16.1.1 Protocol and Protocol Amendments

This section includes the following:

Amended Clinical Trial Protocol 02, dated 22 Sept 2022

AMENDED CLINICAL TRIAL PROTOCOL 02

Protocol title:	**A Phase 4, randomized, double-blind, placebo-controlled, multicenter, parallel-group study of the effect of dupilumab on sleep disturbance in patients with uncontrolled persistent asthma**
Protocol number:	**LPS16677**
Amendment number:	**02**
Compound number (INN/Trademark):	**SAR231893** **dupilumab/Dupixent®**
Study phase:	**Phase 4**
Short title:	**Dupilumab asthma sleep study** **MORPHEO**
Sponsor name:	**Sanofi-Aventis Recherche & Développement (SARD)**
Legal registered address:	**1 avenue Pierre Brossolette,** **91380 Chilly-Mazarin** **France**
Monitoring Team's Representative Name and Contact Information	

Regulatory agency identifier number(s):

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EUDAMED	Not applicable
Other:	Not applicable

Date:	22-Sep-2022	Total number of pages: 106

PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY

Document	Country/countries impacted by amendment	Date, version
Amended Clinical Trial protocol 02	All	22 September 2022, version 1 (electronic 2.0)
Amended Clinical Trial protocol 01	All	17 September 2020, version 1 (electronic 1.0)
Original Protocol		24 April 2020, version 1 (electronic 1.0)

Amended protocol 02 (22 September 2022)

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

OVERALL RATIONALE FOR THE AMENDMENT

The main rationale for the Amendment is for the addition of a virtual site (Metasite) that will enroll approximately 10 participants from the United States. The Metasite will be managed by Science37 (external vendor), using telemedicine (TM), mobile study nurses, and an electronic application (Science37 Platform). These 10 participants will undergo the same procedures and provide the same data as other trial participants and will be conducted at participants' homes. The Investigational Medicinal Product (IMP) supply process for the participants enrolled by the Metasite via direct to participant (DTP) has been detailed. Additionally, minor clarifications and updates were included in the statistical sections, as per statistical analysis plan (SAP), and minor clarifications and corrections have been implemented across the document (see summary of changes table).

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis (Overall Design) 4.1 Overall design	Added details on Science37 Metasite.	A Metasite has been added to support recruitment and decrease patient burden. Approximately 10 participants from the US will be enrolled by Science37 Metasite.
1.1 Synopsis (overall design) 4.1 Overall design Appendix 6: Polysomnography substudy	Added the information that the participants in the [redacted] will be enrolled in the US.	Clarification.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis ((Statistical considerations; primary endpoint) 9.4.2 Primary endpoint(s)	The text has been added to emphasize that the sleep disturbance score at Week 12 will be evaluated/measured in participants who discontinued the study intervention not due to COVID-19 pandemic while the data for those who discontinued the study intervention due to COVID-19 pandemic will not be evaluated and assumed missing.	The COVID-19 pandemic is unexpected and will eventually be over. The objective of the present study is to evaluate the study intervention effect in absence of the pandemic and therefore the data collected after study intervention discontinuation due to pandemic will be set to missing.
1.3 Schedule of activities	Added a footnote on Science37 Metasite. Deleted the row on device deficiencies.	In the Science37 Metasite all the study procedures detailed in Schedule of Activities will be performed by the participants at home.
2.3.1 Risk assessment	Updated the section as per new IB version 16.0 dated 22 June 2022.	Provided the most recent data on exposure to Dupilumab.
2.3.2 Benefit assessment	Update the regulatory information.	Provided the updated data on regulatory information.
5.1 Inclusion criteria (I 03)	The inclusion criterion was not changed; the initial definition of asthma exacerbation (deterioration of asthma that results in emergency treatment, hospitalization due to asthma, or treatment with systemic steroids) remains the same and refers to severe asthma exacerbation. Therefore a clarification has been included.	Clarification of I03
5.2 Exclusion criteria (E 03)	The exclusion criterion was not changed; the same clarification as for the I03 applies to E03.	Clarification of E03
6.1 Study intervention(s) administered 6.2 Preparation/handling/ storage/accountability	Added the text on procedure of IMP supply, preparation, handling and administration for the participants enrolled through Metasite.	Clarification on the IMP supply, handling and administration for the participants in Science37 Metasite.
6.1 Study intervention(s) administered 6.5.1 Rescue medicine	Added the information that the systemic corticosteroids are allowed in case of severe asthma exacerbation, to be aligned with standard asthma care for the treatment of severe exacerbations	Consistency of the information related to systemic corticosteroids across Section 6.5 Concomitant therapy
6.3 Measures to minimize bias: randomization and blinding	Added the procedure for obtaining the intervention kit numbers at randomization and subsequent visits via IVRS/IWRS calls considering the transportation lead time for Science37 Metasite.	To facilitate the participants by Science37 Metasite to perform the study procedures at' home.
6.4 Study intervention compliance	Added text regarding IMP/intervention accountability by Science37 for Science37 Metasite.	To facilitate the participants enrolled by Science37 Metasite to perform the study procedures at home.

Section # and Name	Description of Change	Brief Rationale
8 Study assessments and procedures 8.1.1 Actigraphy 8.1.5 Asthma sleep disturbance questionnaire 8.1.6 Asthma daytime symptom diary Asthma nighttime symptom diary 8.1.7 Sleep diary	Added the procedures for completion of the baseline assessments by Science37 Metasite.	To facilitate the participants enrolled by Science37 Metasite to perform the study procedures at home.
8.1.3 Spirometry	Clarification added for the retest of pre-BD FEV_1.	To highlight that pre-BD FEV1 can be retested one additional time during screening period in case of unsuccessful spirometry effort as defined by ATS criteria or evaluated by the investigator or did not meet the eligibility criterion at SV1.
8.1.9 Asthma control questionnaire 7-question version	7-point scale for FEV1% prediction was added.	Clarification of text.
8.1.10 Asthma quality of life questionnaire with standardized activities (self-administered) (≥12 years)	Clarification added on the overall score.	Clarification of text.
8.3.5 Pregnancy	Updated details of study intervention discontinuation, pregnancy follow up and reporting.	To keep consistent information related to study intervention discontinuation and pregnancy follow-up across the protocol
8.4 Treatment overdose	Update the definition of treatment overdose.	Clarification of text.
9.3 Populations for analyses	Revised the definition of the safety population to include only the randomized participants. Further information has also been provided for the participants for whom it is unclear whether the study intervention was taken or for those having taken more than one IMP.	This is the most common approach, and this is aligned with Sanofi standards.
9.4.3 Secondary endpoint(s)	Deleted the word “weekly average” from the first secondary endpoint.	This was a typo and edited to correct the description of the timeline to monthly average, which is how the endpoint is correctly presented throughout the rest of the document.
10.1.3 Informed consent process	Added details on eConsent process for the participants enrolled by in Science37 Metasite.	A Metasite has been added to facilitate conduct of study procedures remotely.
	Updated the details of source data and verification by study monitors.	To clarify the process for the Science 37 Metasite.
10.1.5 Dissemination of clinical study data	clinicalstudydatarequest.com updated with www.vivli.org	Updated site for the dissemination of clinical study data
10.1.7 Source documents	Added details of eConsent process for Science37 Metasite.	A Metasite has been added to facilitate conduct of study procedures remotely.

Section # and Name	Description of Change	Brief Rationale
10.2 Appendix 2: Clinical laboratory tests	Added text regarding blood sample collection and pregnancy tests (if applicable) by Science37 for Science37 Metasite.	To facilitate the participants enrolled by Science37 Metasite to perform the study procedures at home.
10.3.1 Definition of AE	Added the definition of unsolicited and solicited AE	Information added based on new protocol template
10.7 Appendix 7: Virtual Metasite	Additional appendix (Appendix 7) on Science37 Metasite added. Subsequent appendices were re-numbered.	A Metasite has been added to facilitate conduct of study procedures remotely. Approximately 10 participants from the US will be enrolled by Science37 Metasite.
Whole document	The word patients modified to participant wherever applicable.	To maintain consistency throughout the protocol.
Whole document	The word “treatment” modified to “study intervention”/ “intervention” wherever applicable.	To maintain consistency throughout the protocol.
Whole document	Minor formatting, typo corrections, consistency, and clarification changes.	Consistency.

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1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Protocol title: A Phase 4, randomized, double-blind, placebo-controlled, multicenter, parallel-group study of the effect of dupilumab on sleep disturbance in patients with uncontrolled persistent asthma

Short title: Dupilumab asthma sleep study

Rationale:

Asthma is a chronic inflammatory disease of the airways characterized by airway hyperresponsiveness, acute and chronic bronchoconstriction, airway edema, and mucus plugging. The inflammatory component of asthma involves many cell types, including mast cells, eosinophils, T-lymphocytes, neutrophils, and epithelial cells and their biological products. For most asthma patients, a regimen of controller therapy and reliever therapy provides adequate long-term control.

The prevalence of any sleep disturbance is higher in participants with uncontrolled asthma than with controlled or partially controlled asthma (32.2% versus 19.9% and 20.1% respectively, $p < 0.001$). Poorer sleep quality in severe and non-severe asthma was suggested by the data obtained from participants enrolled in the Severe Asthma Research Program (SARP). Poor sleep quality was associated with worse asthma control and quality of life in patients with both severe and non-severe asthma (1). Poor asthma control is more common in the presence of any sleep disturbance (22.7 versus 13.7%, $p < 0.001$) (2). Sleep disturbances and inability to consolidate sleep often result in excessive daytime sleepiness and may contribute to poor daytime functioning, asthma control, quality of life, and cognitive impairment, which may lead to social and neurobehavioral problems (3, 4, 5, 6, 7). In addition, the nighttime asthma symptom exacerbations are likely due to increased lower airway resistance and decreased nocturnal expiratory flow (8, 9, 10). Since sleep disturbances adversely affect overall patient quality of life, accurate detection and monitoring of their manifestation is important to the management of asthma (11). Therefore, one of the asthma treatment goals is to eliminate asthma symptoms at night and decrease awakenings due to asthma symptoms. Better control of nocturnal asthma symptoms could lead to improved sleep quality and a decrease in daytime sleep-related symptoms (12).

Dupilumab is a human monoclonal antibody (mAb) directed against the interleukin-4 receptor alpha (IL-4Rα) subunit, a component of interleukin (IL)-4 receptors Type I and Type II. The IL-4 receptors mediate the IL-4 signaling (both Type I and Type II) and IL-13 signaling (Type II). Both IL-4 and IL-13 signaling pathways are thought to play key roles in the pathophysiology of Type 2 inflammatory diseases. Dupilumab is approved for the treatment of patients with moderate-to-severe asthma in the United States (US), and for the treatment of patients with severe asthma in Europe and Japan.

In dupilumab pivotal studies, around 60% of patients had sleep disturbances based on the number of nocturnal awakenings reported at baseline.

Dupilumab has shown significant improvements in nighttime symptoms in the [redacted] study, especially in patients with uncontrolled asthma and evidence of Type 2 inflammation and at least one nocturnal awakening at baseline.

Given the importance of disturbed sleep as an outcome in patients with asthma and considering the efficacy of dupilumab in reducing nocturnal awakenings and nighttime symptoms, this study aims at providing further evidence of the effect of dupilumab in improving sleep and reducing asthma symptoms, leading to better asthma control and overall improved quality of life.

Objectives and endpoints

Objectives	Endpoints
Primary	
• To assess the effect of dupilumab on sleep	• Change from baseline to Week 12 in sleep disturbance score using the Asthma Sleep Disturbance Questionnaire
Secondary	
• To evaluate the effect of dupilumab on additional participant reported sleep outcomes	• Change from baseline to Week 12 on the number of nocturnal awakenings (Sleep Diary) • Change from baseline to Week 12 in Patient Reported Outcomes Measurement Information System (PROMIS) Sleep-Related Impairment 8a scale • Change from baseline to Week 12 in sleep quality (Sleep Diary) • Change from baseline to Week 12 in restorative sleep (Sleep Diary) • Change from baseline to Week 12 in wake after sleep onset (WASO) (Sleep Diary)
• To evaluate the effect of dupilumab on objective sleep assessment	• Change from baseline to Week 12 in WASO based on actigraphy data
• To evaluate the effect of dupilumab on asthma symptoms	• Change from baseline to Week 12 in Asthma Daytime Symptom Diary (ADSD) and Asthma Nighttime Symptom Diary (ANSD)
• To evaluate the effect of dupilumab on lung function	• Change from baseline to Week 12 in prebronchodilator forced expiratory volume (pre-BD FEV_1)
• To evaluate the safety of dupilumab	• Incidence of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs) including clinically significant changes in vital signs • Incidence of adverse events of special interest (AESI)

Overall design:

This is a Phase 4, randomized 1:1, multicenter study with 12-week double-blind, parallel-group, placebo-controlled treatment period to assess the effect of dupilumab in improving sleep outcomes, asthma control, and health-related quality of life (HRQoL), and in reducing daytime and nighttime asthma symptoms.

Dupilumab or placebo will be given as add-on therapy, all participants randomized to the study will receive asthma background therapy which will be maintained at a stable dose during the randomized double-blind treatment period. The short-acting β2 agonist (SABA) rescue medications may also be used by all participants as prescribed by the physician.

The participants will be followed-up for safety during the treatment period and up to 12 weeks thereafter or until they switch to commercialized dupilumab or other biologics, whichever comes first.

[redacted]

Science37 Metasite: A virtual site (Metasite) will enroll approximately 10 participants from the US. The Metasite will be managed by Science37, using telemedicine (TM), mobile study nurses, and an electronic application (Science37 Platform). These 10 participants will undergo the same procedures and provide the same data as other trial participants but this will be done at home. As part of this study, Science37 participants will interact with the study doctor by using a telemedicine (TM) model. The goal of TM is to decrease the participants' burden to take part in the study. Further details can be found in Section 10.7 . The participants enrolled by the Science37 Metasite will not participate in [redacted].

Disclosure Statement: This is a parallel, treatment study with 2 arms that is blinded/masked for Participant, Care Provider, and Investigator.

Number of participants:

Approximately 260 participants will be randomly assigned to study intervention, respectively in a 1:1 ratio for dupilumab: placebo (approximately 130 participants to dupilumab group and 130 to placebo group) to achieve 234 evaluable participants (with expected 10% dropout rate) for an estimated total of 117 evaluable participants per intervention group. Randomization will be stratified according to 5 strata: one stratum for all participants included in the [redacted] (regardless of dose level of inhaled corticosteroid [ICS], regardless of region) and 4 strata for participants not included in [redacted], according to region and ICS dose (Eastern Europe with high ICS dose, Eastern Europe with medium ICS dose, rest of world [ROW] with high ICS dose, and ROW with medium ICS dose). In total, no less than 40% participants need to be in "high ICS" strata, and no more than 25% participants need to be in "Eastern Europe" strata.

Intervention groups and duration:

Study intervention groups:

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

- Dupilumab 200 mg every 2 weeks (Q2W).
- Matching placebo.

Duration of study period (per participant):

Study duration per participant will be approximately 16 weeks and up to 29 weeks.

The study includes 3 study periods:

- **Screening period**:
  - Screening Period 1: Day -35 to Day -12, from signed informed consent.
  - Screening Period 2 (Pre-baseline assessments): participants eligible to continue will complete the assessments specified in the schedule of activities (SoA) from Day -11 to Day -1 (right before Day 1).
  - If preferred by the participant and the investigator for logistic reasons, screening visit 1 (SV1) and screening visit 2 (SV2) can be merged into a single on-site visit. Importantly, this single screening visit will have to be done on Day -11 at the latest.
- Randomized, placebo-controlled **treatment period**: 12 weeks from baseline (Day 1).
- Post-treatment **follow-up period**: up to 12 weeks or until the participant switches to commercialized dupilumab (or other biologic product), whichever comes first.

Study intervention(s)

Investigational medicinal product(s)

Dupilumab 200 mg and placebo matching dupilumab 200 mg supplied in visually indistinguishable prefilled syringes.

Dupilumab

- Formulation: Dupilumab 200 mg: a 175 mg/mL dupilumab solution in a prefilled syringe to deliver 200 mg in a 1.14 mL injection.
- Route(s) of administration: subcutaneous (SC) injection.
- Dose regimen: one injection of 200 mg Q2W after an initial loading dose of 400 mg (2 injections of 200 mg) on Day 1.

Placebo

- Formulation: Placebo matching dupilumab 200 mg: identical formulation to the active 200 mg formulation without dupilumab, in a prefilled syringe to deliver placebo in a 1.14 mL injection.
- Route(s) of administration: SC injection.
- Dose regimen: one injection of placebo matching dupilumab 200 mg Q2W after an initial matching placebo loading dose of 400 mg (2 injections of placebo matching dupilumab 200 mg) on Day 1.

Noninvestigational medicinal products(s)

Background asthma therapy with medium to high dose of ICS in combination with a second controller medication (eg, long-acting β2 agonist [LABA], leukotriene receptor antagonist [LTRA) at a stable dose ≥1 month prior to SV1 and during the screening period (Table 3). Participants requiring a third controller for their asthma will be considered eligible for this study, also at a stable dose ≥1 month prior to SV1 and during the screening period. Theophylline is not allowed because it can interfere with sleep and may confound the study assessments.

- Formulation and route(s) of administration: refer to label.
- Dose regimen: as prescribed.

The asthma background therapy should be maintained at a stable dose during the study treatment period.

Posttrial access to study medication

Posttrial access to study medication will be assessed in accordance to the country requirements and the legislation in place.

Statistical considerations:

- **Primary endpoint:** The primary endpoint will be analyzed using a mixed-effect model with repeated measurement (MMRM) approach. The model will include change from baseline in sleep disturbance score up to Week 12 as response variables, and treatment, age, body mass index (BMI), stratification factors, visit, treatment-by-visit interaction, baseline Asthma Control Questionnaire-5 (ACQ-5), baseline sleep disturbance score and baseline-by-visit interaction as covariates. An unstructured correlation matrix will be used to model the within-participant errors. Parameters will be estimated using restricted maximum likelihood method with the Newton-Raphson algorithm. No imputations for missing values will be carried out. To mitigate the risk of potential different responses based on the Sleep Disturbance Questionnaire before and after amendment 01, the primary analysis of change from baseline in sleep disturbance score will exclude the participants who use the original questionnaire at baseline and/or post-baseline.

  Statistical inferences on treatment comparisons for the change from baseline in sleep disturbance score at Week 12 will be derived from the mixed-effect model. The least squares (LS) mean of each treatment group, difference in the LS mean between the

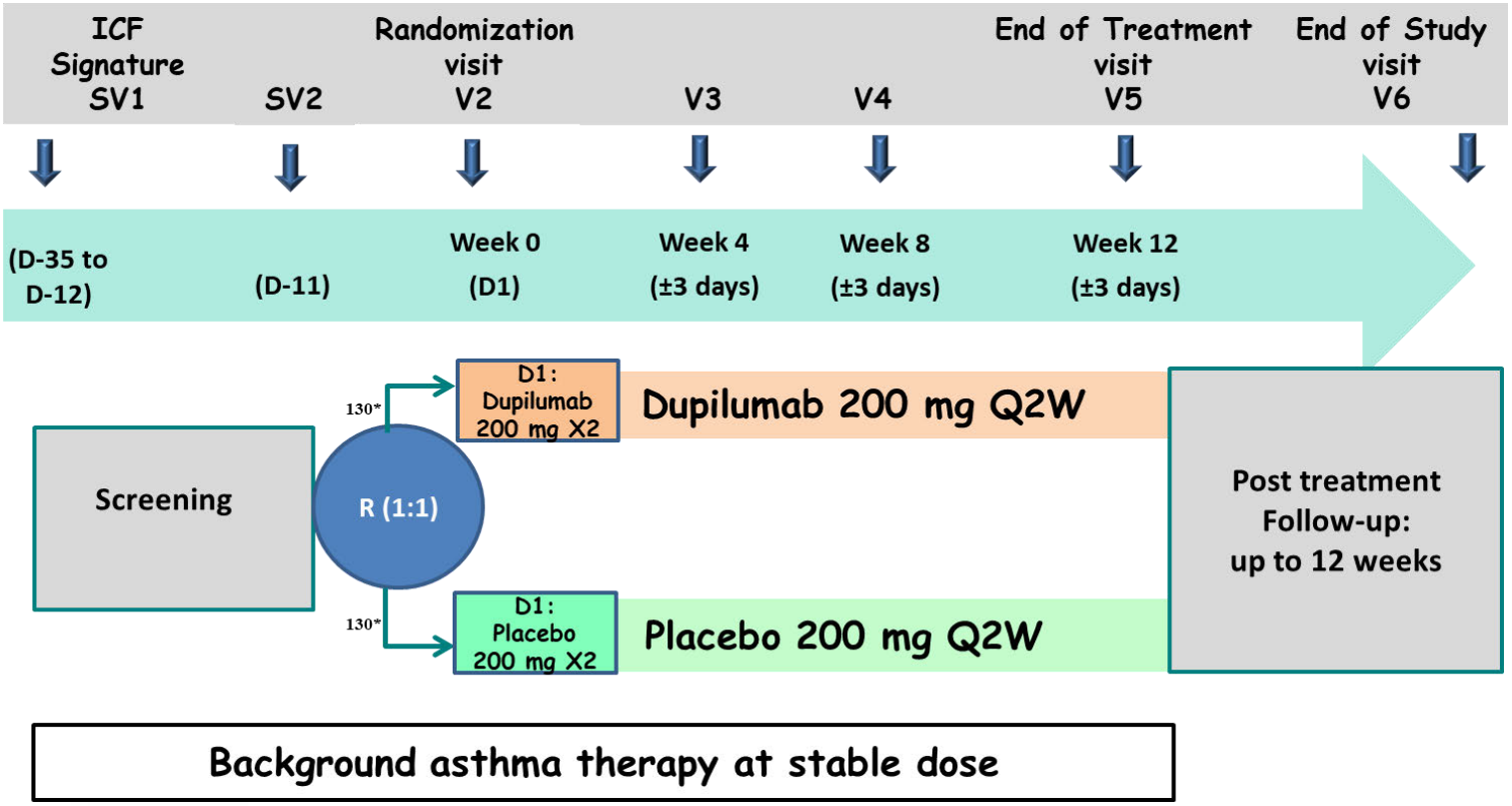
dupilumab group and placebo, and the corresponding 95% confidence interval (CI) of the differences and p-values will be provided. For participants discontinuing the study intervention before Week 12 unrelated to the COVID-19 pandemic, the sleep disturbance scores measured off-study intervention will be included in the primary analysis. In contrast, for any participants discontinuing the study intervention due to the COVID-19 pandemic, off-treatment data will not be included (i.e., set to missing) but will be assumed missing at random.

- **Main secondary endpoints:** The change from baseline in the continuous endpoints to Week 12 will analyzed using the MMRM model in the same fashion as for the primary endpoints based on the intent-to-treat (ITT) population. For the spirometry endpoints, the model will also include sex and baseline height as the covariates.

Data Monitoring Committee: No

1.2 SCHEMA

Figure 1 - Graphical study design



* An interim analysis will be performed to re-estimate sample size when 50% of participants (approximately 130) reach Week 12 visit or discontinue the study.
D1: Day 1; ICF: informed consent form; Q2W: every 2 weeks; R: randomization; SV: screening visit; V: visit.

1.3 SCHEDULE OF ACTIVITIES (SOA)

Procedure[a]	Screening		Intervention Period (weeks)[b]					Follow-up (up to 12 weeks after last IMP dose)[c]	Notes
	D-35 to D-12	D-11	W0 (D1)[r]	W4 ±3 days[s]	W8 ±3 days[s]	W12 ±3 days[s]	E/D		E/D=Early Discontinuation including: • ETD = early treatment discontinuation[d] • ESD = early study discontinuation[e]
Visit	SV1[f]	SV2[f]	V2	V3	V4	V5 (EOT)		V6 (EOS)	SV1, SV2, V2-V5: on-site visits; V6: phone visit. For the participants who switch to commercialized dupilumab (or other biologic product), the call visit should be done prior to the first injection with commercialized dupilumab (or other biologic product).
Informed consent	X								
Inclusion and exclusion criteria	X		X						
Demography	X								
Complete physical examination including height and weight	X		X			X	X		A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal and neurological systems. Body weight (kg) will be measured at SV1, V2, and V5. Height (cm) will be measured only at SV1.
Vital signs	X		X	X	X	X	X		Vital signs, including blood pressure (mmHg), heart rate (beats per minute), respiratory rate (breaths per minute), body temperature (degrees Celsius)
Medical history (includes substance usage)	X								Substances: tobacco usage collected at screening; alcohol usage will be collected in case of ALT increase
Past and current medical conditions	X								It will also include atopic comorbidities (eg, AD, CRSw/sNP) and a question about the weekly average nocturnal awakenings due to asthma symptoms in the week before SV1
Serum pregnancy test (WOCBP only)[g]	X								

Procedure[a]	Screening		Intervention Period (weeks)[b]					Follow-up (up to 12 weeks after last IMP dose)[c]	Notes
	D-35 to D-12	D-11	W0 (D1)[r]	W4 ±3 days[s]	W8 ±3 days[s]	W12 ±3 days[s]	E/D		E/D=Early Discontinuation including: • ETD = early treatment discontinuation[d] • ESD = early study discontinuation[e]
Urine pregnancy test (WOCBP only) [g]			X	X	X	X	X	X	
Hepatitis B and C screening, HIV screening, TB screening[h]	X								
12-lead ECG	X								
Eosinophil count	X[i]		X			X	X		
IVRS/IWRS call	X		X	X	X	X	X	X	
Randomization			X						
Study intervention administration[j]			←=======Q2W after D1=======→						
Study intervention dispensation			X	X	X	X			
Home dosing diary[k]			X	X	X	X	X		Paper diary
Asthma background therapy diary[k]			X	X	X	X	X		Paper diary
[redacted]	X[l]		X	X	X	X	X		[redacted] should be conducted prior to spirometry and the participant should refrain from eating and drinking for ≥1 hour before the procedure.
Spirometry[m]	X[m]		X	X	X	X	X		
Reversibility test	X[n]								Only required if a reversibility test meeting eligibility criterion was not performed within 6 months prior to SV1

Procedure[a]	Screening		Intervention Period (weeks)[b]					Follow-up (up to 12 weeks after last IMP dose)[c]	Notes
	D-35 to D-12	D-11	W0 (D1)[r]	W4 ±3 days[s]	W8 ±3 days[s]	W12 ±3 days[s]	E/D		E/D=Early Discontinuation including: • ETD = early treatment discontinuation[d] • ESD = early study discontinuation[e]
Participant assessments (at home)									
Asthma Sleep Disturbance Questionnaire		←==========daily==========→							Electronic devices; Baseline sleep disturbance scores will be the mean scores recorded for the 7 days prior to randomization.
Sleep Diary		←==========daily==========→							Electronic devices
Actigraphy[o]		X	X	X	X	X	X		Further details on the procedure will be provided in a separate instruction manual
ADSD (Asthma Daytime Symptoms Diary)		X	X	X	X	X	X		Electronic devices: completed by the participant for 7 days prior to the visit, every 4 weeks. The device will be provided to participants at SV2.
ANSD (Asthma Nighttime Symptoms Diary)		X	X	X	X	X	X		Electronic devices: completed by the participant for 7 days including the visit day, every 4 weeks. The device will be provided to participants at SV2.
Participant assessments (at clinic)									
[redacted][p]	X		X	X	X	X	X		Electronic devices
[redacted]			X			X			Type II home [redacted] devices
[redacted]			X	X	X	X	X		Electronic devices
[redacted]				X	X	X	X		Electronic devices

Procedure[a]	Screening		Intervention Period (weeks)[b]					Follow-up (up to 12 weeks after last IMP dose)[c]	Notes
	D-35 to D-12	D-11	W0 (D1)[r]	W4 ±3 days[s]	W8 ±3 days[s]	W12 ±3 days[s]	E/D		E/D=Early Discontinuation including: • ETD = early treatment discontinuation[d] • ESD = early study discontinuation[e]
Change in sleep since starting the treatment)									
PROMIS–Sleep-Related Impairment 8a scale on sleep			X	X	X	X	X		Electronic devices
[redacted]			X	X	X	X	X		Electronic devices
[redacted]			X	X		X	X		Electronic devices
AE, SAE, AESI	←==========							==========→	AE, SAE and AESI will be collected as of SV1
Prior and concomitant medication review	X	X	X	X	X	X	X	X	

a Science37 Metasite: all the study procedures will be done at participant's home by Science37 using telemedicine (TM), mobile study nurses, and an electronic application called the Science37 Platform. As part of this study, Science37 participants will see their study doctors by using a TM model during the study.

b In exceptional situations when the participant cannot attend an on-site visit during the intervention period, the visit can be performed remotely ensuring at least the procedures that can be done at home: PROs completion, actigraphy, home [redacted] if applicable, IMP administration, blood samples collection, pregnancy test, if applicable, safety reporting, and concomitant medications.

c **Post-treatment Follow-up**: up to 12 weeks or until the participant switches to commercialized dupilumab (or other biologic product), whatever comes first.

d **ETD**: Participants who prematurely discontinue the study intervention (prior to completing the 12-week treatment period) should attend an ETD visit at earliest convenience with all the assessments planned for the EOT visit (Visit 5), except IMP. In particular cases when the ETD visit is close to a regular study visit, ETD could be merged and will replace the regular visit. In addition, the participants will be asked and encouraged to complete all the remaining study visits according to the visit schedule until and including the EOT visit (Visit 5). Under exceptional circumstances when a participant cannot come to the site for the scheduled visit, a phone contact can be made after sponsor approval is given. During the phone contact, at least information about AEs and concomitant medications should be collected.

e **ESD**: Participants who prematurely discontinue the study during the intervention period should attend an ESD visit at earliest convenience with all the procedures planned for the EOT Visit (Visit 5) except IMP. Under exceptional circumstances when a participant cannot come to the site for the scheduled visit, a phone contact can be made after sponsor approval is given. During the phone contact, at least information about AEs and, concomitant medications should be collected.

f If preferred by the participant and the investigator for logistic reasons, screening visit 1 (SV1) and screening visit 2 (SV2) can be merged into a single on-site visit. Importantly, this single screening visit will have to be done on Day -11.at the latest.

g Serum pregnancy test at screening visit (SV1) and urine pregnancy tests at the other visits using dipstick. A WOCBP must have a negative highly sensitive pregnancy test at SV1 (serum pregnancy test) and on Day 1 before the first dose of study intervention (urine or serum, if required by local regulations). If a urine test on Day 1 cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive. In case of positive urinary test during the study, a serum pregnancy test should be performed as soon as possible to confirm the pregnancy. A urine pregnancy test will be performed at home at the follow-up visit.

h Hepatitis screening covering hepatitis B surface antigen (HBs Ag), total hepatitis B core antibody (total HBcAb); hepatitis C virus antibodies (HCVAb). In case of results showing HBsAg (negative) and HBcAb (positive), HBV DNA testing will be performed to rule out a false positivity or to clarify the serological status if the Investigator finds it unclear to interpret in absence of known HBV infection. In case of results showing HCVAb (positive), HCV RNA testing may be performed to rule out a false positivity. Human Immunodeficiency Virus screening (Anti-HIV-1 and HIV-2 antibodies). Tuberculosis testing will be performed only on a country by country basis according to the routine clinical practice and the local guidelines if required by Regulatory Authorities or Ethics Committees.

i Retesting of eosinophil count is allowed up to three times during the screening period to meet inclusion criteria for showing eosinophil count ≥150 cells/microliter cells/mL (I 04) before randomization. This is only required if the participant doesn't have the blood eosinophil count measured within 6 months prior to SV1 in the absence of OCS treatment.

j Investigational product administrations (Q2W) should be separated by at least 11 days. The administration is performed on-site during planned visits alternating with Q2W home administration (participant, caregiver, or health care professional) or in a health care facility. On Day 1, loading dose as follows: 400 mg dupilumab for the dupilumab arm (200 mg x 2 syringes injections) and 2 placebo syringes for the placebo arm. Science37 Metasite: Investigational product (IMP) administrations will be done at participant's home by Science37 home nursing service.

k Should be completed by participants regularly to record investigational (home dosing diary) and non-investigational (asthma background therapy diary) product information. Recorded data will be collected by the investigator at each on-site visit.

l Retesting of [redacted] can be performed one additional time during screening if the eligibility criterion for [redacted] was not met at SV1. [redacted] will be rechecked at randomization visit (V2) for eligibility. It will be performed after a wash-out period of bronchodilators according to their action duration. Further details on the procedure will be provided in a separate instruction manual.

m Spirometry test should be performed before IMP administration, in the morning if possible. If testing can only be done at another time during the day, then the testing should be done at approximately the same time of day at each visit throughout the study. Spirometry will be performed after a wash-out period of bronchodilators according to their action duration. This will be verified before performing the measurements. A participant who is unable to complete a successful spirometry effort as defined by 2005 ATS criteria or evaluated by the investigator or did not meet the eligibility criterion for pre-BD FEV1 at SV1 can be retested one additional time during the screening period of the study. For spirometry the investigator will assess the eligibility based on the FEV_1 local values from SV1 and Visit 2 before randomization (the results from central reading will not be available on the same day). Further details on the procedure will be provided in a separate instruction manual.

n 3 attempts may be performed during the screening period to meet the eligibility criteria for reversibility before randomization.

o Actigraphy: The participants will complete baseline assessments from Day -11 to Day -1 (right before Day 1); daily assessment thereafter until Week 4; then only the week before a clinical visit until EOT. Baseline value will be calculated using the data from Day -7 to Day -1. Science37 Metasite: For the completion of the baseline and postbaseline assessments, refer to Appendix 7 (Section 10.7).

p [redacted]

q Each participant in this substudy will have a total of two overnight [redacted]: 1 overnight [redacted] using Type II home devices on Day -1 to collect baseline data and 1 more at Week 12. If the sleep recording is inadequate as judged by the central reading site, the at-home sleep assessment will be repeated within 1 week of the original assessment.

r Science37 Metasite: participant randomization in IVRS/IWRS will occur on Day 1, with first loading dose occurring up to 5 days post randomization to account for the lag between IVRS/IWRS randomization trigger for IMP DTP shipment and IMP availability to participant/mobile study nurse.

s Science37 Metasite: the windows for subsequent at home dosing visits (week 4, week 8, week 12), up to 3 days (maximum visit window) to account for the lag between IWRS trigger for IMP DTP shipment and IMP availability to participant/mobile study nurse.

ACQ-5: Asthma Control Questionnaire-5; [redacted] AD: atopic dermatitis; ADSD: Asthma Daytime Symptoms Diary; AE: adverse event; AESI: adverse event of special interest; ALT: alanine transaminase; ANSD: Asthma Nighttime Symptoms Diary; [redacted] ATS: American Thoracic Society; BD: bronchodilator; CRSw/sNP; chronic rhinosinusitis with/without nasal polyps; D: day; E/D: early discontinuation; ECG: electrocardiogram; EOS: end of study; EOT: end of treatment; ESD: early study discontinuation; ETD: early treatment discontinuation; [redacted] e; FEV_1: forced expiratory volume; HBcAB: hepatitis B core antibody; HBsAg: hepatitis B surface antigen; HBV: hepatitis B virus; HCV: hepatitis C virus; HCVAb: hepatitis C virus antibody; HIV: human immunodeficiency virus; IMP: investigational medicinal product; IVRS: interactive voice response system; IWRS: interactive web response system; OCS: oral corticosteroid; [redacted] PRO: patient-reported outcome; PROMIS: patient-reported outcome measurement information system; [redacted] RNA: ribonucleic acid; SAE: serious adverse event; TB: tuberculosis; W: week; WOCBP: woman of childbearing potential; [redacted].

2 INTRODUCTION

Asthma is a chronic inflammatory disease of the airways characterized by airway hyperresponsiveness, acute and chronic bronchoconstriction, airway edema, and mucus plugging. The inflammatory component of asthma involves many cell types, including mast cells, eosinophils, T-lymphocytes, neutrophils, and epithelial cells and their biological products. For most asthma patients, a regimen of controller therapy and reliever therapy provides adequate long-term control.

Respiratory disturbances during sleep are recognized as extremely common disorders with important clinical consequences in patients with asthma. Difficulties inducing sleep, sleep fragmentation, early morning awakenings, and daytime sleepiness are more common in subjects with asthma compared with subjects without asthma (13).

Dupilumab, a fully human monoclonal antibody, is directed against the IL-4Rα subunit, which is a component of IL-4 heterodimeric receptors Type I (IL4-ligand only) and Type II (both IL-4 and IL-13 ligands). The binding of dupilumab to IL-4Rα results in blockade of downstream signaling initiated by both IL-4 and IL-13. These cytokines play key roles in the pathogenesis of various allergic diseases including asthma (14). The results of dupilumab pivotal studies have demonstrated its efficacy in moderate-to-severe asthma patients by decreasing the rates of severe asthma exacerbation, improving the lung function and asthma control (15), reducing oral glucocorticoid use (16) as well as decreasing disturbance measured by evening symptom score and nocturnal awakening.

Dupilumab is approved in the US for use in adults and adolescents (≥12 years) with moderate-to-severe eosinophilic asthma and in the European Union (EU) for use in adults and adolescents (≥12 years) with severe asthma with Type 2 inflammation. In Japan, dupilumab received Pharmaceuticals and Medical Devices Agency (PMDA) approval for use in adults and adolescents (≥12 years) with severe or refractory bronchial asthma.

2.1 STUDY RATIONALE

Sleep is a significant dimension of a patient's life and the long-term interruption of normal sleeping patterns adversely affects physical, emotional functioning and quality of life (17, 18, 19, 20) as well as increases the risk for poor health outcomes and psychological distress (21, 22).

In addition, poorer sleep quality in severe and non-severe asthma was suggested by the data obtained from participants enrolled in the SARP. Poor sleep quality was associated with worse asthma control and quality of life in patients with both severe and non-severe asthma (1). Sleep disturbances and inability to consolidate sleep often result in excessive daytime sleepiness and may contribute to poor daytime functioning, asthma control, quality of life, and to cognitive impairment, which may lead to social and neurobehavioral problems (3, 4, 5, 6, 7).

The prevalence of any sleep disturbance is higher in participants with uncontrolled asthma than with controlled or partially controlled asthma (32.2% versus 19.9% and 20.1% respectively, p <0.001). There is no significant difference in prevalence of sleep disturbances between subjects with controlled asthma and subjects without asthma. Poor asthma control is more common in the presence of any sleep disturbance (22.7% versus 13.7%, p <0.001) (2). The nighttime asthma symptom exacerbations are likely due to increased lower airway resistance and decreased nocturnal expiratory flow (8, 9, 10).

Since sleep disturbances adversely affect overall patient quality of life, accurate detection and monitoring of their manifestation is important to the management of asthma (11).

One of the asthma treatment goals is to eliminate asthma symptoms at night and decrease awakenings due to asthma symptoms. Better control of nocturnal asthma symptoms could lead to improved sleep quality and a decrease in daytime sleep-related symptoms (12).

A recently published observational study assessing sleep quality in patients with asthma (N=1150) showed that 58% of the patients had impaired sleep quality (Pittsburgh Sleep Quality Index [PSQI] >5), while sleep quality was significantly associated with HRQoL (23).

In dupilumab pivotal studies, around 60% of patients had sleep disturbances based on the number of nocturnal awakenings and the nighttime symptoms reported at baseline.

Dupilumab has shown significant improvements in nighttime symptoms in the [redacted] study, especially in patients with uncontrolled asthma and evidence of Type 2 inflammation and at least one nocturnal awakening at baseline.

There is no published evidence showing a beneficial effect of asthma medication on sleep quality thus far. In fact, the existing literature on this topic is scant.

Therefore, there is a data gap to generate evidence that can potentiate dupilumab therapeutic benefit on sleep quality and disturbances in patients with asthma.

Given the importance of disturbed sleep as an outcome in patients with asthma and considering the efficacy of dupilumab in reducing nocturnal awakenings and night-time symptoms, this study aims at providing further evidence of the effect of dupilumab in improving sleep and reducing asthma symptoms, leading to better asthma control and overall improved quality of life.

2.2 BACKGROUND

Dupilumab is a human mAb directed against the IL-4Rα subunit, a component of IL-4 receptors Type I and Type II. The IL-4 receptors mediate the IL-4 signaling (both Type I and Type II) and IL-13 signaling (Type II). Both IL-4 and IL-13 signaling pathways are thought to play key roles in the pathophysiology of Type 2 inflammatory diseases.

The results of the conducted studies of dupilumab have demonstrated significant improvements, with treatment compared to placebo in some sleep outcomes, such as nocturnal awakenings or nighttime symptoms.

There are several subjective measures to assess sleep quality and disturbances, however the majority of them are not specific to patients with asthma (ie, PSQI) or are not completely dedicated to assessing sleep (ie, ACQ, Asthma Control Test [ACT], AQLQ).

Food and Drug Administration (FDA)-validated questionnaire to assess asthma symptoms at night includes the ADSD, which evaluates the impact of nighttime symptoms due to asthma.

Actigraphy is one of the most common objective measures of sleep disturbances. It is a procedure that records and integrates the occurrence and degree of limb movement activity over time. In addition to providing a graphical summary of wakefulness and sleep patterns over time, actigraphy generates estimates of certain sleep parameters (24).

2.3 BENEFIT/RISK ASSESSMENT

Dupilumab has shown clinically relevant benefit in several Type 2-driven immunological disorders such as AD, bronchial asthma, chronic rhinosinusitis with nasal polyps (CRSwNP), and eosinophilic esophagitis (EoE). A satisfactory safety profile has been observed so far in completed and currently ongoing studies.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of dupilumab may be found in the Investigator's Brochure.

This study aims at evaluating the effect of dupilumab on sleep disturbances due to asthma symptoms, using a combination of participant-reported outcomes and objective measures of sleep quality (actigraphy) in patients with moderate-to-severe asthma and high disease burden. The study is medically and scientifically justified.

The selected dose regimen has been evaluated in dupilumab pivotal trials (loading dose of 400 mg of dupilumab [2 x 200 mg dupilumab SC] on Day 1, followed by 200 mg Q2W) and approved by regulatory authorities, demonstrating a positive benefit/risk.

2.3.1 Risk assessment

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

Dupilumab has an extensive safety database.

As of 28 March 2022 (data cut-off date), approximately 13 577 subjects were enrolled into the development program for dupilumab and are included in the safety population: 564 as healthy volunteers; 4998 from AD studies (including atopic hand and foot dermatitis); 4195 from asthma studies; 880 from the rhinosinusitis (CRSwNP, CRSsNP, and AFRS) studies; 468 from EoE studies; 275 from the allergy (grass and peanut); 1495 from COPD studies; 309 from PN studies; 311 from the urticaria studies (CSU and CICU); 45 from the BP study; and 37 from the ABPA study.

Based on the available sales figures and World Health Organization defined daily dose of 21.4 mg for parenteral formulations, the cumulative patient exposure in marketed experience could be estimated to be 706 212 patient years from 01 March 2017 through 31 March 2022, including 332 123 patient years during the interval period from 01 April 2021 through 31 March 2022.

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

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

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

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

Other potential risks based on the safety profile in particular indications are discussed in the IB. It is anticipated that dupilumab in patients with uncontrolled persistent asthma will have a favorable safety profile as observed across other Type 2-driven immunological disorders.

2.3.2 Benefit assessment

Dupilumab solution for injection is currently authorized:

- In over 60 countries worldwide for asthma indication, including the US, for use as an add-on maintenance treatment of adults and pediatric patients aged 6 years and older with moderate-severe asthma characterized by an eosinophilic phenotype or with OCS dependent asthma; the EU as an add-on maintenance treatment for adult and adolescent (12 years and older) patients as well as in children 6 to 11 years old with severe asthma with type 2 inflammation characterized by raised blood eosinophils and/or raised FeNO who are inadequately controlled appropriate combination therapy (high-dose ICS over 12 years or age, medium-to-high dose in those younger, taken by inhalation) plus another medicinal product for maintenance treatment, and in Japan, for use in adults and adolescents (aged ≥12 years) with severe or refractory bronchial asthma.
- In over 60 countries worldwide, including the US, EU, and Japan for the treatment of adults with inadequately controlled moderate-to-severe AD. In over 50 countries, including the US and EU, it has also been authorized for use in adolescent patients (≥12 years) with inadequately controlled moderate-to-severe AD. Additionally, dupilumab has been approved in over 50 countries for the treatment of inadequately controlled pediatric patients (age 6-11 years) with moderate to severe AD or of pediatric patients with severe AD who are candidates for systemic therapy. In the US, dupilumab is also approved for use in pediatric patients of 6 months to 5 years of age.
- Dupilumab is approved for the CRSwNP indication in more than 50 countries worldwide; including the US for the use as an add-on maintenance treatment for adults with inadequately controlled CRSwNP; in EU for use as an add-on therapy with intranasal corticosteroids (INCs) in adults with severe CRSwNP for whom therapy with systemic corticosteroids (SCSs) and/or surgery do not provide adequate disease control and in Japan, for use in adults with CRSwNP (only patients not adequately controlled with existing therapies).

One of the asthma treatment goals is to eliminate asthma symptoms at night and decrease awakenings due to asthma symptoms, which could lead to improved quality of life (12). Dupilumab has shown significant improvements in nighttime symptoms and nocturnal awakenings in the pivotal clinical studies, especially in patient with uncontrolled asthma and evidence of Type 2 inflammation. Data generated from the present study might provide further evidence of the effect of dupilumab in improving sleep and reducing asthma symptoms, leading to better asthma control and overall improved quality of life.

The participants with moderate-severe asthma uncontrolled by medium to high dose ICS and a second controller +/- a third controller might benefit by the treatment with dupilumab (double-blind, randomized 1:1 study). The asthma background therapy with ICS and a second controller (eg, LABA or LTRA) +/- a third controller will be maintained at a stable dose during the treatment period. The participants will be closely followed-up according to SoA (Section 1.3).

2.3.3 Benefit/risk assessment related to COVID-19

The Sponsor recognizes that the COVID-19 pandemic is having an impact on the conduct of clinical trials. The Sponsor is monitoring the situation closely and may suspend study screening activities until the impact of the COVID-19 pandemic is deemed manageable and no longer interfering with the conduct of trials at individual sites, and patients can safely participate in this study. The continuity of clinical study conduct, and oversight may require implementation of temporary or alternative mechanisms. Thus, a mitigation plan has been put in place at study level, all the contingency measures are described in Appendix 7 (Section 10.7). The participants will be properly informed on all these options by the investigators before the implementation of the contingency measures, as mentioned in the Informed Consent Form. Implementation of such mechanisms may differ country by country, depending on country regulations and local business continuity plans.

Based on the aforementioned potential benefits to patients participating in LPS16677, and the appropriate precautions and mitigations instituted to manage any potential impact of COVID-19 on the conduct of the trial and the safety of the patients, the Sponsor assesses that the overall benefit-risk balance is positive for the conduct of and patient participation in this trial.

2.3.4 Overall benefit: risk conclusion

Taking into account the measures taken to minimize risk to participants participating in this study, the potential risks identified in association with dupilumab are justified by the anticipated benefits that may be afforded to participants with uncontrolled persistent asthma.

3 OBJECTIVES AND ENDPOINTS

Table 1 - Objectives and endpoints

Objectives	Endpoints
Primary	
• To assess the effect of dupilumab on sleep	• Change from baseline to Week 12 in sleep disturbance score using the Asthma Sleep Disturbance Questionnaire
Secondary	
• To evaluate the effect of dupilumab on additional participant reported sleep outcomes	• Change from baseline to Week 12 on the number of nocturnal awakenings (Sleep Diary) • Change from baseline to Week 12 in Patient-Reported Outcomes Measurement Information System (PROMIS) Sleep-Related Impairment 8a scale • Change from baseline to Week 12 in sleep quality (Sleep Diary) • Change from baseline to Week 12 in restorative sleep (Sleep Diary) • Change from baseline to Week 12 in wake after sleep onset (WASO) (Sleep Diary)
• To evaluate the effect of dupilumab on objective sleep assessment	• Change from baseline to Week 12 in WASO based on actigraphy data
• To evaluate the effect of dupilumab on asthma symptoms	• Change from baseline to Week 12 in Asthma Daytime Symptom Diary (ADSD) and Asthma Nighttime Symptom Diary (ANSD)
• To evaluate the effect of dupilumab on lung function	• Change from baseline to Week 12 in prebronchodilator forced expiratory volume (pre-BD FEV_1)
• To evaluate the safety of dupilumab	• Incidence of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs) including clinically significant changes in vital signs • Incidence of adverse events of special interest (AESI)
Tertiary/exploratory	
[redacted]	[redacted]

Objectives	Endpoints
[redacted]	[redacted]

3.1 APPROPRIATENESS OF MEASUREMENTS

The efficacy and exploratory assessments will be done based on the data collected using the following PROs:

- Asthma Sleep Disturbance Questionnaire
- Sleep Diary
- Asthma Daytime Symptom Diary (ADSD)
- Asthma Nighttime Symptom Diary (ANSD)
- [redacted]
- PROMIS–Sleep Related Impairment 8a scale on sleep
- [redacted]

These assessments will be coupled with objective assessments of sleep disturbance (actigraphy [redacted], the latter only for the participants in the substudy), clinical outcomes (pre-BD FEV_1) and [redacted]

4 STUDY DESIGN

4.1 OVERALL DESIGN

This is a Phase 4, randomized 1:1, multicenter study with a 12-week double-blind, parallel-group, placebo-controlled treatment period to assess the effect of dupilumab in improving sleep outcomes, asthma control, and health-related quality of life, and in reducing daytime and nighttime asthma symptoms.

Study duration for each participant will be approximately 16 weeks and up to 29 weeks.

The study includes 3 study periods:

- Screening period:
  - Screening Period 1: Day -35 to Day -12, from signed informed consent.
  - Screening Period 2 (Pre-baseline assessments): participants eligible to continue will complete the assessments specified in the SoA from Day -11 to Day -1 (right before Day 1).
  - If preferred by the participant and the investigator for logistic reasons, screening visit 1 (SV1) and screening visit 2 (SV2) can be merged into a single on-site visit. Importantly, this single screening visit will have to be done on Day -11 at the latest.
- Randomized, placebo-controlled treatment period: 12 weeks from baseline (Day 1).
- Post treatment follow-up period: up to 12 weeks or until the participant switches to commercialized dupilumab (or other biologic product), whichever comes first.

Participants who fulfill the inclusion criteria and do not meet any of the exclusion criteria will be randomized centrally (1:1) to one of the following IMPs:

- Dupilumab: participants will receive a loading dose of 400 mg of dupilumab (two 200 mg dupilumab SC injections) on Day 1, followed by one 200 mg dupilumab SC injection Q2W for 12 weeks.
- Placebo: participants will receive two placebo matching dupilumab 200 mg SC injections on Day 1, followed by one of placebo matching dupilumab 200 mg SC injection Q2W for 12 weeks.

[redacted]

Science37 Metasite: A virtual site (Metasite) will enroll approximately 10 participants from the US. The Metasite will be managed by Science37, using telemedicine (TM), mobile study nurses, and an electronic application (Science37 Platform). These 10 participants will undergo the same procedures and provide the same data as other trial participants but this will be done at home. As part of this study, Science37 participants will interact with their study doctors by using a telemedicine (TM) model during the study. The goal of TM is to decrease the participants' burden to take part in the study. The participants enrolled by Science 37 Metasite will not participate in [redacted]. Further details can be found in Section 10.7.

Randomization will be stratified according to 5 strata: one stratum for all participants included in the [redacted] (regardless of dose level of ICS, regardless of region) and 4 strata for participants not included in [redacted], according to region and ICS dose (Eastern Europe with high ICS dose, Eastern Europe with medium ICS dose, ROW with high ICS dose, and ROW with medium ICS dose). In total, no less than 40% participants need to be in "high ICS" strata, and no more than 25% participants need to be in 'Eastern Europe' strata.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

Given the importance of disturbed sleep as an outcome in patients with asthma and considering the efficacy of dupilumab in reducing nocturnal awakenings and night-time symptoms, this study aims at providing further evidence of the effect of dupilumab in improving sleep and reducing asthma symptoms, leading to better asthma control and overall improved quality of life.

The primary endpoint will be assessed based on the sleep disturbance score using the Asthma Sleep Disturbance Questionnaire.

Secondary and the tertiary endpoints will be based on the data collected in the PROs coupled with key objective assessments such as actigraphy, knowing that this procedure is one of the most common objective measures of sleep disturbance (24), clinical outcomes (pre-BD FEV_1), [redacted]

The randomized double-blind treatment period of 12 weeks was considered relevant for the efficacy assessments.

The aim of this study is to provide further evidence of the effect of dupilumab in improving sleep and reducing asthma symptoms, leading to a better asthma control and overall improved quality of life. A control arm is needed so that the effect of dupilumab on the study endpoints can be distinguished from an effect due to other reasons, such as natural improvement over time or better adherence to treatment as a result of being in a clinical trial. Therefore, the presence of a placebo arm is appropriate for the objectives of this study, since it will provide the most robust assessment of the efficacy and safety of dupilumab. The participants will be appropriately informed of and will provide written consent to the eventuality of receiving placebo during the randomized double-blind treatment period. They may withdraw from the study intervention or from the study at any time and receive the conventional treatment as prescribed by the physician.

The safety follow-up period will be up to 12 weeks or until the participant switches to biologics (including commercialized dupilumab), considering that after the last steady-state dose, the median time for dupilumab concentrations to decrease below the lower limit of detection, estimated by population PK analyses was 9 weeks for the 200 mg Q2W (see the Investigator's Brochure).

4.2.1 Participant input into design

Not applicable.

4.3 JUSTIFICATION FOR DOSE

The dose regimen of SC dupilumab selected for this study is 200 mg Q2W. Participants will receive an initial loading dose of 400 mg (2 x 200 mg) dupilumab on Day 1, and Q2W dosing will commence 2 weeks after the loading dose. The administration of the loading dose of dupilumab will allow systemic concentrations to reach target saturation, potentially reducing the time to onset of clinical effect.

The results from the Phase 2b dose ranging study (DRI12544) (25) showed that 300 mg Q2W and 200 mg Q2W treatment with dupilumab provided comparable efficacy on most of the efficacy endpoints. Both doses were safe and well tolerated with a profile comparable to that seen with placebo except for an increased number of injection site reactions. To further characterize the optimal regimen for patients, both regimens were assessed in the Phase 3 study ([redacted]) (15), which confirmed the findings from previous studies, showing comparable efficacy and safety profile in both 200 mg Q2W and 300 mg Q2W dose regimens, with an overall positive benefit-risk profile for dupilumab in comparison to placebo.

As evidenced by dupilumab's clinical development program, clinical efficacy and safety data for the 200 mg dose is similar to 300 mg, however selecting 300 mg dose would imply potential inclusion of OCS dependent patients, in alignment with approved regulatory labels in some countries. Patients on OCS treatment commonly experience sleep disturbances as AEs (26), therefore OCS use can be a confounding variable in the evaluation of sleep outcomes, given that improvements in sleep outcomes could be seen due to OCS reduction or complete withdrawal that patients experience on dupilumab treatment. This supports the selection of the 200 mg dose for the study purpose.

4.4 END OF STUDY DEFINITION

A participant is considered to have completed the study if he/she has completed all phases of the study including the post treatment follow-up visit (V6).

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

5 STUDY POPULATION

Selection criteria are in line with the approved indication and refer to labeling information. Contraindications, precautions of use and warnings were considered.

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

5.1 INCLUSION CRITERIA

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

Age

I 01. Participant must be 18 to 65 years of age inclusive, at the time of signing the informed consent.

Type of participant and disease characteristics

I 02. Participants with a physician diagnosis of asthma based on the Global Initiative for Asthma (GINA) 2020 (27) for ≥12 months treated with medium to high dose ICS and a second controller (ie, LABA, LTRA). A third controller is allowed but not mandatory. The dose regimen should be stable for at least 1 month before SV1 and during the screening period.

I 03. History of at least one severe asthma exacerbation within 1 year prior to SV1. Severe exacerbation is defined as deterioration of asthma that results in emergency treatment, hospitalization due to asthma, or treatment with systemic steroids (oral or injectable).

I 04. Participants with eosinophils ≥150 cells/µL and FeNO ≥25 ppb during screening, prior to randomization.

NOTES:

- Historical values of blood eosinophil count meeting the eligibility criterion measured within 6 months prior to SV1 in the absence of OCS treatment are allowed.
- FeNO value to be checked for eligibility at V2 as well.

I 05. ACQ-5 ≥2.5 at SV1 and Visit 2, prior to randomization.

I 06. Pre-BD FEV1 ≤80% of predicted normal during screening and at V2, prior to randomization.

I 07. Exhibit bronchodilator reversibility (≥12% and 200 mL improvement in FEV1 post SABA administration) during screening period, prior to randomization, unless reversibility test meeting the inclusion criteria was done within 6 months prior to SV1.

I 08. Weekly average nocturnal awakenings due to asthma symptoms in the week prior to SV1 is ≥1.

I 09. Willing and able to comply with all clinic visits and study-related procedures.

Sex

I 10. Male or female.

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

a) Female 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) of the protocol during the study, ie, at a minimum until 12 weeks after the last dose of study intervention or until the participant switches to commercialized dupilumab (or other biologic product), whichever comes first.
- A WOCBP must have a negative highly sensitive pregnancy test (urine or serum as required by local regulations) on Day 1 before the first dose of study intervention.
- If a urine test on Day 1 cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.
- Additional requirements for pregnancy testing during and after study intervention are located in Appendix 2 (Section 10.2).
- 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 11. Capable of giving signed informed consent as described in Appendix 1 (Section 10.1.3) which includes compliance with the requirements and restrictions listed in the ICF and in this protocol. In countries where legal age of majority is above 18 years, a specific ICF must also be signed by the participant's legally authorized representative.

5.2 EXCLUSION CRITERIA

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

Medical conditions

E 01. Current smoker.

E 02. Former smoker for 10 years with a smoking history of >10 pack-years.

E 03. Severe asthma exacerbation during screening, prior to randomization.

E 04. History or clinical evidence of COPD including Asthma-COPD Overlap Syndrome (ACOS) or any other significant lung disease (eg, lung fibrosis, sarcoidosis, interstitial lung disease, pulmonary hypertension, bronchiectasis, Churg-Strauss Syndrome).

E 05. History of or current evidence of clinically significant non-respiratory diseases (eg, cardiovascular, hepatic, nervous system, gastrointestinal, endocrinological, rheumatological, dermatological), that in the opinion of the investigator may interfere with the aims of the study or put the participant at undue risk.

E 06. Participants with active TB or non-tuberculous mycobacterial infection, or a history of incompletely treated TB will be excluded from the study unless it is well documented by a specialist that the participant has been adequately treated and can now start treatment with a biologic agent, in the medical judgment of the Investigator and/or infectious disease specialist. Tuberculosis testing would be performed on a country-by-country basis, according to local guidelines if required by Regulatory Authorities or ethics boards.

E 07. Diagnosed active endoparasitic infection; suspected or high risk of endoparasitic infection, unless clinical and (if necessary) laboratory assessment have ruled out active infection before randomization.

E 08. History of HIV infection or positive HIV 1/2 serology at SV1.

E 09. Active chronic or acute infection requiring treatment with systemic antibiotics, antivirals, antiprotozoals, or antifungals within 2 weeks before SV1.

E 10. Known or suspected immunodeficiency, including history of invasive opportunistic infections (eg, TB, histoplasmosis, listeriosis, coccidioidomycosis, pneumocystosis, and aspergillosis) despite infection resolution, or otherwise recurrent infections of abnormal frequency or prolonged duration suggesting an immune-compromised status, as judged by the Investigator.

E 11. Current evidence of clinically significant oncological disease, which in the opinion of the investigator may interfere with the objectives of the study or put the participant at undue risk.

E 12. History of systemic hypersensitivity or anaphylaxis to any biologic therapy (including dupilumab or any of its excipients; see Section 10.9).

E 13. Participant with severe uncontrolled depression.

E 14. Sleep disturbances not related to asthma, including sleep apnea, hypersomnia, or insomnia secondary to chronic pain, AD, COPD, etc, as determined by the Investigator.

E 15. Participants who work night shifts (ie, any work between 8 PM and 6 AM).

E 16. Participants with erratic sleep habits, as determined by the Investigator.

E 17. Evidence of restless leg syndrome or periodic limb movement disorder.

Prior/concomitant therapy

E 18. Chronic treatment with OCS within 2 weeks prior to SV1.

E 19. Participants taking sedative, anxiolytic, or hypnotic treatments, including melatonin, within 3 months before randomization.

E 20. Participants taking systemic sedative antihistamines (this does not include the newer generations of antihistamines) or theophylline.

E 21. Current treatment with antidepressants, lipophilic beta blockers, clonidine, opioids, or other medications known to interfere with sleep and may confound the study assessments, as determined by the Investigator.

Note: In most cases, chronic treatments administered regularly and at stable dosing should be acceptable. Investigators should assess the degree to which an individual medication may cause changes in sleep pattern or sleep quality during the study, compared to the pre-baseline state.

E 22. Participant who has taken biologic therapy (including dupilumab)/systemic immunosuppressant to treat inflammatory disease or autoimmune disease (eg, rheumatoid arthritis, inflammatory bowel disease, primary biliary cirrhosis, systemic lupus erythematosus, multiple sclerosis, etc) within 2 months or 5 half-lives before SV1, whichever is longer.

E 23. Treatment with live (attenuated) vaccine within 4 weeks before SV1.

NOTE: For participants who have vaccination with live, attenuated vaccines planned during the course of the study (based on national vaccination schedule/local guidelines), it will be determined, after consultation with a physician, whether the administration of vaccine can be postponed until after the end of the study (ie, after the 12-week follow-up period off-treatment or until the participant switches to commercialized dupilumab or other biologic product, whichever comes first), or preponed to before the start of the study without compromising the health of the participant:

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

E 24. Planned or anticipated use of any prohibited medications (Section 6.5) and procedures during screening and study treatment period.

Prior/concurrent clinical study experience

E 25. Enrolled in other ongoing studies regardless of the investigational product.

E 26. Treatment with an investigational drug within 1 month or within 5 half-lives (if known), whichever is longer, prior to SV1.

Diagnostic assessments

E 27. Participants with any of the following results at SV1:

- Positive (or indeterminate) HBsAg or,
- Positive total HBcAb confirmed by positive HBV DNA or,
- Positive HCVAb confirmed by positive HCV RNA.

Other exclusions

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

E 29. Participant not suitable for participation, whatever the reason, as judged by the Investigator, including medical or clinical conditions, or participants potentially at risk of noncompliance to study procedures.

E 30. 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).

E 31. Any specific situation during study implementation/course that may rise ethics considerations.

E 32. Sensitivity to any of the study interventions, or components thereof, or drug or other allergy that, in the opinion of the Investigator, contraindicates participation in the study.

5.3 LIFESTYLE CONSIDERATIONS

No restrictions are required.

5.4 SCREEN FAILURES

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

Reasons for screen failure may be unfulfilled eligibility criteria and withdrawal of consent during screening period, between screening and randomization.

Participants who do not meet the eligibility criteria for participation in this study and for whom resolution of the screen failure reason may not be expected within a reasonable time frame will be deemed a screen failure.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. The participants may be rescreened once during the open screening period. There is no requirement for a waiting period between the screen failure date and the rescreening date. Participants who are rescreened must sign a new consent form and all SV1 procedures must be repeated. A different participant identification number will be issued. The interactive voice recognition system (IVRS)/ interactive web response system (IWRS) report will flag rescreened participants.

If certain dynamic laboratory tests do not meet the eligibility criteria, these laboratory assessments may be repeated, at the discretion of the Investigator, if it is judged that they are likely to return to acceptable range for study inclusion within the screening visit window prior to Day 1. These participants do not need to sign a new ICF and a new participant number will not be allocated.

Retesting of eosinophil values is allowed up to 3 times during the screening period to meet inclusion criteria for showing eosinophil count ≥150 cells/µL (I 04) before randomization. This is only required if the participant doesn't have the blood eosinophils measured within 6 months prior to SV1 in the absence of OCS treatment.

A participant who is unable to complete a successful spirometry effort as defined by ATS criteria or assessed by the Investigator or did not meet the eligibility criterion for pre-BD FEV1 at SV1 can be retested one additional time during the screening period of the study.

Three attempts may be performed during the screening period to meet the eligibility criteria for reversibility before randomization. This is only required if a reversibility test meeting the eligibility criterion was not performed within 6 months prior to SV1.

FeNO can be assessed one additional time during the screening if the FeNO value measured at SV1 doesn't meet the eligibility criterion.

5.5 CRITERIA FOR TEMPORARILY DELAYING SCREENING, RANDOMIZATION, OR STUDY INTERVENTION ADMINISTRATION

During a regional or national emergency declared by a governmental agency, if the site is unable to adequately follow protocol mandated procedures, contingency measures proposed in Appendix 8 (Section 10.8) should be considered for the screening, randomization, or administration of study intervention.

6 STUDY INTERVENTION

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

6.1 STUDY INTERVENTION(S) ADMINISTERED

Table 2 - Overview of study interventions administered

ARM name	Dupilumab 200 mg	Placebo
Intervention name	Dupilumab 200 mg	Placebo matching dupilumab 200 mg
Type	Biological	Other
Dose formulation	Dupilumab 200 mg: a 175 mg/mL dupilumab solution in a prefilled syringe to deliver 200 mg in 1.14 mL	Placebo matching dupilumab 200 mg will be supplied as an identical formulation to the active 200 mg formulation without dupilumab, in a prefilled syringe to deliver placebo in 1.14 mL
Unit dose strength(s)	200 mg	0 mg
Dosage level(s)	200 mg every 14 ±3 days after an initial loading dose of 400 mg	0 mg every 14 ±3 days after an initial loading dose of 0 mg
Route of administration	SC injection[a]	SC injection[a]
Use	experimental	placebo- comparator
IMP and NIMP	IMP	IMP
Packaging and labeling	One glass prefilled syringe packed in a participant kit box. Both glass prefilled syringe and box will be labeled as required per country requirement.	One glass prefilled syringe packed in a participant kit box. Both glass prefilled syringe and box will be labeled as required per country requirement.
Current/Former name(s) or alias(es)	Dupixent	

a SC injection sites should alternate between the upper thighs, 4 quadrants of the abdomen or the upper arms, so that the same site is not injected twice during consecutive administrations. Injection in the upper arms can only be done by a trained person (caregiver) trained by Investigator or Delegate) or health care professional but not the participants themselves.

IMP: investigational medicinal product; SC: subcutaneous.

In specific situation, between the protocol-scheduled on-site visits, interim visits may be required for IMP dispensing. As an alternative to the on-site IMP dispensing, IMP may be supplied from the site to the participant via a Sponsor-approved courier company where allowed by local regulations and approved by the participant.

For participants enrolled through virtual site (Metasite), IMP will be supplied from the virtual site to the participant via DTP service which will be handled and under the responsibility of Science37. 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 8 (Section 10.8).

The Investigator or delegate will train the participant (or caregiver) how to prepare and inject IMP at Visit 2. The site staff will inject the first dose of the two injections. The participant (or caregiver) will perform the second injection under the supervision of the Investigator or delegate. This training must be documented in the participant's study file. At subsequent administrations, participants are allowed to self-inject IMP at home.

For participants enrolled through Science37 Metasite, IMP will be administered by a mobile study nurse at the randomization dosing visit. As described above, the participants/caregivers will be instructed how to prepare and self-inject/inject the IMP at the first dosing visit and will be allowed to self-administer/administer for the remainder of the treatment period. If the participant is not comfortable with self-administration, the mobile study nurse will perform the administrations at home visits at every 2 weeks, according to the scheduled IMP administrations. The mobile study nursing management with all related activities will be under the responsibility of Science37.

Participants should be instructed to avoid missing any dose of medication during the study. Any participant who misses one dose should be reminded to be diligent, in order to avoid further missing doses thereafter. In case of missed dose(s), no loading dose of two injections will be administered when restarting the treatment, whatever the number of missed doses. The participants should continue their scheduled IMP treatment and visits, even if more than two consecutive doses were missed.

When the participant has a study visit, the IMP will be administered following clinical procedures and blood collection. Participants should be monitored for at least 30 minutes. The monitoring period may be extended as per country-specific or local site-specific requirements.

If the participant (or caregiver) is unable or unwilling to administer IMP, injections can be performed at the site by way of unscheduled visits; or arrangements can be made for qualified site personnel and/or health care professionals (eg, visiting nurse service) to administer IMP for the doses that are not scheduled to be given at the study site or if the participant can't attend the on-site visit.

Subcutaneous injection sites should alternate between the upper thighs, 4 quadrants of the abdomen or the upper arms, so that the same site is not injected twice during consecutive administrations. Injection in the upper arms can only be done by a trained person (caregiver or delegate) or health care professional but not the participants themselves.

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

A home dosing diary will be provided to collect information related to at home injections. The diary will be kept as source data in the participant's study file.

Noninvestigational medicinal product(s)

Participants should be on a stable dose of medium to high dose ICS in combination with a second controller medication (eg, LABA, LTRA) ≥1 month prior to SV1 and during the Screening Period (Table 3).

Participants requiring a third controller for their asthma will be considered eligible for this study, also at a stable dose ≥1 month prior to SV1 and during the Screening Period. Theophylline is not allowed knowing that it can interfere with sleep and may confound the study assessments.

- Formulation and route(s) of administration: refer to label.
- Dose regimen: as prescribed.

The asthma background therapy should be maintained on a stable dose during the study treatment period.

Short-acting β2 agonists may be used as rescue medication during the study if needed.

Systemic corticosteroids are allowed for the treatment of severe asthma exacerbations.

Table 3 - Medium and high daily doses of inhaled corticosteroids (mcg)

Inhaled corticosteroid	Medium	High
Beclometasone dipropionate (pMDI[a], HFA)	>500-1000	>1000
Beclometasone dipropionate (pMDI, extrafine particle, HFA)	>200-400	>400
Budesonide (DPI)	>400-800	>800
Ciclesonide (pMDI, extrafine particle, HFA)	>160-320	>320
Fluticasone furoate (DPI)	100.	200
Fluticasone propionate (DPI)	>250-500	>500
Fluticasone propionate (pMDI[a], HFA)	>250-500	>500
Mometasone furoate (DPI)	200	440
Mometasone furoate (pMDI[a], HFA)	200-400	400

DPI = Dry powder inhaler; HFA = Hydrofluoroalkane propellant (non-CFC), pMDI = pressurized metered dose inhaler.
a standard (non-fine) particles.

The GINA table above refers to metered doses. This is not a table of equivalence but suggested total daily ICS doses for the “medium” and “high” dose options. It is based on available studies and product information. Doses may be country-specific depending on local availability, regulatory labelling, and clinical guidelines. For new preparations, the manufacturer’s product information should be reviewed carefully, as products containing the same molecule may not be clinically equivalent (27). The list presents examples of ICS and might support future changes.

An asthma background therapy diary will be provided to collect information related to noninvestigational medicinal product (NIMP) use. The diary will be kept as source data in the participant’s study file.

6.1.1 Devices

Not applicable.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

1. The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.
3. The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
4. Science 37 Metasite: For the preparation, handling, storage and accountability of study intervention, refer to Appendix 7 (Section 10.7).

Responsibilities

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

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

Under no circumstances will the Investigator supply IMP to a third party DTP shipment, unless the courier company has been approved by the Sponsor (or Science37 for the virtual site), or allow the IMP to be used other than as directed by this clinical trial protocol, or dispose of IMP in any other manner.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Randomization

A randomized intervention kit number list will be generated centrally by Sanofi. The IMP (dupilumab or placebo) will be packaged in accordance with this list.

The Sanofi Clinical Supplies team will provide the randomized intervention kit number list and the Study Biostatistician will provide the randomization scheme to the centralized intervention allocation system. This centralized intervention allocation system will generate the participant randomization list according to which it will allocate the intervention to the participants.

The Investigator obtains intervention kit numbers at randomization (Visit 2) and subsequent scheduled visits via an IVRS/IWRS that will be available 24 hours a day.

Science37 Metasite: The investigator of Metasite obtains intervention kit numbers at randomization (Visit 2) and subsequent scheduled visits via IVRS/IWRS. Science37 participant randomization in IVRS/IWRS will occur on Day 1, with first loading dose occurring up to 5 days post randomization to account for the lag between IVRS/IWRS randomization trigger for IMP DTP shipment and IMP availability to participant/mobile study nurse.

Science37 participant windows increased up to 3 days (the maximum visit window) for the subsequent at home dosing visits (week 4, week 8, week 12), to account for the lag between IVRS/IWRS trigger for IMP DTP shipment and IMP availability to participant/mobile study nurse.

Participants who meet the entry criteria will be randomized to receive either dupilumab or placebo. Participants will be randomized centrally using a 1:1 randomization ratio for dupilumab 200 mg Q2W and placebo Q2W. Randomization will be stratified according to 5 strata: one stratum for all participants included in the [redacted] (regardless of dose level of ICS, regardless of region) and 4 strata for participants not included in [redacted], according to region and ICS dose (Eastern Europe with high ICS dose, Eastern Europe with medium ICS dose, ROW with high ICS dose, and ROW with medium ICS dose). In total, no less than 40% participants need to be in “high ICS” strata, and no more than 25% participants need to be in “Eastern Europe” strata.

A randomized participant is defined as a participant who is registered and assigned with an intervention kit number from the centralized intervention allocation system, as documented from its log file, regardless whether the intervention kit was used or not. A participant cannot be randomized more than once in the study.

Returned IMP from the participant’s home should not be re-dispensed to the participants.

Methods of blinding

Dupilumab and placebo will be provided in identically matched 1.14 mL prefilled syringes. To protect the blind, each intervention kit of 1.14 mL (dupilumab/placebo) glass prefilled syringes will be prepared such that the treatments (dupilumab and its matching placebo) are identical and indistinguishable and will be labeled with a treatment kit number. The randomized treatment kit number list will be generated by Sanofi.

Both the participant and Investigator will be blinded to assigned active drug or placebo. Study participants, investigators, and study site personnel will not have access to the randomization (treatment codes).

Randomization code breaking during the study

In case of an AE, the code must only be broken in circumstances when knowledge of the IMP is required for treating the participant.

Code breaking can be performed at any time by using the proper module of the IVRS/IWRS and/or by calling any other phone number provided by the Sponsor for that purpose. If the blind is broken, the Investigator must document the date, time of day, and reason for code breaking.

Participant withdrawal will only occur when the code break call is made at the site level, not the study level. This means that if the Emergency Unblinding transaction is performed by the Investigator (ie, at the site level), then the participant will be withdrawn from treatment. However, if the Emergency Unblinding transaction is performed by the Global Safety Officer (ie, at the study level, as the Global Safety Officer is not site based), then the participant will not be withdrawn from treatment.

Participants who are withdrawn from treatment should be encouraged to remain in the study and the Investigator should discuss with them the key visits to attend (see Section 7.1).

6.4 STUDY INTERVENTION COMPLIANCE

Measures taken to ensure and document intervention compliance and IMP accountability include:

- Proper recording of intervention kit number as required on appropriate electronic case report form (e-CRF) page for accounting purposes.
- All intervention kits (whether empty or unused) are returned by the participant at each visit when an intervention dispensing is planned:
- Science37 Metasite: All intervention kits accountability and return (whether empty or unused) will be managed and under the responsibility of Science37.
  - The completed participant home dosing diary (returned to the site at each visit), returned intervention kits and any unused prefilled syringes will be used for drug accountability purposes.
- The Investigator or designee tracks intervention accountability/compliance, either by diary, or by counting the number of used intervention kits and fills in the appropriate page of the participant treatment log.

The monitor in charge of the study then checks the data entered on the IMP administration page by comparing them with the IMP that has been retrieved and the participant treatment log form.

The Investigator, pharmacist, or qualified nurse will also keep accurate records of the quantities of the IMP received, dispensed, used, unused, and returned/destroyed. The product accountability and inventory form/system are to be updated each time IMP is dispensed.

All used, partially used, or unused interventions will be destroyed at each respective site, after accountability and reconciliation have been performed. The site must not destroy the unused IMP unless the Sponsor provides written authorization. Confirmation of destruction will be provided to the Sponsor.

6.5 CONCOMITANT THERAPY

Any medication or vaccine (including over-the-counter or prescription medicines) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

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

During the FU period the asthma treatment will be administered based on Investigator's medical judgment and normal clinical practice.

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

Prohibited concomitant therapy:

- Any biologic therapy (including experimental treatments) or systemic immunosuppressive drugs.
- Treatment with systemic corticosteroids (systemic corticosteroids can only be used to treat a severe asthma exacerbation and are not allowed to be used for other conditions).
- Treatment with live (attenuated) vaccine.
- Sedative, anxiolytic, or hypnotic treatments including melatonin.
- Antihistamines, except the newer generations of antihistamines (eg, cetirizine, loratadine and fexofenadine).
- Theophylline.
- Lipophilic beta blockers, opioids, clonidine, antidepressants or other medications known to interfere with sleep, as determined by the Investigators.

Note: In most cases, chronic treatments administered regularly and at stable dosing are acceptable. Investigators should assess the degree to which an individual medication may cause changes in sleep pattern or sleep quality during the study, compared to the prebaseline state.

6.5.1 Rescue medicine

The SABA rescue medications may be used. The rescue medication will be administered as prescribed by the physician. Systemic corticosteroids are allowed for the treatment of severe asthma exacerbations.

Although the use of rescue medications is allowed at any time during the study, every attempt should be made to perform all necessary measurements prior to the use of rescue medications. If SABA rescue medications are given prior to [redacted] or spirometry, the measurements should be performed after a wash-out time mentioned in Table 4 (Section 8.1.3). The date and time of rescue medication administration as well as the name and dosage regimen of the rescue medication must be recorded.

6.6 DOSE MODIFICATION

Not applicable.

6.7 INTERVENTION AFTER THE END OF THE STUDY

No intervention is planned after the end of the study.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

Withdrawal of consent for treatment (ie, treatment discontinuation at participant request) should be distinguished from (additional) withdrawal of consent for follow-up visits. The site should document any case of withdrawal of consent.

7.1 DISCONTINUATION OF STUDY INTERVENTION

7.1.1 Definitive discontinuation

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

Discontinuation of study intervention for abnormal liver function should be considered by the Investigator when a participant meets one of the conditions outlined in the algorithm “Increase in ALT” (Section 10.5) or if the Investigator believes that it is in best interest of the participant.

List of criteria for permanent discontinuation of study intervention

Every effort should be made to document the reason(s) for discontinuation of study intervention and this should be documented in the e-CRF.

Participants may be withdrawn from the study intervention for the following reasons:

- At their own request or at the request of their legally authorized representative (legally authorized representative means an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective participant to 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.
- If the Emergency Unblinding transaction is performed by the Investigator (ie, at the site level).
- Pregnancy.
- Anaphylactic reactions or systemic allergic reactions that are related to IMP and require treatment (see Section 10.9).
- Diagnosis of a malignancy during study, excluding carcinoma in situ of the cervix, or squamous or basal cell carcinoma of the skin.

- Any opportunistic infection, such as tuberculosis or other infections whose nature or course may suggest an immunocompromised status.
- Serum ALT >3 upper limit of normal (ULN) and Total Bilirubin > 2 ULN (see Section 10.5, Appendix 5).
- Serum ALT >5 ULN if baseline ALT ≤2 ULN or ALT >8 ULN if baseline ALT >2 ULN (see Section 10.5, Appendix 5). "Baseline" refers to ALT sampled at baseline visit or, if baseline value is unavailable, to the latest ALT value before the baseline visit.

See the SoA (Section 1.3) for data to be collected at the time of intervention discontinuation and follow-up and for any further evaluations that need to be completed.

Any abnormal laboratory value will be immediately rechecked for confirmation before making a decision of definitive discontinuation of the IMP for the concerned participant.

Handling of participants after definitive intervention discontinuation

Participants will be followed-up according to the study procedures specified in this protocol up to the scheduled date of EOT visit (Visit 5), or up to recovery or stabilization of any AE to be followed-up as specified in this protocol, whichever comes last.

Participants who prematurely discontinue the study intervention (prior to completing the 12-week treatment period) should attend an ETD visit at earliest convenience with all procedures required at the EOT visit, except IMP. In particular cases when the ETD visit is closed to a regular study visit, ETD could be merged and will replace the regular visit. In addition, the participants will be asked and encouraged to complete all the remaining study visits according to the visit schedule until and including the EOT visit (Visit 5). Participants will be followed-up according to the study procedures specified in this protocol in SoA (Section 1.3). Under exceptional circumstances when a participant cannot come to the site for the scheduled visit, a phone contact can be made after sponsor approval is given. During the phone contact, at least information about AEs and concomitant medication should be collected.

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

7.1.2 Temporary discontinuation

Temporary intervention discontinuation may be considered by the Investigator because of suspected AEs or disruption of the clinical trial due to a regional or national emergency declared by a governmental agency. For a regional or national emergency declared by a governmental agency, contingency measures are included in Appendix 8 (Section 10.8). For all temporary intervention discontinuations, duration should be recorded by the Investigator in the appropriate pages of the e-CRF.

The following definition can be considered: temporary intervention discontinuation decided by the Investigator corresponds to more than one dose not administered to the participant.

In addition, the following conditions will be causes for temporary discontinuation of study intervention:

- Infections or infestations that do not respond to medical treatment.
- Treatment with a live (attenuated) vaccine.
- Treatment with immunomodulating biologics (including experimental treatments).
- Treatment with systemic corticosteroids (except systemic corticosteroids used to treat a severe asthma exacerbation) or systemic immunosuppressive drugs.
- Any laboratory abnormality that meets temporary treatment discontinuation criteria as per Appendix 5 (Section 10.5).

7.1.2.1 Rechallenge

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

For a regional or national emergency declared by a governmental agency, contingency measures are included in Appendix 8 (Section 10.8).

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

- A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons. This is expected to be uncommon.
- A participant who prematurely discontinues the study should attend an ESD visit at the earliest convenience with all the procedures planned for the End of Treatment Visit (Visit 5) except IMP, as shown in the SoA (Section 1.3). See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- The participant will be permanently discontinued both from the study intervention and from the study at that time.
- If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

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

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

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

All study withdrawals should be recorded by the Investigator in the appropriate screens of the e-CRF and in the participant's medical records. In the medical record, at least the date of the withdrawal and the reason should be documented.

In addition, a participant may withdraw his/her consent to stop participating in the study. Withdrawal of consent for intervention should be distinguished from withdrawal of consent for follow-up visits and from withdrawal of consent for non-participant contact follow-up, eg, medical record checks. The site should document any case of withdrawal of consent.

Participants who have withdrawn from the study cannot be 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 he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

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

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

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 1 (Section 10.1.8).

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA (Section 1.3). Protocol waivers or exemptions are not allowed.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood eosinophil count, reversibility test) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.
- The laboratory tests will be done locally, the maximum amount of blood collected from each participant over the duration of the study will be according to the routine clinical practice in each country and site. As the blood analysis will be performed by the local laboratories, any leftover blood sample will not be used for any other research purposes related to the study (re-analyses) or for future exploratory use (secondary use). Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.
- Patient-reported outcome measures completed at the clinical site should be completed by the participants before the consultation and/or clinical tests, in a quiet place when completed at study visits. The questionnaires should be completed by the participants themselves, independently from their physician, the study nurse or any other medical personnel and without any help from friends or relatives.
- Science37 Metasite: For the study procedures performed by the participants enrolled by the Metasite, refer to Appendix 7 (Section 10.7)

For a regional or national emergency declared by a governmental agency, contingency measures are included in Appendix 8 (Section 10.8).

8.1 EFFICACY ASSESSMENTS

8.1.1 Actigraphy

Actigraphy is a procedure that records and integrates the occurrence and degree of limb movement activity over time. For sleep applications, the devices are typically worn on the wrist or ankle. Mathematical algorithms are then applied to these data to estimate wakefulness and sleep. In addition to providing a graphical summary of wakefulness and sleep patterns over time, actigraphy generates estimates of certain sleep parameters (24).

Wrist actigraphy is a technique for measuring movement of a limb over an extended recording period (days to weeks). The signals generated by wrist movement are sensed by a tiny microcomputer contained within the watch and translated into activity counts. Algorithms have been developed to translate these activity counts or "epochs" (or "periods") that correspond to times when a person is likely to be asleep or wake. Actigraphy provides the ability to estimate sleep duration, sleep patterns (including timing of sleep and napping) and disturbed sleep (awakenings during the sleep period).

Actigraph will be worn on the wrist of the non-dominant hand in this study to provide estimates of the duration, timing and patterns of sleep in study participants (eg, [redacted] WASO, and [redacted].

The equipment that will be used for this study, the Actiwatch Spectrum® (from Philips Respironics, Inc.) is a small device that contains a solid-state piezoelectric accelerometer (sensitive to 0.025G and above), lithium battery, microprocessor, nonvolatile 1 MB of memory, and associated circuitry. The orientation and sensitivity of the accelerometer are optimized for highly effective sleep/wake inference from wrist activity, which has been previously validated.

The device is designed to be compact, lightweight, waterproof, and to detect movement, time "off the wrist", and environmental light. After the watch data are scored by a selected expert center, a number of summary measurements will be generated for each participant, including average sleep duration and sleep efficiency (percentage of time in bed spent asleep).

At SV2 the participants will be trained on how to use the sleep watch. The participants will complete assessments from Day -11 to Day -1 (right before Day 1); daily assessment thereafter until Week 4; then only the week before a clinical visit until EOT. The baseline value will be calculated using the data from Day -7 to Day -1. An operational manual will be provided to the Investigators.

Science37 Metasite: For the completion of the baseline and post baseline assessments, refer to Appendix 7 (Section 10.7).

[redacted]

8.1.3 Spirometry

A spirometer that meets the 2005 ATS/European Respiratory Society (ERS) recommendations (28) will be used. Spirometry should be performed in accordance with these recommendations.

For prebronchodilator measured parameters, including FEV_1 and forced vital capacity (FVC), spirometry will be performed before IMP administration and after withholding the standard of care asthma treatment as follows:

Table 4 - Wash-out period of asthma controllers and rescue medication before [redacted] and lung function assessments

Oral Xanthine derivatives	72 hours
Long-acting beta agonists (LABA) (eg, salmeterol)	24 hours
Long-acting muscarinic antagonist (LAMA) (eg, Tiotropium)	48 hours
Inhaled ICS/LABA	24 hours
Inhaled Ultralong ICS/LABA combinations	48 hours
Inhaled and/or nebulized SABAs (eg, salbutamol)	6 hours
Inhaled and/or nebulized SAMAs (eg, ipratropium)	8 hours
SABA/SAMA combination	8 hours
Inhaled and/or nebulized corticosteroids (ICS)	12 hours
Systemic corticosteroids (oral, IM, IV)	4 weeks

ICS: inhaled corticosteroid; IM: intramuscular; IV: intravenous; LABA: long-acting beta agonist; LAMA: long-acting muscarinic antagonist; SABA: short-acting beta2 agonist; SAMA: short-acting muscarinic antagonist

This will be verified before performing the measurements.

For post-bronchodilator FEV_1, the measurement should follow the steps as that at screening test for reversibility validation.

At all visits, spirometry should be performed before IMP administration, in the morning, if possible. The spirometer provided by the service provider should be used 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. Afternoon/evening is allowable in the exceptional circumstance when morning spirometry cannot be performed. Spirometry should be done at approximately the same time at each visit throughout the study.

Pulmonary function tests will be measured in the sitting position if possible. If the testing was made with the participant in another position, this should be noted on the spirometry report. For any participant, the position should be consistent throughout the study.

Three measurements fulfilling the ATS acceptability and repeatability criteria should be obtained at each visit. The acceptability criteria must be applied before the repeatability criteria. Unacceptable maneuvers must be discarded before applying the repeatability criteria. If a participant fails to provide repeatable maneuvers, an explanation should be recorded in the e-CRF. At least two acceptable curves must be obtained.

The largest FEV_1 and largest FVC should be recorded after the data from all of the acceptable curves have been examined, even if they do not come from the same curve.

The spirometer must be calibrated following the principles of the ATS/ERS guidelines every day that a participant is seen and subjected to spirometry. The calibration records should be kept in a reviewable log. It is preferred that the equipment that is used to calibrate the spirometer (ie, 3-liter syringe) be subjected to a validated calibration according to the manufacturer's specifications. A participant who is unable to complete a successful spirometry effort as defined by ATS criteria or evaluated by the investigator or did not meet the eligibility criterion for pre-BD FEV1 at SV1 can be retested one additional time during the screening period of the study. The spirometry will be centrally read. Further details on the procedure will be provided in a separate instruction manual.

8.1.4 Reversibility test

A reversibility test will be administered following pulmonary function testing after asthma medications have been withheld for the appropriate intervals mentioned in Table 4. Participants will receive 2 to 4 puffs of albuterol/salbutamol from a primed metered dose inhaler (MDI). Alternatively, and only if it is consistent with usual office practice (to be documented), reversibility may be performed using inhalation of nebulized albuterol/salbutamol. Spirometry may be repeated several times within 30 minutes after administration of bronchodilator. Reversibility, which is defined as an increase in absolute FEV_1 of ≥12% over the baseline value, with an absolute increase of at least 200 mL, must be demonstrated within 30 minutes of bronchodilator administration. If the participant does not meet the reversibility at SV1, up to 3 repeat attempts can be performed at any time (ie, unscheduled visits) prior to the randomization visit (Visit 2). This is only required if a reversibility test meeting eligibility criterion was not performed within 6 months prior to SV1.

8.1.5 Asthma sleep disturbance questionnaire

The Asthma Sleep Disturbance Questionnaire is a PRO measure designed to assess the impact of asthma on participants' sleep. Scores range between 0 to 4 with 0 indicating no impact of asthma on sleep and 4 indicating higher impact of asthma on sleep.

Participants will be instructed to record the severity of the disturbance of their sleep due to asthma as follows:

- 0 = Slept through the night, no asthma symptoms,
- 1 = Slept well, no nighttime awakenings because of asthma, but some asthma symptoms in the morning,
- 2 = Woke up once because of asthma (may or may not include early awakening),
- 3 = Woke up several times because of asthma (may or may not include early awakening),
- 4 = Bad night, awake most of the night because of asthma.

The participants will record their sleep disturbance in an electronic diary, once a day upon awakening. The participants will complete Asthma Sleep Disturbance Questionnaire as per SoA (see Section 1.3).

Science37 Metasite: For the completion of the baseline and postbaseline assessments, refer to Appendix 7 (Section 10.7).

8.1.6 Asthma daytime symptom diary - Asthma nighttime symptom diary

The ADSD and ANSD are PRO measures developed by the PRO Consortium' Asthma Working Group. Both instruments have been designed to measure asthma symptoms in adult and adolescent (12 years of age and older) participants diagnosed with mild to severe asthma. ADSD and ANSD assess asthma severity based on patient self-report of asthma core symptoms, ie, difficulty breathing; wheezing; shortness of breath; chest tightness; chest pain; and cough. Participants are asked to complete the ADSD every night before they go to bed, thinking about their asthma symptoms today, from when they got up this morning until now; the ANSD when getting up, thinking about their asthma symptoms last night from when they went to bed until now.

They have demonstrated adequate evidence of content validity and cross-sectional measurement properties (ie, internal consistency reliability, test-retest reliability, convergent validity, and known-groups validity) to measure symptoms of asthma. Both the ADSD and ANSD are composed of 6 items rated using an 11-point NRS that ranges from 0 = None to 10 = As bad as you can imagine (29).

The participants will complete the ADSD and the ANSD as per SoA (see Section 1.3).

Science37 Metasite: For the completion of the baseline and postbaseline assessments, refer to Appendix 7 (Section 10.7).

8.1.7 Sleep diary

The Sleep Diary is composed of seven generic, patient-reported questions that assess sleep concepts of relevance and importance to adults who report sleep disturbance due to asthma.

The Sleep Diary features two subjective, patient-rated items that use a 0-to-10 NRS to assess sleep quality and feeling rested upon awakening (ie, restorative sleep). Additional items include the patient-estimated initial sleep attempt time and sleep onset time, number of nighttime awakenings after sleep onset, total time spent awake after sleep onset, and wake time the next day. Participants are instructed to complete all questions upon awakening each day. All questions except the one about restorative sleep ask participants to recall "last night"; question about restorative sleep asks participants to recall "when they got up for the day today". Items about sleep quality and restorative sleep are scored; the other items are reported/described separately, as appropriate for each item.

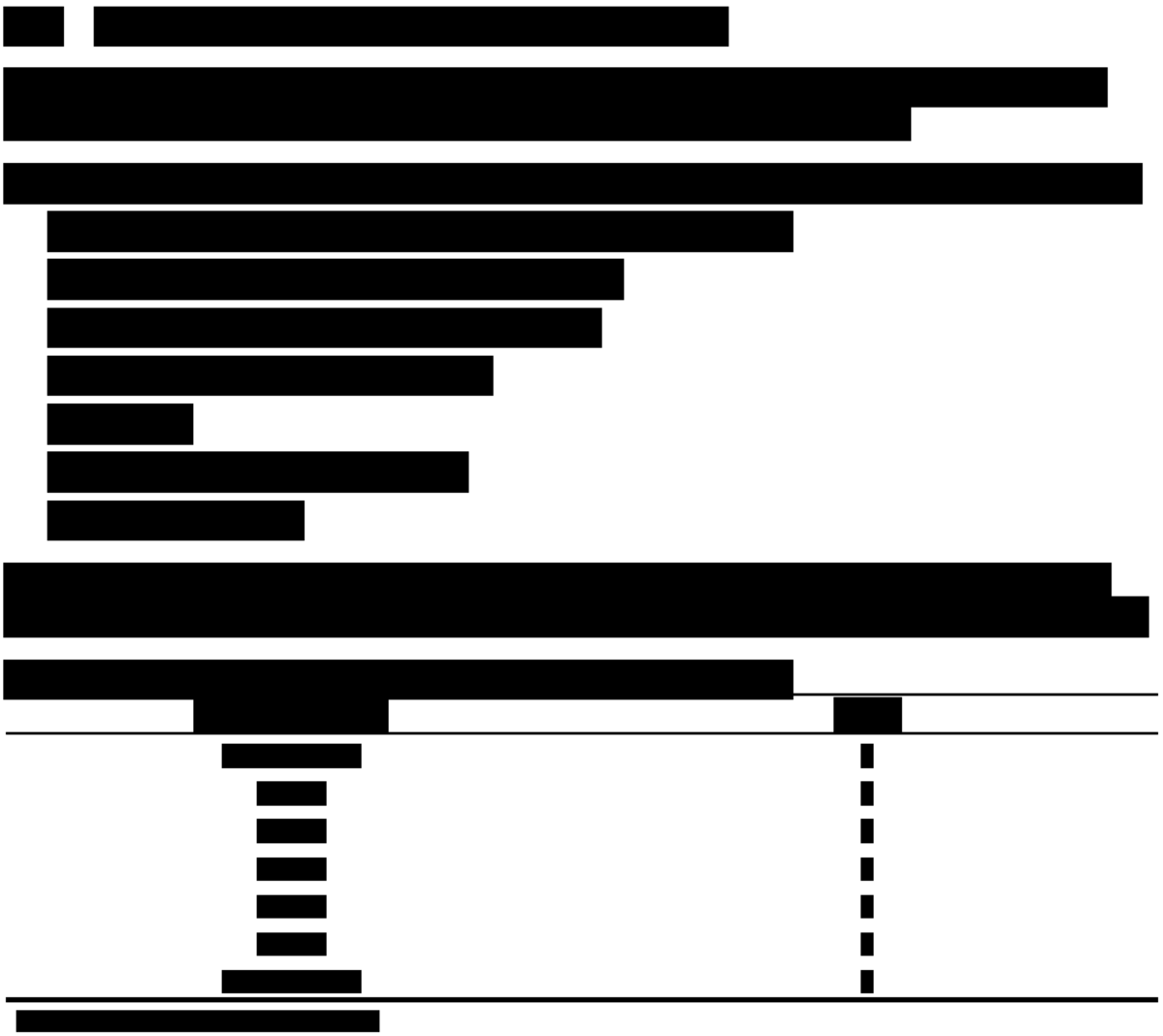
The participants will complete the items of the Sleep Diary daily, as per SoA (see Section 1.3).

Science37 Metasite: For the completion of the baseline and postbaseline assessments, refer to Appendix 7 (Section 10.7).

8.1.8 PROMIS SF v1.0 - Sleep-Related Impairment 8a

To assess the impact of Sleep-Related Impairment during waking hours, the PROMIS Sleep-Related Impairment Short Form 8-item version (PROMIS SF v1.0 Sleep-Related Impairment 8a) will be administered. The questionnaire focuses on self-reported perceptions of alertness, sleepiness, and tiredness during usual waking hours, and the perceived functional impairments during wakefulness associated with sleep problems or impaired alertness. Though Sleep-Related Impairment does not directly assess cognitive, affective, or performance impairment, it does measure waking alertness, sleepiness, and function within the context of overall sleep-wake function. It assesses Sleep-Related Impairment over the past seven days. Each item is rated on a 5-point scale (1 = not at all; 2 = a little bit; 3 = somewhat; 4 = quite a bit; and 5 = very much) with a range in score from 8 to 40 with higher scores indicating greater sleep impairment.

The participants will complete the PROMIS SF v1.0 - Sleep-Related Impairment 8a as per SoA (Section 1.3).



[redacted]

Approximately 30 participants (approximately 15 dupilumab and 15 placebo participants) will be included in the [redacted] at selected sites in the US. Each participant in this [redacted] will have a total of two overnight [redacted] using Type II home devices as described in the SoA (Section 1.3). The procedure is detailed in Section 10.6.

8.2 SAFETY ASSESSMENTS

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

8.2.1 Physical examinations

- A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal and neurological systems. Height and weight will also be measured and recorded. Height (cm) will be measured only at SV1.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.
- Any new finding or worsening of previous finding should be reported as a new AE.

8.2.2 Vital signs

- Temperature (degrees Celsius), heart rate (beats per minute), respiratory rate (breaths per minute), and blood pressure (mmHg) will be assessed.
- Blood pressure and pulse measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.
- 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) and will consist of 1 pulse and 3 blood pressure measurements (3 consecutive blood pressure readings will be recorded at intervals of at least 1 minute). The average of the 3 blood pressure readings will be recorded in the e-CRF.

8.2.3 Electrocardiograms

- 12-lead ECG will be obtained at SV1 as outlined in the SoA (see Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT intervals.

8.2.4 Clinical safety laboratory assessments

- See Appendix 2 (Section 10.2) for the list of clinical laboratory tests to be performed and the SoA (Section 1.3) for the timing and frequency.
- The laboratory tests will be performed by the local laboratories according to routine clinical practice at site and country level. Considering this, any leftover blood sample will not be used for any other research purposes related to the study (re-analyses) or for future exploratory use (secondary use).
- The Investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.

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

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

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

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

8.3.1 Time period and frequency for collecting AE and SAE information

All SAEs will be collected from the signing of the ICF until the EOS Visit (Visit 6) at the time points specified in the SoA (Section 1.3).

All AEs will be collected from the signing of the ICF until the EOS Visit (Visit 6) at the time points specified in the SoA (Section 1.3).

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

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

8.3.2 Method of detecting AEs and SAEs

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

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

8.3.3 Follow-up of AEs and SAEs

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

8.3.4 Regulatory reporting requirements for SAEs

- Prompt notification by the Investigator to the Sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and Investigators.
- Adverse events that are considered expected will be specified in the reference safety information (the IB and its updates).
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs.) according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.
- An Investigator who receives an Investigator safety report describing a SAE, SUSAR or any other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements. It is the responsibility of the Sponsor to assess whether an event meets the criteria for a SUSAR, and therefore, is expedited to regulatory authorities.

8.3.5 Pregnancy

- The pregnancy information for female participants or female partners of male participants will be collected after the start of study intervention and until the outcome has been determined. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date.

- If a pregnancy is reported, the Investigator should inform the Sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4 (Section 10.4).
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.
- 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. While the Investigator is not obligated to actively seek this information in former study participants /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 the study intervention.

8.3.6 Adverse event of special interest

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

For these AESIs, the Sponsor will be informed immediately (ie, within 24 hours), per SAE notification described in Section 10.3.4, even if not fulfilling a seriousness criterion, using the screens in the e-CRF.

- Anaphylactic reactions (see Section 10.9).
- Systemic hypersensitivity reactions.
- Helminthic infections.
- Keratitis.
- Any severe type of conjunctivitis or blepharitis.
- Clinically symptomatic eosinophilia (or eosinophilia associated with clinical symptoms).
- Significant ALT elevation
  - ALT >5 × the ULN in participants with baseline ALT ≤2 × ULN; "Baseline" refers to ALT sampled at baseline visit or, if baseline value is unavailable, to the latest ALT value before the baseline visit,

  or
  - ALT >8 × ULN if baseline ALT >2 × ULN.
- Pregnancy of a female participant entered in a study as well as pregnancy occurring in a female partner of a male participant entered in a study with IMP.

- Pregnancy occurring in a female participant entered in the clinical trial or in a female partner of a male participant entered in the clinical trial. It will be qualified as an SAE only if it fulfills one of the seriousness criteria (see Appendix 3 [Section 10.3]).
- In the event of pregnancy in a female participant, IMP should be discontinued.
- Follow-up of the pregnancy in a female participant or in a female partner of a male participant is mandatory until the outcome has been determined (See Appendix 4 [Section 10.4])

- Symptomatic overdose (serious or nonserious) with IMP/NIMP
  - An overdose (accidental or intentional) with the IMP is an event suspected by the Investigator or spontaneously notified by the participant and defined as at least twice the intended dose during an interval of less than 11 days. The circumstances (ie, accidental or intentional) should be clearly specified in the verbatim and symptoms, if any, entered on separate adverse event forms.
  - An overdose (accidental or intentional) with any NIMP is an event suspected by the Investigator or spontaneously notified by the participant and defined as at least twice the maximum prescribed daily dose, within the intended therapeutic interval.

8.3.7 Guidelines for reporting product complaints

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

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

8.4 TREATMENT OF OVERDOSE

The overdose of dupilumab is defined as at least twice the intended dose during an interval of less than 11 days. Symptomatic overdose (serious or nonserious) is an AESI (defined in Section 8.3.6). No antidote is available for dupilumab.

In the event of an overdose, the Investigator should:

1. Contact the Medical Monitor immediately.
2. Closely monitor the participant for any AE/SAE and laboratory abnormalities until dupilumab can no longer be detected systemically.
3. Obtain a plasma sample for pharmacokinetic analysis as soon as possible from the date of the last dose of study intervention if requested by the Medical Monitor (determined on a case-by-case basis).
4. Document appropriately in the e-CRF.

Decisions regarding dose interruptions or modifications will be made by the Investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

8.5 PHARMACOKINETICS

PK parameters are not evaluated in this study.

8.6 PHARMACODYNAMICS

Pharmacodynamic parameters are not evaluated in this study.

8.7 GENETICS

Pharmacogenetic testing is not performed in this study.

8.8 BIOMARKERS

- Whole blood biomarkers: blood eosinophil count. Eosinophil counts will be measured at the time points mentioned in the SoA (Section 1.3).
- [redacted] levels will be measured at the time points mentioned in the SoA (Section 1.3).

8.9 IMMUNOGENICITY ASSESSMENTS

Immunogenicity assessments will not be performed.

8.10 MEDICAL RESOURCE UTILIZATION AND HEALTH ECONOMICS

The [redacted] is presented in Section 8.1.12.

8.11 USE OF DATA FOR FUTURE RESEARCH

Future research may help further the understanding of disease subtypes, disease biology, related conditions, drug response and toxicity, and can help identify new drug targets or biomarkers that predict participant response to treatment. Therefore, data will be stored and used for future research when consented to by participants (see Section 10.1.3) unless prohibited by local laws or IRBs/IECs.

For participants who consent to the storage and use of their data, data may be used after the study ends for future research related either to the drug, the mechanism of action, and the disease or its associated conditions.

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

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

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

Study participant coded data will be stored for future research for up to 25 years after the end of the study. If data are still considered of important scientific value after this period, coded data already available will be anonymized unless otherwise required by applicable laws.

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

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

The alternative statistical hypothesis tested is that the effect of dupilumab on sleep disturbance score in adult participants with moderate-to-severe uncontrolled asthma and evidence of Type 2 inflammation is superior to placebo at the 2-sided 5% alpha level.

9.2 SAMPLE SIZE DETERMINATION

The sample size was chosen to enable an adequate characterization of the efficacy between dupilumab 200 mg Q2W and placebo with regards to the primary endpoint, change from baseline in sleep disturbance score at Week 12.

The sample size calculation was based on the subset of adult participants who had more than 1 weekly average nocturnal awakening at baseline, baseline ACQ-5 ≥2.5, EOS ≥150 cells /µL and FeNO ≥25 ppb in the previous [redacted] evaluating efficacy of dupilumab for participants with moderate-to-severe asthma.

The observed treatment difference on mean sleep disturbance score of the dupilumab group with 200 mg Q2W dosing in [redacted] versus placebo at Week 12 was [redacted] A conservative estimate was used that assumes the treatment difference to be [redacted] at Week 12. Assuming normal distribution of the change in sleep disturbance score, a common standard deviation (SD) of [redacted], which came from the observed data in [redacted], with 117 participants per group, the study will have 90% power to detect an effect size of [redacted] using a two-sided test with alpha=0.05 for change from baseline in sleep disturbance score at Week 12 in the dupilumab 200 mg Q2W group versus placebo.

Assuming a 10% dropout rate, approximately 260 participants will be randomly assigned to study intervention to achieve 234 evaluable participants for an estimated total of 117 evaluable participants per intervention group.

In order to mitigate the risk of potential different responses based on the Sleep Disturbance Questionnaire before and after amendment 01, the primary analysis of change from baseline in sleep disturbance score will exclude the participants who use the original questionnaire at baseline. The number of participants randomized up to the implementation of this protocol amendment is limited (ie, ≤10), therefore the study power can be preserved at ≥89% and therefore no participant replacement is planned.

A large variability of placebo effects was observed between 200 mg and 300 mg placebo arms from [redacted] The current treatment effect assumption was based on 200 mg placebo and 200 mg dupilumab arm. The impact of large variability of placebo effects on study power will be mitigated by conducting an interim analysis (see Section 9.5), and the final sample size will be determined by sample size re-estimation procedure based on the observed treatment effect at the time of interim analysis. The sample size may be increased up to a cap of 520 total participants (260 each arm).

9.3 POPULATIONS FOR ANALYSES

The following populations are defined (Table 5):

Table 5 - Populations for analyses

Population	Description
Screened	All participants who sign the informed consent form.
Randomized	Randomized participants consist of all participants with a treatment kit number allocated and recorded in the IVRS database, regardless of whether the treatment kit was used or not. Participants treated without being randomized will not be considered as randomized and will not be included in any efficacy population. Data from these participants will be summarized separately.
ITT	The analysis population for the efficacy endpoints (except the primary endpoint) will be the intent-to-treat population: all randomized participants will be included in the ITT population and analyzed according to the treatment group allocated by randomization.
ITT for primary endpoint (ITTp)	All ITT participants excluding those who used the original version of sleep disturbance questionnaire at baseline and/or post-baseline. This analysis population is only applied to primary endpoint analysis.
Safety (As-treated)	All randomized participants who take at least 1 dose of study intervention will be the safety population. Participants will be analyzed according to the intervention they actually received. Randomized participants for whom it is unclear whether the study medication or intervention was taken will be included in the safety population as randomized. For participants receiving more than one IMP during the study (i.e., placebo and dupilumab), the actual study intervention group for as treated analysis will be the dupilumab group.

ITT: intent-to-treat; ITTp: intent-to-treat for primary endpoint; IVRS: interactive voice recognition system

9.4 STATISTICAL ANALYSES

The statistical analysis plan (SAP) will be developed and finalized prior to 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.

9.4.1 General considerations

The multiplicity procedure is proposed to control the overall Type I error rate for testing the primary and selected secondary endpoints assessed for dupilumab 200 mg Q2W versus placebo. The overall alpha is 0.05. The list of secondary endpoints to be tested in the hierarchical order will be specified in the SAP.

The baseline value is defined generally as the last available value before randomization.

The primary analysis will be performed on the ITTp population, and all other efficacy analyses will be performed on the ITT population, unless otherwise noted. All safety analyses will be performed on the Safety Population.

9.4.2 Primary endpoint(s)

The primary endpoint is change from baseline in sleep disturbance score at Week 12 assessed using the Asthma Sleep Disturbance Questionnaire for dupilumab 200 mg Q2W versus placebo.

The primary endpoint will be analyzed on the ITTp population using an MMRM approach. The model will include change form baseline in sleep disturbance score up to Week 12 as response variables, and treatment, age, BMI, stratification factors, visit, treatment-by-visit interaction, baseline ACQ-5, baseline sleep disturbance score and baseline-by-visit interaction as covariates. An unstructured correlation matrix will be used to model the within-participant errors. Parameters will be estimated using restricted maximum likelihood method with the Newton-Raphson algorithm. No imputations for missing values will be carried out. Statistical inferences on treatment comparisons for the change from baseline in sleep disturbance score at Week 12 will be derived from the mixed-effect model. The least square (LS) mean of each treatment group, difference in the LS mean between the dupilumab group and placebo, and the corresponding 95% CI of the differences and p-values will be provided. For participants discontinuing the study intervention before Week 12 unrelated to the COVID-19 pandemic, the sleep disturbance scores measured off-study intervention will be included in the primary analysis. In contrast, for any participants discontinuing the study intervention due to the COVID-19 pandemic, off-study intervention data will not be included (i.e., set to missing) but will be assumed missing at random.

The sensitivity analysis will be conducted using the ITT population.

9.4.3 Secondary endpoint(s)

Differences will be assessed between dupilumab and placebo in the following secondary efficacy endpoints:

- Change from baseline to Week 12 on the number of nocturnal awakenings (Sleep Diary).
- Change from baseline to Week 12 in prebronchodilator FEV1.
- Change from baseline to Week 12 in ADSD and ANSD.
- Change from baseline to Week 12 in PROMIS Sleep-Related Impairment 8a scale.
- Change from baseline to Week 12 in Sleep Diary Questions: sleep quality, restorative sleep, and WASO.
- Change from baseline to Week 12 in WASO from actigraphy data.

The change from baseline in the above continuous endpoints to Week 12 will be analyzed using the MMRM model in the same fashion as for the primary endpoint, based on the ITT population.

For the spirometry endpoints, the model will also include sex and baseline height as the covariates.

The details for the analysis for actigraphy will be provided in the SAP.

The incidence of TEAEs, SAEs including clinically significant changes in vital signs, and AESI will be used to evaluate the safety of dupilumab.

[redacted]

9.4.5 Other safety analyse(s)

All safety analyses will be performed on the Safety Population.

The incidence of AEs, TEAEs, SAEs, AE leading to permanent treatment discontinuation, AESI and death will be summarized by treatment group.

Treatment-emergent adverse event (TEAE) incidence tables will be presented by system organ class (SOC) (sorted by internationally agreed order), high-level group term (HLGT), high-level term (HLT) and preferred term (PT), the number (n) and percentage (%) of participants experiencing a TEAE. Multiple occurrences of the same event in the same participant will be counted only once in the tables. The denominator for computation of percentages is the safety population within each treatment group.

Proportion of participants with at least one TEAE, serious TEAE, AESI, and TEAE leading to discontinuation of the study will be tabulated by treatment group. In addition, TEAEs will be described according to maximum intensity and relation to the study drug. Serious AEs and AEs leading to study discontinuation that occur outside the treatment-emergent period will be summarized separately.

AESI definitions and the method to identify AESIs will be specified in the SAP.

9.4.6 Other analyse(s)

For a regional or national emergency declared by a governmental agency, contingency measures are included in Appendix 8 (Section 10.8). The sensitivity analysis may be conducted, and details will be specified in SAP.

9.5 INTERIM ANALYSES

An interim analysis (IA) in the study is planned for the purpose of [redacted] when approximately 50% of participants (approximately 130 participants from the ITTp population) would have completed Week 12 visit or discontinued the study. The sample size re-estimation is planned to mitigate risk of power loss, given the large variability of placebo effects observed in [redacted] Interim analysis will be performed as follows:

- The sample size re-estimation will be performed based on the observed treatment effects at the time of IA. Sample size may be increased if conditional power falls into the promising zone. No additional IA will be performed in the case of sample size increase. The test statistic at the final analysis may be adjusted as appropriate and details will be specified in the SAP.
- There is no plan to stop trial early for superiority at the time of IA. In order to preserve the overall Type I error rate of 0.05 (2-sided), gamma family alpha spending function will be utilized.

The IA will be performed by an internal independent statistical team, who are separate from personnel involved in the trial conduct. An independent Interim Analysis Committee (IAC) consisting of two clinicians and one statistician will review the results and make decision if the sample size needs to be adjusted based on prespecified criteria. A detailed plan will be defined in the SAP, including the plan to describe the processes intended to control access to comparative interim results to preserve trial integrity. People involved in the conduct of the study (participants, Investigators, Study Team, and Project Team) will have no access to the IA results.

At the time of IA, the primary efficacy endpoint will be analyzed using the same method described in the primary endpoint section (Section 9.4.2). The analysis population for the IA will be approximately 130 randomized participants from the ITTp population. The analysis of the endpoints will use all the data collected for the analysis population up to the IA cut-off time.

The database lock for final analysis is planned based on the date when the last participant completes the Week 12 visit or discontinues from the study before Week 12. Analyses will be based on all data collected up to this database lock and will be considered as the final analysis in the CSR.

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

finding relates to a communicable disease, Investigators should seek independent ethical advice before determining next steps.

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

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

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

10.1.2 Financial disclosure

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

10.1.3 Informed consent process

- The Investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study, including what happens to the participant when his/her participation ends (posttrial access strategy for the study).
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Privacy and Data Protection requirements including those of the GDPR and of the French law, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- Science37 Metasite participants will complete the consent process remotely with Science37 study staff and sign the eConsent in the Science37 platform, accessible via an App on a smartphone or tablet, or on a computer desktop browser.
- 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 participant or the participant's legally authorized representative.
- Science37 Metasite participants will be informed that they may download and print a copy of the eICF, or a copy may be emailed to them upon the participant's request.
- Participants who are rescreened are required to sign a new ICF.

The ICF contains two separate sections that addresses the use for research of participants' data. Optional exploratory research must be detailed in the section "Optional tests/procedures" and future research is to be defined in Core Study Informed Consent Form (CSICF) Part 2. Each option is subject to an independent consent and must be confirmed by ticking a checkbox in CSICF Part 3. The Investigator or authorized designee will explain to each participant the objectives of the exploratory research and why data 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 8 (Section 10.8).

10.1.4 Data protection

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

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

Protection of participant data

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

Participant race and ethnicity will be collected in this study because they are expected to modify the drug response/because they are required by regulatory agencies (eg, on 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 will be identifiable only by the unique identifier; participant names or any information which would make the participant identifiable will not be transferred to the Sponsor.
- The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with applicable data protection laws. The level of disclosure must also be explained to the participant as described in the informed consent.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- Participants must be informed that their study-related data will be used for the whole "drug development program", ie, for this trial as well as for the following steps necessary for the development of the investigational product, including to support negotiations with payers and publication of results.

Protection of data related to professionals involved in the study

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

  - The standard contractual clauses of the European Commission for transfers towards our partners and service providers,
  - Sanofi's Binding Corporate Rules for intra-group transfers.

- Professionals have the possibility to lodge a complaint with Sanofi leading Supervisory Authority, the "Commission Nationale de l'Informatique et des Libertés" (CNIL) or with any competent local regulatory authority.
- Personal data of professionals will be retained by Sanofi for up to thirty (30) years, unless further retention is required by applicable regulations.
- In order to facilitate the maintenance of Investigators personal data, especially if they contribute to studies sponsored by several pharmaceuticals companies, Sanofi participates in the Shared Investigator Platform (SIP) and in the Transcelerate Investigator Registry (IR) project (https://transceleratebiopharmainc.com/initiatives/investigator-registry/). Therefore, personal data will be securely shared by Sanofi with other phamaceutical company members of the Transcelerate project. This sharing allows Investigators to keep their data up-to-date once for all across pharmaceutical companies participating in the project, with the right to object to the transfer of the data to the Transcelerate project.
- Professionals have the right to request the access to and the rectification of their personal data, as well as their erasure (where applicable) by contacting the Sanofi Data Protection Officer: Sanofi DPO - 54 rue La Boétie - 75008 PARIS - France (to contact Sanofi by email, visit https://www.sanofi.com/en/our-responsibility/sanofi-global-privacy-policy/contact).

10.1.5 Dissemination of clinical study data

Study participants

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

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

Individual participant data and supporting clinical documents are available for request at www.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: www.vivli.org.

Professionals involved in the study or in the drug development program

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

10.1.6 Data quality assurance

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

10.1.7 Source documents

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

- Data entered in the e-CRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data: source data is all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Source documents are original documents, data and records such as hospital records, clinic and office charts, laboratory reports, notes, memoranda, pharmacy dispensing records, home dosing diary, asthma background therapy diary, recorded data from automated instruments etc. Data downloaded from the local laboratories, spirometry, actigraphy, [redacted], ECG, patient diaries, electronic PROs will be considered source data.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- For the Science37 Metasite, the Science37 platform is the repository for all source documents and participant information.

10.1.8 Study and site start and closure

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

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

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

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

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

- For study termination:
  - Information on the product leads to doubt as to the benefit/risk ratio.
  - Discontinuation of further study intervention development.

- For site termination:
  - Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines.
  - Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the Investigator.
  - Total number of participants included earlier than expected.

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

10.1.9 Publication policy

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

10.2 APPENDIX 2: CLINICAL LABORATORY TESTS

- The tests detailed in Table 6 will be performed by the local laboratory.
- 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 (urine or serum as required by local regulations) should be conducted as mentioned in the SoA (Section 1.3).
- Pregnancy testing (urine or serum as required by local regulations) should be conducted at the end of relevant systemic exposure corresponding with the time frame for female participant contraception in Section 5.1, Inclusion Criteria.
- Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participant's participation in the study.

- In exceptional situations when the participants cannot attend the on-site visits, arrangements can be made for qualified site personnel and/or health care professionals (eg, visiting nurse service) for blood sample collection, if allowed by local regulations and approved by the participant.
- Science37 Metasite: the blood sample collection and pregnancy tests (if applicable) will be done at participants' home by the Science37 home nursing service. The processing, shipment, analysis of the blood samples are under Science37 responsibility.

Table 6 - Protocol-required laboratory assessments

Laboratory assessments	Parameters
Hematology	Eosinophils
Other screening tests	Highly sensitive (Serum at screening and urine at the other visits) human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential).
	Hepatitis screening covering hepatitis B surface antigen (HBsAg), total hepatitis B core antibody (total HBcAb); hepatitis C virus antibodies (HCVAb). In case of results showing HBs Ag (negative), and HBcAb (positive), an HBV DNA testing will be performed to rule out a false positivity if the Investigator believes the participant is a false positive, or to clarify the serological status if the Investigator finds it unclear to interpret in absence of known HBV infection. In case of results showing HCVAb (positive), an HCV RNA testing may be performed to rule out a false positivity, if the Investigator believes the participant is a false positive.
	Human Immunodeficiency Virus screening (Anti-HIV-1 and HIV-2 antibodies).
	Tuberculosis test performed only on a country by country basis according to the routine clinical practice and the local guidelines if required by Regulatory Authorities or Ethics Committees.
	The results of each test must be entered into the CRF.

NOTES:
Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 7.1 and Appendix 5 (Section 10.5). Although the liver function tests are not requested in the protocol, the routinely done lab tests might identify increased values of ALT, bilirubin. All events related to ALT, bilirubin which may indicate severe liver injury (possible Hy's Law) must be reported as an SAE.

Investigators must document their review of each laboratory safety report.

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

10.3.1 Definition of AE

AE definition

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

Definition of unsolicited and solicited AE

- An unsolicited adverse event is an adverse event that was not solicited using a home dosing diary and that is communicated by a participant who has signed the informed consent. Unsolicited AEs include serious and non-serious AEs.
- Potential unsolicited AEs may be medically attended (ie, symptoms or illnesses requiring a hospitalization, or 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 participant will be collected during interview with the participants and by review of available medical records at the next visit.
- Solicited AEs are predefined local and systemic events for which the participant is specifically questioned, and which are noted by the participants in their home dosing diary.

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

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital 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), eg:
  - Symptomatic and/or,
  - Requiring either corrective treatment or consultation, and/or,
  - Leading to IMP discontinuation or modification of dosing, and/or,
  - Fulfilling a seriousness criterion, and/or,
  - Defined as an AESI.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.
- The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE. Also, "lack of efficacy" or "failure of expected pharmacological action" also constitutes an AE or SAE.

Events NOT meeting the AE definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2 Definition of SAE

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

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

a) Results in death

b) Is life-threatening

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

c) Requires inpatient hospitalization or prolongation of existing hospitalization

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

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d) Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.

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

e) Is a congenital anomaly/birth defect

f) Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

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

AE and SAE recording

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the Investigator to send photocopies of the participant's medical records to the Sponsor's representative in lieu of completion of the AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor. 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.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of intensity

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

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.

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

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

Assessment of causality

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

Follow-up of AEs and SAEs

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by 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 post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.

- The Investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

10.3.4 Reporting of SAEs

SAE reporting to the Sponsor via an electronic data collection tool

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

SAE reporting to the Sponsor via paper CRF

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

10.4 APPENDIX 4: CONTRACEPTIVE GUIDANCE AND COLLECTION OF PREGNANCY INFORMATION

DEFINITIONS:

Woman of childbearing potential (WOCBP)

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

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

Women in the following categories are not considered WOCBP

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

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

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

CONTRACEPTION GUIDANCE:

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:

Highly Effective Methods[b] That Have Low User Dependency Failure rate of <1% per year when used consistently and correctly.

- Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]
  - Intrauterine device (IUD)
  - Intrauterine hormone-releasing system (IUS)[c]
- Bilateral tubal occlusion

Vasectomized partner

(Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.)

Highly Effective Methods[b] That Are User Dependent Failure rate of <1% per year when used consistently and correctly.
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c] - oral - intravaginal - transdermal - injectable • Progestogen-only hormone contraception associated with inhibition of ovulation[c] - oral - injectable
Sexual abstinence *(Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)*

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 If locally required, in accordance with Clinical Trial Facilitation Group 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 lactational amenorrhoea method (LAM) are not acceptable methods of contraception. Male condom and female condom should not be used together (due to risk of failure with friction).

COLLECTION OF PREGNANCY INFORMATION:

Male participants with partners who become pregnant

- The Investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive study intervention.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

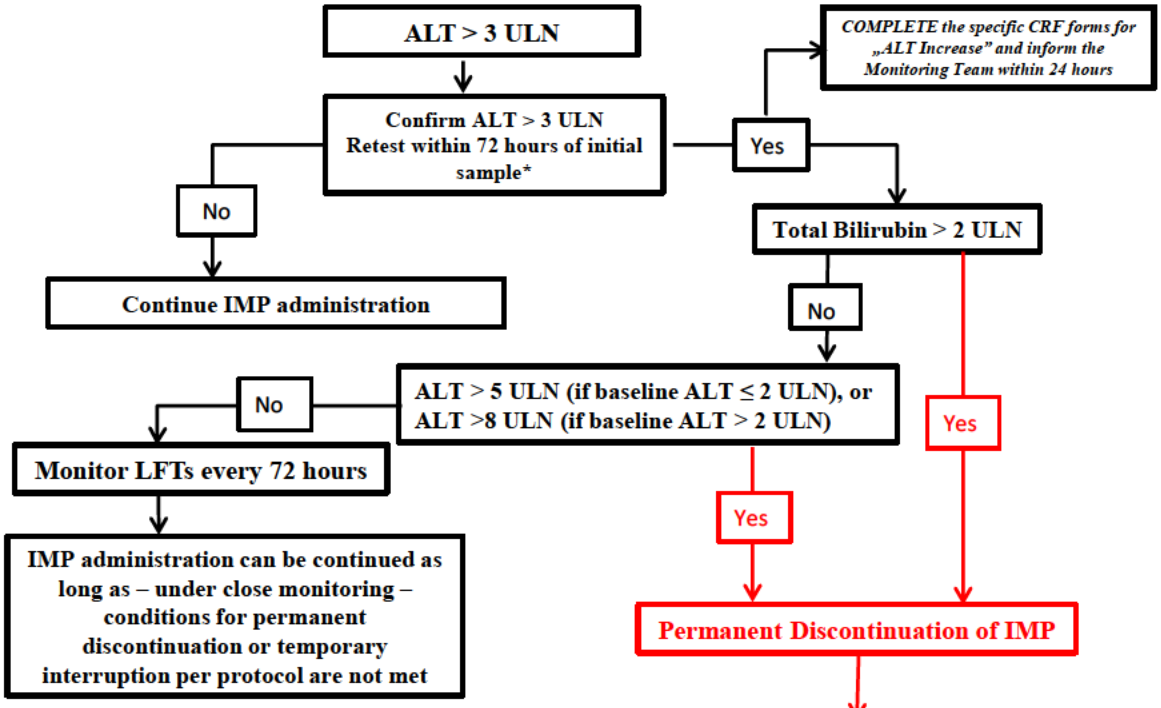
Female participants who become pregnant

- The Investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. The initial information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a participant's pregnancy.

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

10.5 APPENDIX 5: LIVER AND OTHER SAFETY: SUGGESTED ACTIONS AND FOLLOW-UP ASSESSMENTS

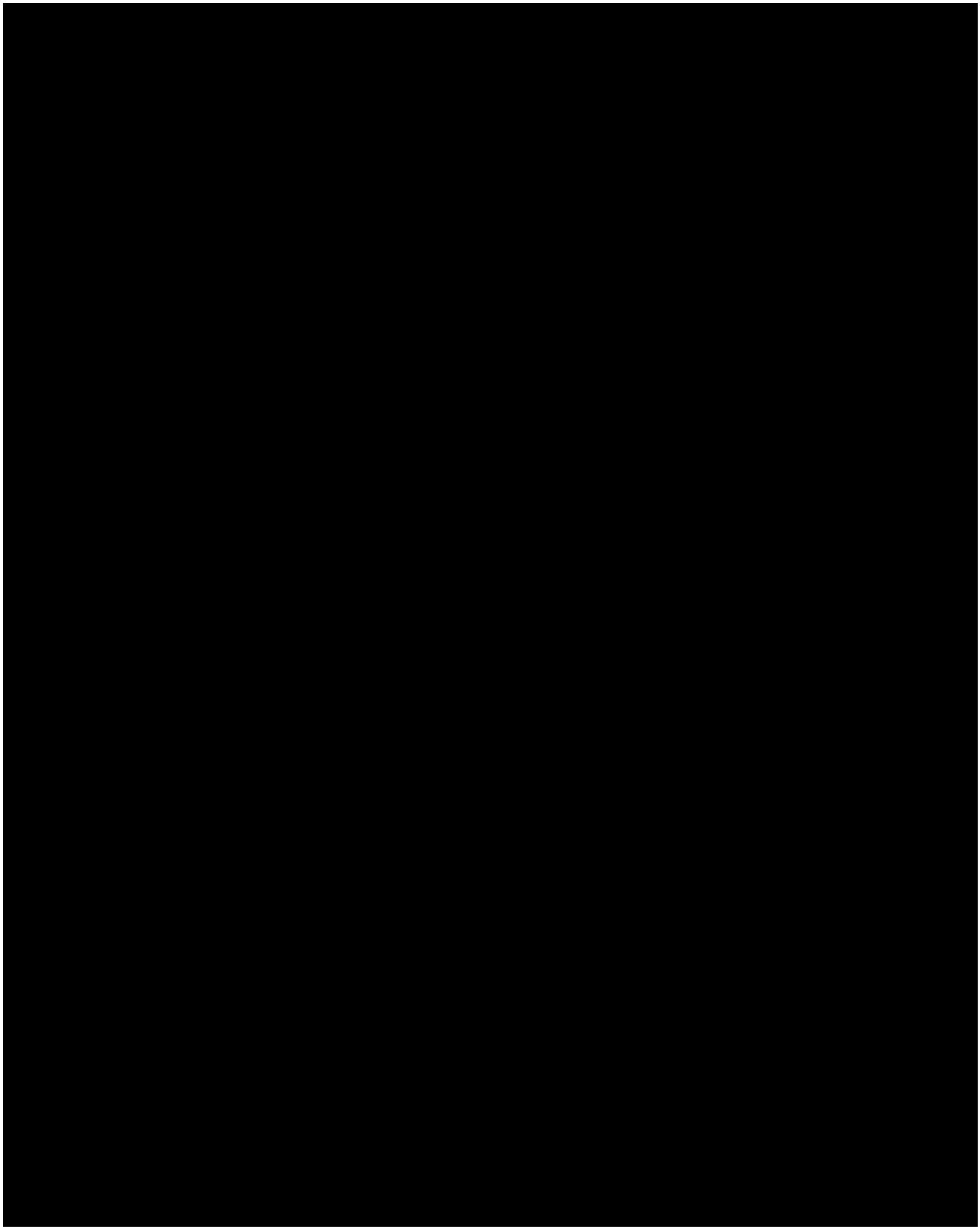
INCREASE IN ALT

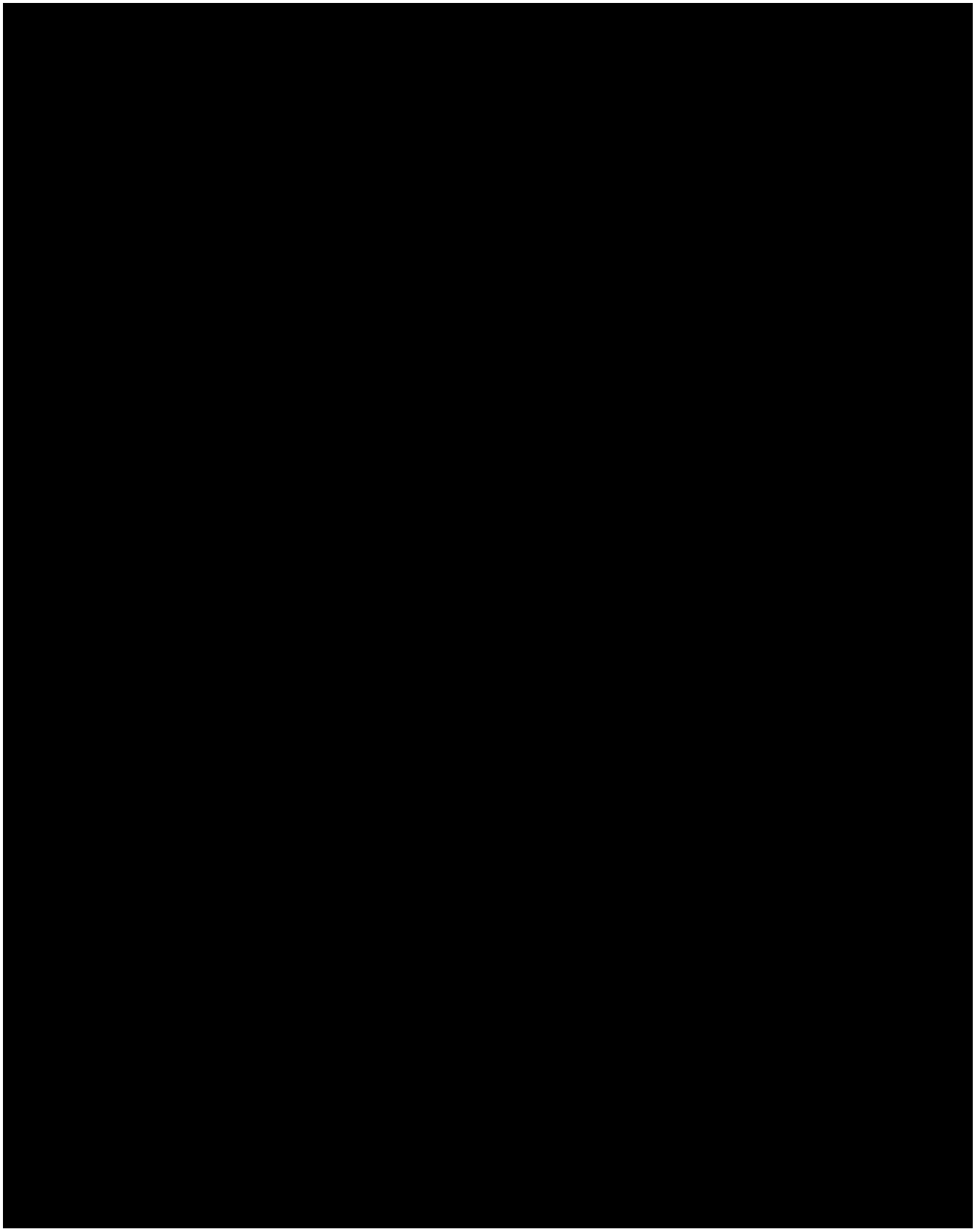


In ANY CASE, FOLLOW the instructions listed in the box below:

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

Although the liver function tests are not requested in the protocol, the routinely done lab tests might identify increased values of ALT, bilirubin.
*If unable to retest in 72 hours, use original lab results to decide on further reporting/monitoring/discontinuation.
Note:
"Baseline" refers to ALT sampled at baseline visit; or if baseline value unavailable, to the latest ALT value before the baseline visit. The algorithm does not apply to the instances of increase in ALT during screening.
See Section 8.3.1 for guidance on safety reporting.
Normalization is defined as ≤ ULN or baseline value, if baseline value is > ULN.





[redacted]

10.7 APPENDIX 7: SCIENCE37 METASITE

One study center will be managed by Sponsor designee Science37, using TM, mobile study nurses, and an electronic application called the Science37 Platform.

Study participants will undergo the same procedures and provide the same data as other trial participants as outlined in the protocol. The difference is that Science37 will interact with their participants using an innovative model, an electronic application and/or mobile nurses.

As part of this study, Science37 participants will see their study doctors by using a TM model during the study. The goal of TM is to make it easier for the participants to take part in the study. Telemedicine will use secure video conferences, phone calls, and a web portal and/or mobile application as a way of communicating with and monitoring participants. Science37 will provide mobile study nurses to the participant's home or location for study procedures, rather than a traditional investigative site. As part of this process, an electronic application called the Science37 Platform will be utilized for data collection.

The Science37 Platform is an electronic application developed by Science37. The Science37 Platform is password protected and only the study participant can access their own login. No one other than the participant and the study staff is able to view personal identifiable (e.g. photographs) and/or trial data in the Science37 Platform. As a function of the platform, information and/or photographs are transmitted to the research staff securely via the platform. Data submitted by the participant via the Science37 mobile application (whether trial related information and/or photographs) are never saved locally on the device (tablet/phone). All information and/or photographs received by the study personnel via the Science37 Platform will be stored securely and confidentially within the platform. A participant's personal use of information stored on the device will not be monitored. Participants will still be able to visit all local doctors as they normally would, but the Science37 study doctors and nurses will also communicate with the participant's doctor to explain the study and coordinate participant care during the study. Participants will also be provided and requested to sign an informed consent document (e-ICF) which explains rights as a participant in the study. Science37 Metasite participants will complete the consent process remotely with Science37 study staff and sign the eConsent in the platform, accessible via an App on a smartphone or tablet, or on a computer desktop browser. The participants will be informed that they may download and print a copy of the e-ICF, or a copy may be emailed to them upon the participant's request.

For participants enrolled through virtual site (Metasite), IMP (and some other study materials, if needed) will be supplied from the virtual site to the participant via DTP service which will be handled and under the responsibility of Science37.

The IMP will be administered by a mobile study nurse at the randomization dosing visit. Participants/caregivers will be instructed as per Section 6.1 how to prepare and self-inject/inject the IMP at the first dosing visit and will be allowed to self-administer for the remainder of the treatment period. This training must be documented in the participant's study file. If the participant is not comfortable with self-administration, the mobile study nurse will perform the administrations at home visits at every 2 weeks, according to the scheduled IMP administrations.

The mobile study nursing management with all related activities will be under the responsibility of Science37. The investigator of Metasite obtains intervention kit numbers at randomization (Day 1) and subsequent scheduled visits via IVRS/IWRS.

Science37 participant randomization in IVRS/IWRS will occur on Day 1, with first loading dose occurring up to 5 days after randomization to account for the lag between IVRS/IWRS randomization trigger for IMP DTP shipment and IMP availability to participant/mobile study nurse.

For the subsequent at home dosing visits (week 4, week 8, week 12) the window may increase up to 3 days (maximum visit window) to account for the lag between IVRS/IWRS trigger for IMP DTP shipment and IMP availability to participant/mobile study nurse.

All intervention kits accountability and return (whether used or empty or unused) of participants enrolled through Metasite will be managed and under the responsibility of Science37.

Study procedures:

Asthma Sleep Disturbance Questionnaire, sleep diary: the completion of the daily questionnaires for the baseline and for postbaseline assessments will be done as per SoA and will continue until the IMP dose administrations, considering the lag between IVRS/IWRS trigger for IMP DTP shipment and IMP availability to participant/mobile study nurse.

Actigraphy: the participants will perform the baseline and postbaseline assessments as per SoA and will continue until the day prior to IMP dose administrations.

ADSD: will be completed by the participants until the day prior to IMP dose administrations, every 4 weeks.

ANSD: will be completed by the participants until and including the day of IMP administrations, every 4 weeks.

All the other study assessments will be done as per SoA, (see Section 1.3).

Approximately 10 participants will be enrolled to the Decentralized Clinical Trial Site (DCTS), a clinical trial operating model that enables remote participation in clinical trials. One DCTS in the US will be included in the study. The DCTS is a remote study model that integrates TM technology into the clinical research process and supports management of research activities, including data collection. As part of this model, study visits are completed using the DCTS technology platform. This 21 CFR Part 11 compliant software interface facilitates recruitment,

enrollment, and study data collection within a single cloud-based technology. It connects participants to their investigators and study team through a study-issued smartphone.

Decentralizing research studies from traditional site-based centers, making them "site-less," aims to eliminate participation barriers, such as inaccessibility due to geography and the inconvenience of traveling to site visits. A DCTS complies with all regulatory requirements applicable to study investigators, as delineated in 21 CFR 312 and ICH E6 (R2). As such, it does not assume any Sponsor or CRO obligations.

The participants enrolled by Science37 Metasite will not participate in [redacted].

10.8 APPENDIX 8: 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 below and in sections (Section 2.3.3, Section 5.5, Section 6.1, Section 7.1.2, Section 7.1.2.1, Section 8, Section 9.4.6, Section 10.1.3) 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 Good Clinical Practice in Conduct of Clinical Trials Guidance. Sponsor agreement MUST be obtained prior to the implementation of these procedures for the duration of the emergency.

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

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

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

- If onsite visits are not possible during the intervention period, the visit can be performed remotely ensuring at least the procedures that can be done at home: PROs completion, actigraphy, home [redacted] (if applicable), IMP administration, blood samples collection, pregnancy test if applicable, safety reporting, and concomitant medications.
- If on-site visits are not possible visit windows may be extended for assessment of safety and/or efficacy data that cannot be obtained remotely (eg, spirometry, [redacted] on-site PROs, vital signs).

- Use of local laboratory locations may be allowed.
- Arrangements can be made for qualified site personnel and/or health care professionals (eg, visiting nurse service) for blood sample collection and study drug administration, if allowed by local regulations and approved by the participant

As an alternative to the on-site IMP dispensing, IMP may be supplied from the site to the participant via a Sponsor-approved courier company where allowed by local regulations and approved by the participant.

Rechallenge: In case of missed dose(s), no loading dose of two injections will be administered when restarting the treatment, whatever the number of missed doses. The participants should continue their scheduled IMP treatment and visits, even if more than two consecutive doses were missed.

Contingencies implemented due to emergency will be documented.

Statistical analysis: a sensitivity analysis may be conducted; details will be specified in the SAP.

For a regional or national emergency declared by a governmental agency, contingency procedures may be implemented for the duration of the emergency. The participants 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/treatment extension, use of local labs).

10.9 APPENDIX 9: DEFINITION OF ANAPHYLAXIS

"Anaphylaxis is a serious allergic reaction that is rapid in onset and may cause death (36)".

Clinical criteria for diagnosing anaphylaxis

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

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

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

10.10 APPENDIX 10: ABBREVIATIONS

ACOS: asthma-COPD overlap syndrome
ACQ: asthma control questionnaire
ACT: asthma control test
AD: atopic dermatitis
ADR: adverse drug reaction
ADSD: asthma daytime symptom diary
AE: adverse event
AESI: adverse event of special interest
[redacted]
ALT: alanine transaminase
ANSD: asthma nighttime symptom diary
[redacted]
ATS: American Thoracic Society
BD: bronchodilator
BMI: body mass index
CFR: code of federal regulations
CI: confidence interval
CIOMS: Council for International Organizations of Medical Sciences
CONSORT: Consolidated Standards of Reporting Trials
CRO: contract research organization
CRSwNP: chronic rhinosinusitis with nasal polyps
CSICF: core study informed consent form
DCTS: decentralized clinical trial site
DPI: dry powder inhaler
DTP: direct to participant
E/D: early discontinuation
ECG: electrocardiogram
e-CRF: electronic case report form
e-ICF: electronic informed consent form
EoE: eosinophilic esophagitis
EOS: end of study
EOT: end of treatment
ERS: European Respiratory Society
ESD: early study discontinuation
ETD: early treatment discontinuation
FDA: Food and Drug Administration
FeNO: fractional exhaled nitric oxide
FEV_1: forced expiratory volume
FSH: follicle stimulating hormone
FVC: forced vital capacity
GCP: Good Clinical Practice
GDPR: General Data Protections Regulation
GINA: Global Initiative for Asthma

HBcAB:	hepatitis B core antibody
HBsAg:	hepatitis B surface antigen
HBV:	hepatitis B virus
HCV:	hepatitis C virus
HCVAb:	hepatitis C virus antibody
HFA:	hydrofluoroalkane propellant
HIPAA:	Health Insurance Portability and Accountability Act
HIV:	human immunodeficiency virus
HLGT:	high-level group term
HLT:	high-level term
HRQoL:	health-related quality of life
HRT:	hormonal replacement therapy
IA:	interim analysis
IAC:	interim analysis committee
IB:	Investigator's Brochure
ICF:	informed consent form
ICH:	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICS:	inhaled corticosteroid
IEC:	Independent Ethics Committee
IL:	interleukin
IL-4Rα:	interleukin-4 receptor alpha
IM:	intramuscular
IMP:	investigational medicinal product
IRB:	Institutional Review Board
ITT:	intent-to-treat
ITTp:	intent-to-treat for primary endpoint
IV:	intravenous
IVRS:	interactive voice recognition system
IWRS:	interactive web response system
LABA:	long-acting beta2 agonist
LAMA:	long-acting muscarinic antagonist
LS:	least squares
LTRA:	leukotriene receptor antagonist
mAb:	monoclonal antibody
MCID:	minimal clinically important difference
MDI:	metered dose inhaler
MHRA:	Medicines and Healthcare products Regulatory Agency
MMRM:	mixed-effect model with repeated measurement
NIMP:	noninvestigational medicinal product
NRS:	numerical rating scale
OCS:	oral corticosteroid
[redacted]	[redacted]
PMDA:	Pharmaceuticals and Medical Devices Agency

pMDI: pressurized metered dose inhaler
pre-BD FEV_1: prebronchodilator forced expiratory volume
PRO: patient-reported outcome
PROMIS: patient-reported outcome measurement information system
[redacted] [redacted]
PSQI: Pittsburgh Sleep Quality Index
PT: preferred term
Q2W: every 2 weeks
RNA: ribonucleic acid
ROW: rest of world
SABA: short-acting beta2 agonist
SAE: serious adverse event
SAMA: short-acting muscarinic antagonist
SAP: statistical analysis plan
SARP: severe asthma research program
SC: subcutaneous
SD: standard deviation
[redacted] [redacted]
SoA: schedule of activities
SOC: system organ class
[redacted] [redacted]
SUSAR: suspected unexpected serious adverse reaction
TB: tuberculosis
TEAE: treatment-emergent adverse event
[redacted] [redacted]
ULN: upper limit of normal
WASO: Wake after sleep onset
WOCBP: women of childbearing potential
[redacted] [redacted]

10.11 APPENDIX 11: PROTOCOL AMENDMENT HISTORY

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

10.11.1 Amended protocol 01 (17 September 2020)

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

OVERALL RATIONALE FOR THE AMENDMENT

The main rationale for the Amendment is the decision to perform the [redacted] assessments in the substudy at patient's home using Type II [redacted] devices instead of on-site overnight assessments as initially planned. This decision was taken considering that the patients' safety is of outmost importance in the context of the coronavirus disease 2019 (COVID-19) pandemic with unpredictable evolution. In addition, an updated version of the sleep disturbance questionnaire has been implemented based on patient feedback to improve its understanding.

Further updates have been done in adverse events of special interest (AESI) listing and Benefit/Risk assessment chapter based on the new SAR231893 Investigator's Brochure (IB) dated 19-Jun-2020.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis; 1.3 Schedule of Activities (SoA); 4.1 Overall design; [redacted]	The [redacted] parameters will be assessed using Type II home [redacted] devices instead of on-site [redacted] assessments.	Patients' safety is of outmost importance in the context of COVID-19 pandemic and its unpredictable evolution, thus it was decided to perform the [redacted] assessment at home using Type II devices, instead of on-site overnight [redacted] as initially planned.
1.1 Synopsis; 1.3 Schedule of Activities (SoA); 4.1 Overall design; [redacted]	The [redacted] assessments will be done at home at two timepoints (on Day -1 and at End of Treatment [EOT] visit); the assessment on Day -2 for the control of "first night effect" has been removed.	The [redacted] assessment on Day -2 for the control of any "first night effect" is not needed in case of home [redacted]
1.1 Synopsis; 1.3 Schedule of Activities (SoA); 4.1 Overall design; 10.6 Appendix 6: Polysomnography substudy	If the sleep recording is inadequate as judged by the central reading site, the at-home sleep assessment will be repeated within 1 week of the original assessment.	To mitigate the risk of missing data due to inadequate recording
3 Objectives and Endpoints	Exploratory endpoint: [redacted]	Parameters added [redacted]
1.3 Schedule of Activities (SoA); 5.1 Inclusion criteria; 8.1.2 Fractional exhaled nitric oxide;	FeNO will be rechecked at randomization.	Ensure eligibility.
8.3.6 Adverse event of special interest	Any severe type of conjunctivitis or blepharitis has been added to the AESI list.	In agreement with latest IB.

Section # and Name	Description of Change	Brief Rationale
5.1 Inclusion criteria	I04. Historical values of blood eosinophil count meeting the eligibility criterion I04 measured within 6 months prior to SV1 in the absence of OCS treatment are allowed.	To clarify in the inclusion criterion I04 that the historical values of blood eosinophil count measured within 6 months prior to SV1 in the absence of OCS treatment are allowed.
5.2 Exclusion criteria	E18. Chronic treatment with oral corticosteroids (OCS) is forbidden within 2 weeks prior to Screening Visit 1 (SV1).	To clarify timeframe for chronic OCS treatment and to avoid confounding effects on sleep quality assessment.
5.2 Exclusion criteria	E23. Clarifications regarding the vaccination prohibition until the end of the study.	Clarification based on the comment raised by the Medicines and Healthcare products Regulatory Agency (MHRA) (Health Authorities from the United Kingdom).
5.2 Exclusion criteria	E.26. Treatment with an investigational drug is not allowed within 1 month or within 5 half-lives (if known), whichever is longer, prior to SV1.	An interdiction of non-antibody investigational drugs for 2 months before SV1 is unnecessary.
2.3.1 Risk assessment; 2.3.2 Benefit assessment;	Updated regulatory information and safety information based on recent Investigator's Brochure update.	Provide most recent safety data in the protocol.
2.3.3 Benefit/risk assessment related to COVID-19; 5.5 Criteria for temporarily delaying screening, randomization, or study intervention administration; 6.1 Study intervention(s) administered; 7.1.2 Temporary discontinuation; 7.1.2.1 Rechallenge; 8 Study assessments and procedures; 9.4.6 Other analyse(s); 10.1.3 Informed consent process; 10.7 Appendix 7 Contingency measures for a regional or national emergency that is declared by a governmental agency	Contingency measures to apply during a regional or national emergency declared by a governmental agency are described.	To ensure trial continuity in case of regional or national emergency declared by a governmental agency.
1.3 Schedule of Activities (SoA)	Complete physical examinations will be performed at SV1, V2, and V5.	The number of complete physical examinations has been reassessed in order to decrease the participants' burden.
1.3 Schedule of Activities	[redacted] will be provided to participants at SV2.	Devices must be provided to participants at SV2 so that they can start using them for 7 days before V2.
1.3 Schedule of Activities (SoA)	ACQ-5 score is the mean of the responses to the first 5 questions.	Correction related to the calculation of ACQ-5 score.

Section # and Name	Description of Change	Brief Rationale
6.1 Study intervention(s) administered; 7.1.1 Definitive discontinuation; 10.7 Appendix 7 Contingency measures for a regional or national emergency that is declared by a governmental agency	Process in case of missed IMP doses is detailed.	To clarify the process in case a participant misses IMP administration(s). The participants will not be prematurely discontinued from treatment in case they miss 2 consecutive doses to align with the pivotal study [redacted]
8.1.1 Actigraphy	No training on actigraphy diary completion will be provided.	There are no actigraphy diaries.
8.1.5 Asthma sleep disturbance questionnaire	Updated questionnaire.	Wording changes in the questionnaire have been implemented following the feedback received from asthma patients to enhance its understanding
8.1.6 Asthma daytime symptom diary - Asthma nighttime symptom diary	Details of asthma symptoms recording have been removed	Clarification: the sentence was confusing.
1.1 Synopsis; 9.2 Sample Size Determination; 9.3 Populations for analyses; 9.4.1 General considerations; 9.4.2 Primary endpoint(s); 9.4.3 Secondary endpoint(s); 9.4.4 Tertiary/exploratory endpoint(s); 9.5 Interim analysis	In order to mitigate the risk of potential different responses based on the Sleep Disturbance Questionnaire before and after amendment 01, the primary analysis of change from baseline in sleep disturbance score will exclude the participants who use the original questionnaire at baseline. The number of participants randomized up to the implementation of this protocol amendment is limited (ie, ≤10), therefore the study power can be preserved at ≥89% and therefore no participant replacement is planned.	The Sleep Disturbance Questionnaire (assessment of primary endpoint) has been updated. The participants already enrolled in the study completed the initial version of the questionnaire. These participants will be excluded from the primary analysis to mitigate the risk of potential different responses before and after this amendment.
8.3.4 Regulatory reporting requirements for SAEs	Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary	Correction of the instructions for the preparation of Investigators safety reports in case of SUSARs
8.11 Use of data for future research; 10.1.3 Informed consent process	Details on retention and use of data for future research.	In agreement with current legal requirements and Sponsor's policy.
10.1.4 Data protection; 10.1.5 Dissemination of clinical study data	Description of data measures for professionals involved in the study.	In agreement with current legal requirements and Sponsor's policy.
5.2 Exclusion criteria; 7.1.1 Definitive discontinuation; 8.3.6 Adverse event of special interest; 10.8 Appendix 8: Definition of anaphylaxis	Definition of anaphylaxis was added as an appendix.	Clarification.

Section # and Name	Description of Change	Brief Rationale
7.1.1 Definitive discontinuation; 8.3.6 Adverse event of special interest	Definition of baseline alanine transaminase (ALT) has been added.	Clarification.
Whole document	Minor formatting, typo corrections, and consistency changes.	Consistency.

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