ULN) or clinical resolution.
12. **FREEZE** serum sample (5ml x 2)
13. **In case of suspicion of GILBERT Syndrome**, a DNA diagnostic test should be done

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 adverse events in Section 10.3 is met.

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



Increase in creatine phosphokinase (CPK) is to be recorded as an AE only if at least 1 of the criteria in the general guidelines for reporting adverse events in Section 10.3 is met.

10.7 APPENDIX 7: MEDICAL DEVICES AES, ADES, SAES, SADES, USADES AND DEVICE DEFICIENCIES: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING IN MEDICAL DEVICE STUDIES

The definitions and procedures detailed in this appendix are in accordance with ISO 14155 and the European Medical Device Regulation (MDR) 2017/745 for clinical device research (if applicable).

Both the Investigator and the Sponsor will comply with all local medical device reporting requirements for medical devices.

The detection and documentation procedures described in this protocol apply to all Sponsor medical devices provided for use in the study (see Section 6.1.4) for the list of Sponsor medical devices).

10.7.1 Definition of medical device AE and ADE

Medical device AE and ADE definition

- A medical device AE is any untoward medical occurrence in a clinical study participant, users, or other persons, temporally associated with the use of study intervention, whether or not considered related to the investigational medical device. 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 an investigational medical device. This definition includes events related to the investigational medical device or comparator and events related to the procedures involved except for events in users or other persons, which only include events related to investigational devices.
- An ADE is defined as an AE related to the use of an investigational medical device. This definition includes any AE resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device as well as any event resulting from use error or from intentional misuse of the investigational medical device.

10.8 APPENDIX 8: COUNTRY-SPECIFIC/REGION REQUIREMENTS

10.8.1 China

China participants should be on daily treatment with INCS prior to screening and will continue their daily INCS with a stable dose as background treatment during the screening and throughout the study.

Genetic analyses as described in Section 8.7 will be optional for participants enrolled in China. All biomarkers (except for blood neutrophil and eosinophil count) can be considered optional in China.

Future use of biological samples as described in Section 8.11 is not applicable for participants in China.

10.8.2 Japan

In Japan, participants on INCS (MFNS or other INCS) will continue taking their daily INCS with a stable dose through all periods of the study. In Japan, participants not on INCS prior to screening, will receive MFNS during screening and throughout the study.

10.8.3 Germany

Informed consent process: all references to "legally authorized representative" are not applicable in Germany; only participants who can give written consent themselves are included in the study. References to "legally authorized representative" are found in Section 7.1.1, Section 8.4, Section 8.4.7, and Section 10.9.

10.8.4 France

Exclusion criterion specific to France:

E 32. The participant is not affiliated to a social security scheme.

E 33. The participant is under tutorship or curatorship; the participant is under safeguard of justice or deprived of his/her liberty by an administrative or court decision.

10.8.5 Czechia

In addition to E 23, the following is required for Czechia (see underlined text): participants from Czechia with a positive TB skin test or a positive Quantiferon assay are excluded from the study unless all of the following conditions are met:

- Have a history of completed chemoprophylaxis for latent TB infection (with a treatment regimen as per local guidelines), OR has completed treatment for active TB infection (with a treatment regimen as per local guidelines),

  AND

- Have obtained consultation with a specialist to rule out active and latent TB infection,

  AND

- For whom review and approval from Sponsor has been granted.

In addition to E 20, the following is required for participants randomized in Czechia:

1. If a participant has anti-HBc Ab positivity at screening but is confirmed to have no detectable HBV DNA by PCR testing at screening, the participant must be willing to have repeat HBV DNA PCR testing performed at least every 3 months until the end of trial.

2. If a participant has anti-HBs Ab positivity at screening but is confirmed to have no detectable HBV DNA by PCR testing at screening, the participant must be willing to repeat HBV DNA PCR testing performed at least every 3 months until the end of trial, unless the participant has completed HBV vaccination previously as proven by medical records.
3. If a participant has total anti-HCV Ab positivity at screening but is confirmed to have no detectable HCV RNA by PCR testing, the participant will repeat HCV RNA PCR testing at least every 3 months until the end of trial.

10.8.6 European Union

10.8.6.1 Safety reporting to the agency

In the EU, the Sponsor will comply with safety reporting requirements and procedures as described in the European Clinical Trials Regulation No 536/2014. All SUSARs to IMP will be reported to the EudraVigilance database within the required regulatory timelines.

A single Annual Safety Report, aligned with ICH E2F, will include safety information for all IMPs (including the reference compound[s]).

Safety reporting with regard to authorized AxMPs shall be made in accordance with Chapter 3 of Title IX of Directive 2001/83/EC, irrespective if they are used in accordance with the terms of the marketing authorizations of these products. The Investigator is requested to report any suspected adverse reactions assessed as solely related to an authorized AxMP to the National Competent Authority via the national reporting system.

10.9 APPENDIX 9: CONTINGENCY MEASURES FOR A REGIONAL OR NATIONAL EMERGENCY THAT IS DECLARED BY A GOVERNMENTAL AGENCY

Continuation of the study in the event of a regional or national emergency 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 trial site.
- Contingency procedures are suggested in this appendix and in Section 8, for an emergency that prevents access to the study site, to ensure the safety of the participants, to consider continuity of the clinical study conduct, protect trial 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, alternative treatment outside the clinical trial should be postponed, and screening/enrollment, and administration of study intervention may be temporarily delayed/halted.

- For a regional or national emergency declared by a governmental agency, contingency procedures may be implemented for the duration of the emergency. The participant or their legally authorized representative should be verbally informed prior to initiating any changes that are to be implemented for the duration of the emergency (eg, study visit delays/intervention extension, use of local laboratories).

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 a regional or national emergency, focus should be given to assessments necessary to ensure the safety of participants and those assessments 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 for the duration of the emergency (after Sponsor agreement is obtained):

- The DTP supply of itepekimab/placebo from the Sponsor where allowed by local regulations and agreed upon by the participant.
- If on-site visits are not possible for visits other than Screening visit (Visit 1 [Week -3 to -5]) and enrollment visit (Visit 2 [Week 0]), remote visits (eg, with home nurses, home health vendor) may be planned for the collection of possible safety and/or pharmacodynamic data. Vital signs, hematology and clinical chemistry, routine urine analysis plus dipstick test (pregnancy) and AE reporting should have priority from a safety perspective.
- If on-site visits are not possible, visit windows may be extended for assessment of safety and/or pharmacodynamic data that cannot be obtained remotely (eg, spirometry visit window +/- 2 weeks for the IMP intervention period, and +/- 2 weeks for the visits during the post IMP intervention follow-up period).
- Use of local clinic or laboratory locations may be allowed for hematology and clinical chemistry samples.

Contingencies implemented due to a regional or national emergency will be documented.

If in case of unforeseen circumstances, a decision for each individual participant to remain and/or start in the study has to be made; this should be done on a case-by-case basis by the Investigator based on his/her best medical judgment. Clinical judgment of the treating physician should guide the management plan of each participant based on individual benefit/risk assessment.
All applicable local laws, institutional, and IEC/IRB regulations regarding study visits should be followed. Local guidelines related to Personal Protective Equipment use should also be followed. As previously mentioned, attempts should be made to perform all assessments in accordance with the protocol, but only if and when possible. Investigators should closely monitor and document all deviations to the study protocol and share them with the Sponsor contact on a real-time basis.

For Germany contingency measures are currently only applicable for the COVID-19 pandemic.

10.10 APPENDIX 10: CLINICAL OUTCOMES ASSESSMENTS

10.10.1 CRSwNP Nasal Symptom Diary

The following questions will ask you to rate your nasal disorder symptoms over the past 24 hours. Please make sure you assess your nasal symptoms shortly after getting up in the morning (before 12:00 noon).

Rate the symptoms over the past 24 hours using the following ratings:

0 = No symptoms.

1 = Mild symptoms (symptoms clearly present, but minimal awareness and easily tolerated).

2 = Moderate symptoms (definitive awareness of symptoms that is bothersome but tolerable).

3 = Severe symptoms (symptoms that are hard to tolerate, cause interference with activities of daily living).

Please rate your <u>nasal congestion/obstruction</u> symptoms over the past 24 hours

- ☐ No symptoms
- ☐ Mild symptoms
- ☐ Moderate symptoms
- ☐ Severe symptoms

Please rate your <u>loss of sense of smell</u> symptoms over the past 24 hours

- ☐ No symptoms
- ☐ Mild symptoms
- ☐ Moderate symptoms
- ☐ Severe symptoms

Please rate your <u>runny nose</u> symptoms over the past 24 hours

- ☐ No symptoms
- ☐ Mild symptoms
- ☐ Moderate symptoms
- ☐ Severe symptoms

Please rate your <u>post-nasal drip</u> (dripping at the back of your nose) symptoms over the past 24 hours

- ☐ No symptoms
- ☐ Mild symptoms
- ☐ Moderate symptoms
- ☐ Severe symptoms

Please rate your <u>facial pain/pressure</u> symptoms over the past 24 hours

- ☐ No symptoms
- ☐ Mild symptoms
- ☐ Moderate symptoms
- ☐ Severe symptoms

Please rate your <u>headache</u> over the past 24 hours

- ☐ No symptoms
- ☐ Mild symptoms
- ☐ Moderate symptoms
- ☐ Severe symptoms

10.10.2 SNOT-22

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

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

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

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

10.10.3 PGIS

Patient Global Impression of Severity (PGIS)

Please choose the response below that best describes the severity of your nasal congestion/obstruction over the past week.

- ☐ None (1)
- ☐ Mild (2)
- ☐ Moderate (3)
- ☐ Severe (4)

Please choose the response below that best describes the severity of your loss of sense of smell over the past week.

- ☐ None (1)
- ☐ Mild (2)
- ☐ Moderate (3)
- ☐ Severe (4)

Please choose the response below that best describes the severity of your runny nose over the past week.

- ☐ None (1)
- ☐ Mild (2)
- ☐ Moderate (3)
- ☐ Severe (4)

Please choose the response below that best describes the severity of your post-nasal drip (dripping at the back of your nose) over the past week.

- ☐ None (1)
- ☐ Mild (2)
- ☐ Moderate (3)
- ☐ Severe (4)

Please choose the response below that best describes the severity of your facial pain/pressure over the past week.

- ☐ None (1)
- ☐ Mild (2)
- ☐ Moderate (3)
- ☐ Severe (4)

Please choose the response below that best describes the severity of your headache over the past week.

- ☐ None (1)
- ☐ Mild (2)
- ☐ Moderate (3)
- ☐ Severe (4)

Please choose the response below that best describes overall the severity of your rhinosinusitis symptoms (for example, congestion, runny nose, loss of smell, and pain) over the past week.

- ☐ None (1)
- ☐ Mild (2)
- ☐ Moderate (3)
- ☐ Severe (4)

10.10.4 PGIC

Patient Global Impression of Change (PGIC)

Please choose the response below that best describes the change in your nasal congestion/obstruction since you started taking the study injection.

- ☐ Much better (1)
- ☐ A little better (2)
- ☐ No change (3)
- ☐ A little worse (4)
- ☐ Much worse (5)

Please choose the response below that best describes the change in your loss of sense of smell since you started taking the study injection.

- ☐ Much better (1)
- ☐ A little better (2)
- ☐ No change (3)
- ☐ A little worse (4)
- ☐ Much worse (5)

Please choose the response below that best describes the change in your runny nose since you started taking the study injection.

- ☐ Much better (1)
- ☐ A little better (2)
- ☐ No change (3)
- ☐ A little worse (4)
- ☐ Much worse (5)

Please choose the response below that best describes the change in your post-nasal drip (dripping at the back of your nose) since you started taking the study injection.

- ☐ Much better (1)
- ☐ A little better (2)
- ☐ No change (3)
- ☐ A little worse (4)
- ☐ Much worse (5)

Please choose the response below that best describes the change in your facial pain/pressure since you started taking the study injection.

- ☐ Much better (1)
- ☐ A little better (2)
- ☐ No change (3)
- ☐ A little worse (4)
- ☐ Much worse (5)

Please choose the response below that best describes the change in your headache since you started taking the study injection.

- ☐ Much better (1)
- ☐ A little better (2)
- ☐ No change (3)
- ☐ A little worse (4)
- ☐ Much worse (5)

Please choose the response below that best describes overall the change in your rhinosinusitis symptoms (for example, congestion, runny nose, loss of smell, and pain) since you started taking the study injection.

- ☐ Much better (1)
- ☐ A little better (2)
- ☐ No change (3)
- ☐ A little worse (4)
- ☐ Much worse (5)

10.10.5 ACQ-5

ASTHMA CONTROL QUESTIONNAIRE©
(LANGUAGE VERSION FOR COUNTRY)

PATIENT ID: _____

DATE: _____

Page 1 of 1

Please answer questions 1 - 5.

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

1.	On average, during the past week, how often were you **woken by your asthma** during the night?	0 1 2 3 4 5 6	Never Hardly ever A few times Several times Many times A great many times Unable to sleep because of asthma
2.	On average, during the past week, how **bad were your asthma symptoms when you woke up** in the morning?	0 1 2 3 4 5 6	No symptoms Very mild symptoms Mild symptoms Moderate symptoms Quite severe symptoms Severe symptoms Very severe symptoms
3.	In general, during the past week, how **limited were you in your activities** because of your asthma?	0 1 2 3 4 5 6	Not limited at all Very slightly limited Slightly limited Moderately limited Very limited Extremely limited Totally limited
4.	In general, during the past week, how much **shortness of breath** did you experience because of your asthma?	0 1 2 3 4 5 6	None A very little A little A moderate amount Quite a lot A great deal A very great deal
5.	In general, during the past week, how much of the time did you **wheeze**?	0 1 2 3 4 5 6	Not at all Hardly any of the time A little of the time A moderate amount of the time A lot of the time Most of the time All the time

10.10.6 EQ-5D-5L

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

MOBILITY

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

SELF-CARE

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

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

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

PAIN / DISCOMFORT

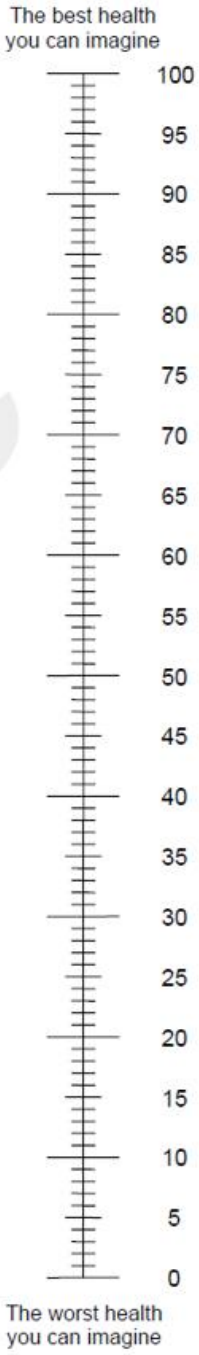
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

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

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

YOUR HEALTH TODAY = ☐



10.10.7 WPAI-SHP

Work Productivity and Activity Impairment Questionnaire: Specific Health Problem V2.0 (WPAI:SHP)

The following questions ask about the effect of your rhinosinusitis on your ability to work and perform regular activities. Please fill in the blanks or circle a number, as indicated.

1. Are you currently employed (working for pay)? _____ NO ___ YES
   If NO, check "NO" and skip to question 6.

The next questions are about the **past seven days**, not including today.

2. During the past seven days, how many hours did you miss from work because of problems associated with your rhinosinusitis? *Include hours you missed on sick days, times you went in late, left early, etc., because of your rhinosinusitis. Do not include time you missed to participate in this study.*
   _____ HOURS

3. During the past seven days, how many hours did you miss from work because of any other reason, such as vacation, holidays, time off to participate in this study?

   _____ HOURS

4. During the past seven days, how many hours did you actually work?

   _____ HOURS *(If "0", skip to question 6.)*

5. During the past seven days, how much did your rhinosinusitis affect your productivity while you were working?

   Think about days you were limited in the amount or kind of work you could do, days you accomplished less than you would like, or days you could not do your work as carefully as usual. If rhinosinusitis affected your work only a little, choose a low number. Choose a high number if rhinosinusitis affected your work a great deal.

   Consider only how much rhinosinusitis affected productivity while you were working.

Rhinosinusitis had no effect on my work	0	1	2	3	4	5	6	7	8	9	10	Rhinosinusitis completely prevented me from working

   CIRCLE A NUMBER

6. During the past seven days, how much did your rhinosinusitis affect your ability to do your regular daily activities, other than work at a job?

   By regular activities, we mean the usual activities you do, such as work around the house, shopping, childcare, exercising, studying, etc. Think about times you were limited in the amount or kind of activities you could do and times you accomplished less than you would like. If rhinosinusitis affected your activities only a little, choose a low number. Choose a high number if rhinosinusitis affected your activities a great deal.

   Consider only how much rhinosinusitis affected your ability to do your regular daily activities, other than work at a job.

Rhinosinusitis had no effect on my daily activities	0	1	2	3	4	5	6	7	8	9	10	Rhinosinusitis completely prevented me from doing my daily activities

   CIRCLE A NUMBER

WPAI:SHP V2.0 (US English)

10.10.8 PROMIS SD-SF-8b

PROMIS® Item Bank v1.0 – Sleep Disturbance – Short Form 8b

Sleep Disturbance – Short Form 8b

Please respond to each question or statement by marking one box per row.

In the past 7 days...

		Not at all	A little bit	Somewhat	Quite a bit	Very much
Sleep108	My sleep was restless	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Sleep115	I was satisfied with my sleep.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Sleep116	My sleep was refreshing.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Sleep44	I had difficulty falling asleep.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
	In the past 7 days…	**Never**	**Rarely**	**Sometimes**	**Often**	**Always**
Sleep87	I had trouble staying asleep.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Sleep90	I had trouble sleeping	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Sleep110	I got enough sleep.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
	In the past 7 days…	**Very poor**	**Poor**	**Fair**	**Good**	**Very good**
Sleep109	My sleep quality was.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

10.10.9 Leicester cough questionnaire

This questionnaire is designed to assess the impact of cough on various aspects of your life. Read each question carefully and answer by CIRCLING the response that best applies to you. Please answer ALL questions, as honestly as you can.

1. In the last 2 weeks, have you had chest or stomach pains as a result of your cough?

1	2	3	4	5	6	7
All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time

2. In the last 2 weeks, have you been bothered by sputum (phlegm) production when you cough?

1	2	3	4	5	6	7
Every time	Most times	Several times	Some times	Occasionally	Rarely	Never

3. In the last 2 weeks, have you been tired because of your cough?

1	2	3	4	5	6	7
All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time

4. In the last 2 weeks, have you felt in control of your cough?

1	2	3	4	5	6	7
None of the time	Hardly any of the time	A little of the time	Some of the time	A good bit of the time	Most of the time	All of the time

5. How often during the last 2 weeks have you felt embarrassed by your coughing?

1	2	3	4	5	6	7
All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time

6. In the last 2 weeks, my cough has made me feel anxious

1	2	3	4	5	6	7
All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time

7. In the last 2 weeks, my cough has interfered with my job, or other daily tasks

1	2	3	4	5	6	7
All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time

8. In the last 2 weeks, I felt that my cough interfered with the overall enjoyment of my life

1	2	3	4	5	6	7
All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time

9. In the last 2 weeks, exposure to paints or fumes has made me cough

1	2	3	4	5	6	7
All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time

10. In the last 2 weeks, has your cough disturbed your sleep?

1	2	3	4	5	6	7
All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time

11. In the last 2 weeks, how many times a day have you had coughing bouts?

1	2	3	4	5	6	7
All of the time (continuously)	Most times during the day	Several times during the day	Some times during the day	Occasionally through the day	Rarely	None

12. In the last 2 weeks, my cough has made me feel frustrated

1	2	3	4	5	6	7
All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time

13. In the last 2 weeks, my cough has made me feel fed up

1	2	3	4	5	6	7
All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time

14. In the last 2 weeks, have you suffered from a hoarse voice as a result of your cough?

1	2	3	4	5	6	7
All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time

15. In the last 2 weeks, have you had a lot of energy?

1	2	3	4	5	6	7
None of the time	Hardly any of the time	A little of the time	Some of the time	A good bit of the time	Most of the time	All of the time

16. In the last 2 weeks, have you worried that your cough may indicate serious illness?

1	2	3	4	5	6	7
All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time

17. In the last 2 weeks, have you been concerned that other people think something is wrong with you, because of your cough?

1	2	3	4	5	6	7
All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time

18. In the last 2 weeks, my cough has interrupted conversation or telephone calls

1	2	3	4	5	6	7
Every time	Most times	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time

19. In the last 2 weeks, I feel that my cough has annoyed my partner, family or friends

1	2	3	4	5	6	7
Every time I cough	Most times when I cough	Several times when I cough	Some times when I cough	Occasionally when I cough	Rarely	Never

Thank you for completing this questionnaire.

10.11 APPENDIX 11: COLLECTION, STORAGE AND FUTURE USE OF DATA AND HUMAN BIOLOGICAL SAMPLES

10.11.1 Compliance with Member State applicable rules for the collection, storage and future use of human biological samples (Article 7.1h)

This appendix is provided separately.

10.11.2 Compliance with Member State applicable rules for the collection, storage and future use of (personal) data (article 7 (1 d) of EU Regulation 536/2014)

This appendix is provided separately.

10.12 APPENDIX 12: LIST OF OPPORTUNISTIC INFECTIONS

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

This list is indicative and not exhaustive.

10.13 APPENDIX 13: DEFINITION OF ANAPHYLAXIS

Anaphylaxis is a serious allergic reaction that is rapid in onset and may cause death (55). Clinical criteria for diagnosing anaphylaxis:

Table 13 - Clinical criteria for diagnosing anaphylaxis

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

Abbreviations: BP = blood pressure; GI = gastrointestinal; Hg = hydrargyrum; PEF = peak expiratory flow.

a 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.

10.14 APPENDIX 14: DIAGNOSIS OF AERD IN CRSWNP PATIENTS (+/- DIAGNOSED ASTHMA)

QUESTION 1 - Have you ever had respiratory, nasal and/or bronchial, symptoms following the intake of aspirin or/and NSAID?

- **NO, I usually take aspirin or NSAID drugs ➔** the patient does not have AERD.
- **NO, I don't take aspirin or NSAID drugs ➔** the patient unlikely has AERD but cannot be totally ruled out.
- **YES, only to 1 drug ➔** the patient likely has AERD. 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 AERD.

QUESTION 2 - While having a positive clinical history of AERD, 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 AERD but cannot be totally ruled out.
- **YES, positive ➔** confirms the patient has AERD.

DIAGNOSIS OF AERD:

- **Conditional**: only based on clinical history (question 1).
- **Strong**: based on both clinical history and provocation test (questions 1 and 2).

References 56, 57, 58, 59.

10.15 APPENDIX 15: LIST OF PROHIBITED LIVE ATTENUATED VACCINES

- Bacillus Calmette–Guérin (BCG) anti-TB vaccine.
- 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.

10.16 APPENDIX 16: PROTOCOL AMENDMENT HISTORY

Not applicable.

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