Supplementary Online Content


**Trial Protocol**

This supplementary material has been provided by the authors to give readers additional information about their work.
CLINICAL TRIAL PROTOCOL

A randomized, double-blind, phase 2, placebo controlled, 2 arm study to evaluate Dupilumab in patients with bilateral nasal polyposis and chronic symptoms of sinusitis.

COMPOUND: DUPILUMAB - SAR231893

STUDY NUMBER: SAR231893 - ACT12340

CLINICAL STUDY DIRECTOR:

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### NAMES AND ADDRESSES OF
#### COORDINATING INVESTIGATOR
- **Name:**
- **Address:**
- **Tel:**
- **Fax:**
- **E-mail:**

#### MONITORING TEAM’S REPRESENTATIVE
- **Name:**
- **Address:**
- **Tel:**
- **Fax:**
- **E-mail:**

#### SPONSOR
- **Company:**
- **Address:**

#### OTHER EMERGENCY TELEPHONE NUMBERS
### CLINICAL TRIAL SUMMARY

**COMPOUND:** Dupilumab (SAR231893)  
**STUDY No:** SAR231893 - ACT12340

**TITLE**  
A randomized, double-blind, phase 2, placebo controlled, 2 arm study to evaluate Dupilumab in patients with bilateral nasal polyposis (NP) and chronic symptoms of sinusitis

**INVESTIGATOR/TRIAL LOCATION**  
worldwide

**PHASE OF DEVELOPMENT**  
2

**STUDY OBJECTIVE(S)**

- **Primary objective**
  - To evaluate the efficacy of dupilumab in the treatment of bilateral NP by assessment of the endoscopic nasal polyp score in comparison to placebo

- **Secondary objective(s)**
  - To evaluate:
    - Effect of dupilumab on symptoms of sinusitis
    - Effect of dupilumab in CT scan
    - Effect of dupilumab in nasal polyp score in the sub-group of patients with co-morbid asthma
    - Safety and tolerability
    - Pharmacodynamic responses based on suppression of TH2 biomarkers
    - Concentrations of dupilumab in serum
    - Immune response to dupilumab (Anti-drug antibodies (ADA))
    - Effect of dupilumab in patient reported outcomes and QoL scales

**STUDY DESIGN**

**General design**

Multinational, multicenter, randomized, double-blind, placebo-controlled, parallel group study evaluating the effect of 300 mg of dupilumab administered once per week (QW) subcutaneously (SC) for 16 weeks following an initial loading dose of 600mg on D1

**Study periods**

The clinical trial consists of 3 periods:

- **Screening run in Period:** (4 weeks +/- 2 days)
  - All patients will enter a run-in period of 4 weeks on mometasone furoate nasal spray (MFNS) of 2 actuations (50 μg/actuation) in each nostril twice daily (BID), total daily dose of 400 μg, at V1, unless they're intolerant to BID INCS in which case, they can stay on the lower dose regimen

- **Randomized Treatment Period:** (dupilumab/placebo for 16 weeks)
  - Patients will be randomized to one of the following treatments:
    - Dupilumab 300 mg weekly SC administration for 16 weeks with an initial loading dose of 600 mg at Day 1
    - Placebo weekly SC administration for 16 weeks (loading at Day 1)
  - Randomization into the 2 treatment arms will be stratified by history of co-morbid asthma at Visit 1 and by polyp biopsy sampling at V2
  - During the double blind randomized treatment:
    - All patients will continue MFNS (200 μg) BID or QD

- **Post-treatment Period for PK, immune response, safety, efficacy (16 weeks)**
weeks) After completing 16 weeks of treatment with the investigational medicinal product (or following early discontinuation of IMP), patients will be instructed to:

- Return to the study site every 4 weeks during the Post-treatment Period for evaluations of PK and ADA, physical examination, QoL, efficacy, safety and a last endoscopy at the end of study
- Continue to complete e-diary for symptom evaluation
- Continue on MFNS stable dose during post-treatment period
- Contact the Investigator during the Post-treatment Period if the symptoms worsen requiring medical attention
- Report any AE

Patients who discontinue prematurely from treatment are assessed as soon as possible using the procedures normally planned for the End of Treatment Visit and the 4 Post-treatment Period Visits

<table>
<thead>
<tr>
<th>STUDY POPULATION</th>
<th>Inclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Main selection criteria</strong></td>
<td><strong>Patients with:</strong></td>
</tr>
<tr>
<td></td>
<td>1. A minimum bilateral nasal polyp score of 5 out of a maximum score of 8 for both nostrils (with at least a score of 2 for each nostril) despite completion of a prior INCS treatment for at least 8 weeks before screening</td>
</tr>
<tr>
<td></td>
<td>2. Presence of at least two of the following symptoms prior to screening: nasal blockade/obstruction/congestion or nasal discharge (anterior/posterior nasal drip); facial pain/pressure; reduction or loss of smell</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Main exclusion criteria</strong> (see Section 7.2 for complete list)</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Patients &lt;18 or &gt;65 years of age</td>
</tr>
<tr>
<td>- SNOT22&lt;7</td>
</tr>
<tr>
<td>- Patients who have taken other investigational drugs or the following prohibited therapy within 2 months before screening or 5 half-lives, whichever is longer:</td>
</tr>
<tr>
<td>- Burst of oral corticosteroids (OCS) or intranasal corticosteroid drops within the 2 months before screening or are scheduled to receive OCS during the study period for another condition</td>
</tr>
<tr>
<td>- Monoclonal antibody (mAB) and immunosuppressive treatment</td>
</tr>
<tr>
<td>- Anti-immunoglobulin E (IgE) therapy (omalizumab) within 130 days of Visit 1</td>
</tr>
<tr>
<td>- Leukotriene antagonists / modifiers unless patient is on a continuous treatment for at least 30 days prior to Visit 1</td>
</tr>
<tr>
<td>- Patients who have undergone nasal surgery within 6 months before screening or have had more than 2 surgeries in the past for NP</td>
</tr>
<tr>
<td>- Patients with conditions/concomitant diseases making them non evaluable for the primary efficacy endpoint such as:</td>
</tr>
<tr>
<td>- Antrochoanal polyps</td>
</tr>
<tr>
<td>- Nasal septal deviation that would occlude at least one nostril</td>
</tr>
<tr>
<td>- Acute sinusitis, nasal infection or upper respiratory infection at screening or in the 2 weeks before screening</td>
</tr>
</tbody>
</table>
### Ongoing rhinitis medicamentosa
- Churg-Strauss syndrome, Young’s syndrome, Kartagener’s syndrome or dyskinetic ciliary syndromes, concomitant cystic fibrosis
- Signs or a CT scan suggestive of Allergic fungal rhinosinusitis

Among patients with co-morbid asthma are excluded if one of the following criteria is meet:
- Patients with FEV1 < 60% (of predicted normal)
- Patients with an asthma exacerbation requiring systemic (oral and/or parenteral) steroid treatment or hospitalization for >24h for treatment of asthma, within 3 month prior to screening or are on a dose of greater than 1000 μg fluticasone or an equivalent inhaled corticosteroids [Appendix B](#).

### Total expected number of patients
A total of 56 NP patients (with or without co-morbid asthma) will be randomized
To ensure at least 28 patients with co-morbid asthma needed for subgroup analysis:
- Recruitment of NP patients without co-morbid asthma will stop when approximately 28 patients without asthma are randomized

### STUDY TREATMENT(s)

<table>
<thead>
<tr>
<th>Investigational medicinal product(s)</th>
<th>Dupilumab or matching placebo:</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Formulation</strong></td>
<td>Sterile dupilumab in 5 mL glass vials; each vial will contain a withdrawable volume of 2 mL: 150 mg/mL solution (300 mg dose / 2 mL)</td>
</tr>
<tr>
<td></td>
<td>Sterile placebo in identically matched glass 5 mL vials; each vial contains a withdrawable volume of 2 mL</td>
</tr>
<tr>
<td><strong>Route(s) of administration</strong></td>
<td>Subcutaneous injection</td>
</tr>
<tr>
<td><strong>Dose regimen</strong></td>
<td>Dupilumab 600 mg SC on D1 followed by weekly 300 mg SC injection for 15 weeks</td>
</tr>
<tr>
<td></td>
<td>Placebo SC loading dose on D1 followed by weekly SC injection for 15 weeks</td>
</tr>
<tr>
<td><strong>Noninvestigational medicinal product(s) (if applicable)</strong></td>
<td>Mometasone furoate (NASONEX ©) 50 μg/actuation nasal spray, suspension</td>
</tr>
<tr>
<td><strong>Formulation</strong></td>
<td>Nasal Spray is contained in a bottle, that contains 18 g (140 actuations) of product formulation</td>
</tr>
<tr>
<td><strong>Route(s) of administration</strong></td>
<td>Nasal spray</td>
</tr>
<tr>
<td><strong>Dose regimen</strong></td>
<td>Mometasone furoate nasal spray (MFNS) two actuations (50 μg/actuation) in each nostril twice daily (total daily dose of 400 μg) or once daily (total daily dose of 200 μg)</td>
</tr>
</tbody>
</table>

### ENDPOINT(S)
Primary endpoint
### Secondary endpoint(s):
Change from baseline at Week 16 in:
- Patient reported symptoms
  - 22-item Sinonasal Outcome Test (SNOT-22)
  - Subject-assessed nasal congestion/obstruction, anterior rhinorrhea (runny nose), posterior rhinorrhea (post nasal drip), and, loss of sense of smell
  - Daily subject-assessed nasal peak inspiratory flow (NPIF)
  - Patient-rated rhinosinusitis symptoms severity using a visual analog scale (VAS)
- Smell test (UPSIT)
- CT scan assessments
- In NPS in patients with co-morbid asthma

Time to first response (≥1 point improvement) in NPS

### Safety, tolerability and other exploratory endpoints:
- Spirometry
- 5-item asthma control questionnaire (ACQ-5) in asthma sub-group
- Time to study treatment discontinuation
- Incidence of treatment discontinuation due to need for OCS or nasal surgery
- Adverse events (AE)
- Vital signs
- Physical examination
- Electrocardiogram (ECG)
- Clinical laboratory tests

### Pharmacokinetic and Immune Response to Dupilumab
- Serum dupilumab concentrations
- Anti-drug antibodies (ADA)

### Biomarkers:
- Serum: total IgE, Staphylococcal enterotoxin A IgE, Staphylococcal enterotoxin B IgE, ECP, TARC, periostin
- Plasma: Eotaxin-3

### Quality of life (QoL) measurements:
Change from baseline at Week 16 in:
- 36-item short form health survey (SF36)
- European quality of life scale (EQ-5D)
- Nasal polyp related resource use questionnaire

### ASSESSMENT SCHEDULE
- Screening period: 4 weeks
- Randomized treatment period: 16 weeks
- Post-treatment period: 16 weeks
- Total of 36 weeks

For detailed assessment schedule across the study report to Section 1.2
### STATISTICAL CONSIDERATIONS

The sample size estimation is based on the comparison between dupilumab 300 mg vs. placebo with regard to the primary endpoint: change from baseline in NPS at week 16.

Assuming a common standard deviation of 1.5, a two-sided and significance level of 0.05, 20% discontinuation rate, 28 patients per group will provide 80% power to detect a difference of 1.3 between dupilumab and placebo groups in the change of NPS from baseline to Week 16.

#### Randomization:

Patients will be randomized using a 1:1 randomization ratio for Dupilumab 300 mg QW for 16 weeks, placebo QW for 16 weeks. The randomization will be stratified based on asthma comorbidity status and nasal biopsy sampling.

#### Analysis Population:

The primary analysis population for the efficacy endpoints will be the double blind randomized ITT population who have been allocated to a randomized treatment regardless of whether the treatment kit was used or not. The efficacy analyses will be conducted according to the treatment to which they are randomized.

The analysis population for safety endpoints is defined as all randomized patients exposed to study medication, regardless of the amount of treatment administered. The safety analyses will be conducted according to the treatment patients actually received.

The treatment emergent period for the safety population is defined as the time from the first administration of study medication to the end of the Post-treatment Period.

#### Primary Analysis:

The change from baseline in NPS will be analyzed using a mixed-effect model with repeated measures (MMRM) approach. The model will include change from baseline values up to Week 16 as response variables, and factors (fixed effects) for treatment, stratification factor, visit, treatment-by-visit interaction, baseline value and baseline-by-visit interaction. An unstructured correlation matrix will be used to model the within-patient errors. Parameters will be estimated using restricted maximum likelihood method with the Newton-Raphson algorithm. Statistical inferences on treatment comparisons for the primary endpoint, change from baseline in NPS at Week 16, will be derived from the mixed-effect model.

#### Analysis of secondary endpoints:

Proportion of patients with binary event (eg, improvement in NPS) will be analyzed respectively using a logistic model.

The time to event analysis will be analyzed using Cox regression model.

The change from baseline for continuous endpoints will be analyzed using MMRM same as the primary endpoints.

The safety variables, including AEs, laboratory parameter, vital signs, ECG and physical examinations will be summarized using descriptive statistics.

#### Missing data handling

For the primary analysis, no imputation will be done for the MMRM model. Analysis of covariance (ANCOVA) model based on last value carry forward (LOCF) will be used as a sensitivity analysis. For responder analysis, if a patient discontinued the treatment before Week 16, the values measured at the end of treatments will be used to determine whether the patient can be considered as a responder or not. For other endpoints analyzed using MMRM, no imputation will be done.
Interim Analyses:
An early analysis will be performed when the last patient completes the end of treatment phase. This analysis will be the final on-treatment analysis. Procedure to maintain study integrity with respect to the subsequent post-treatment follow up visits, safety visits and analyses are described in Section 6.3. A Key Results Summary for the early analysis will be prepared.

Planned Database lock date:
A primary database lock will be performed at the end of the treatment phase of all patients. The database will be updated at the end of the study phase of all patients to include the additional post-treatment follow up information and updates for the events previously ongoing at the time of previous lock.

| DURATION OF STUDY PERIOD (per patient) | Screening period (4 weeks) + Randomized Treatment Period (16 weeks)+ Post-Treatment Period (16 weeks) = Approximately 36 weeks |
IMP: Patients will be randomized to one of the following treatments for 16 weeks, receiving QW SC administrations of dupilumab or placebo according to one of the following doses and regimens: Dupilumab 300 mg QW with 600 mg loading dose (LD) at D1 (V2) or Placebo QW (P) with placebo loading dose at D1 (V2). Weekly investigational product administrations must be separated by at least 5 days. At Visit 2 the Investigator or delegate will perform 2 injections. After V2 one injection of IMP will be performed weekly at the investigational site throughout the randomized treatment period. Patients will stay under observation at the study site for a minimum of 1 hour after injections.

NIMP: MFNS will be self-administered by the patient BID or QD (if they cannot tolerate QD). At each visit the investigator must ensure that the patient has the necessary doses up to the next visit, knowing that one MFNS device (1 bottle) contains sufficient doses for: either 2 weeks of BID treatment/regimen or 4 weeks of QD treatment/regimen
### 1.2 STUDY FLOW CHART

<table>
<thead>
<tr>
<th>Study Period</th>
<th>Screening</th>
<th>Randomized Treatment Period</th>
<th>Post-treatment Period</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>VISIT</strong></td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td><strong>Week (DAY)</strong></td>
<td>W-4(D-28)</td>
<td>W0 (D1)</td>
<td>1</td>
</tr>
<tr>
<td>Inclusion Criteria</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Exclusion Criteria</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Physical Examination</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Spirometry</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Randomization</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IMP weekly SC administration</td>
<td>X (loading)</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Call (IVRS/IWRS)</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Dispense or download electronic diary/NPIF</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>NIMP (MFNS see Section 8.2)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Record concomitant medication</td>
<td></td>
<td></td>
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<tr>
<td><strong>Efficacy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nasal endoscopy</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>CT scan</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>SNOT-22</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Visual analogue scale (VAS)</td>
<td>X</td>
<td>X</td>
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</tr>
<tr>
<td>Oral allergy questionnaires</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Nasal polyp related resource use questionnaire</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>ACQ-5</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td><strong>Safety</strong></td>
<td></td>
<td></td>
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<tr>
<td>AE: SAE recording (F ami)</td>
<td></td>
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<td></td>
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<tr>
<td>Vital Signs</td>
<td>X</td>
<td>X</td>
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</tr>
<tr>
<td>ECG</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Laboratory Testing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical laboratory testing</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Urinalysis (dipstick)</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

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Clinical Trial Protocol
SAR231893 - ACT12340-dupilumab
30-Apr-2013
Version number: 1

| VISIT | Week (DAY) | W-NO-28 | V2 | W0 (D1) | 1  | 2  | 3  | 4  | 5  | 6  | 7  | 8  | 9  | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 |
|-------|------------|---------|----|---------|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|
| 1     |            |         |    |         |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |

- **Screening Period**: 28 days in duration to run in any patient on MFNS, and to collect baseline data. V2 will take place 28 days +/- 2 day window after V1.
- **No IMP administration during this visit. Patients who discontinue treatment early will be assessed as soon as possible using the procedures normally planned for the End-of-treatment Visit and the 4 Post-treatment Period Visits.**
- Prior to screening, patients must be on a stable dose of INCS for more than 8 weeks.
- Spirometry: all patients should have the result of FEV1 (% of predicted normal) recorded in e-CRF: anytime during Screening Period (before V2) and at the other scheduled visits during the Randomized treatment period. If a patient’s FEV1 does not qualify, then he/she will not be randomized on that day.
- Weekly IMP administrations starting from V2 at the site investigational site must be separated by at least 5 days.
- Nasal endoscopy: endoscopy (including use of decongestants before the procedure) will be performed after all other efficacy assessments have been completed for each visit; Standard video sequences will be downloaded by the investigator to the central reader’s secured Internet site. For eligibility central reading of V1 will be used. At V2 investigator review V1 results from central reader to confirm entry criteria and reconfirm eligibility based on review of Inclusion/Exclusion Criteria and the V2 endoscopy local reading.
- CT scan should be performed anytime during Screening Period before a first administration of IMP and at EOT. Central reading will be used for comparison baseline (BL) to EOT.
- Only for patients with co-morbid asthma, ACQ-5 is completed in the patient’s electronic diary during clinic visits.
- Hematology: hemoglobin, hematocrit, platelet count, total white blood cell count with five-part differential count, differential count, and total red blood cell count. Serum chemistry (Obtain fasting at planned visits but V2): creatinine, blood urea nitrogen, glucose, uric acid, total cholesterol, albumin, total bilirubin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, electrolytes (sodium, potassium, chloride), bicarbonate, and creatine phosphokinase. Clinical laboratory testing at Visit 1 includes hepatitis screen (hepatitis B surface antigen (HBsAg), Hepatitis B IgM core antibody (HBeAb-igM), hepatitis C antibodies (HC Ab), HIV screen (Anti-HIV-1 and HIV-2 antibodies), anti-nuclear antibody (ANA). Clinical laboratory testing at Visit 2 is limited to hematology. Note: Anti-ds DNA antibody will be tested if ANA is positive (1:160 titer).
Serum pregnancy test at Visit 1 and urine pregnancy tests at other visits. A negative result must be obtained at Visits 1 and 2 prior to randomization visits.

Serum pharmacokinetic samples, immune response assessment (ADA) samples and optional whole blood RNA samples will be collected prior to administration of investigational product during the Randomized Treatment Period. During the post-treatment period PK samples will be collected at all visits and ADA samples only at EOS visit. Patients with titers >1000 of the ADA at last visit may be followed after the study. Blood samples for PK and ADA assessment will be collected at any time in case an SAE occurs.

Biomarkers to be assayed: total IgE, Staphylococcal enterotoxin A IgE, Staphylococcal enterotoxin B IgE, ECP, TARC, periostin

Nasal secretion samples will be collected and stored for potential future discovery efforts to identify predictors of treatment response.

Optional polyp biopsies will be collected in selected clinical centers

Samples will be collected prior to administration of investigational product during the Randomized Treatment Period

Optional sampling for exploratory analysis of DNA and RNA, requiring separate pharmacogenetics informed consent.
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<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>ACQ-5</td>
<td>Asthma Control Questionnaire, 5-question version</td>
</tr>
<tr>
<td>ADA</td>
<td>Anti-drug Antibodies</td>
</tr>
<tr>
<td>ADI</td>
<td>Actual Dose Intensity</td>
</tr>
<tr>
<td>AE</td>
<td>Adverse Event</td>
</tr>
<tr>
<td>AESI</td>
<td>Adverse Event of Special Interest</td>
</tr>
<tr>
<td>ALT</td>
<td>Alanine aminotransferase</td>
</tr>
<tr>
<td>AM</td>
<td>Ante meridiem</td>
</tr>
<tr>
<td>ANA</td>
<td>Anti-Nuclear antibody</td>
</tr>
<tr>
<td>ANCOVA</td>
<td>Analysis of covariance</td>
</tr>
<tr>
<td>AST</td>
<td>Aspartate aminotransferase</td>
</tr>
<tr>
<td>β-hCG</td>
<td>Human chorionic gonadotrophin</td>
</tr>
<tr>
<td>BID</td>
<td>Two times per day</td>
</tr>
<tr>
<td>BP</td>
<td>Blood pressure</td>
</tr>
<tr>
<td>CRS</td>
<td>Chronic Rhinosinusitis</td>
</tr>
<tr>
<td>CT</td>
<td>Computed Tomography</td>
</tr>
<tr>
<td>D</td>
<td>Day</td>
</tr>
<tr>
<td>DB</td>
<td>Double-Blind</td>
</tr>
<tr>
<td>DMC</td>
<td>Data Monitoring Committee</td>
</tr>
<tr>
<td>DNA</td>
<td>Deoxyribonucleic acid</td>
</tr>
<tr>
<td>DRF</td>
<td>Discrepancy Resolution Form</td>
</tr>
<tr>
<td>EDTA</td>
<td>Ethylene diamine tetra acetic acid</td>
</tr>
<tr>
<td>EBV</td>
<td>Epstein-Barr virus</td>
</tr>
<tr>
<td>ECG</td>
<td>Electrocardiogram</td>
</tr>
<tr>
<td>ECP</td>
<td>Eosinophil cationic protein</td>
</tr>
<tr>
<td>EOS</td>
<td>Eosinophils</td>
</tr>
<tr>
<td>EOT</td>
<td>End of treatment</td>
</tr>
<tr>
<td>EP</td>
<td>End point</td>
</tr>
<tr>
<td>EQ-5D</td>
<td>EuroQOL-5D</td>
</tr>
<tr>
<td>FEV</td>
<td>Forced expiratory volume</td>
</tr>
<tr>
<td>GCP</td>
<td>Good Clinical Practice</td>
</tr>
<tr>
<td>GCS</td>
<td>Glucocorticosteroid</td>
</tr>
<tr>
<td>GH</td>
<td>General Health</td>
</tr>
<tr>
<td>GSO</td>
<td>Global Safety Officer</td>
</tr>
<tr>
<td>HBcAb-IgM</td>
<td>Hepatitis B IgM Core Antibody</td>
</tr>
<tr>
<td>HBsAg</td>
<td>Hepatitis B Surface Antigen</td>
</tr>
<tr>
<td>HC Ab</td>
<td>Hepatitis C Core Antibody</td>
</tr>
<tr>
<td>HLGT</td>
<td>High-Level Group Term</td>
</tr>
</tbody>
</table>
QoL: Quality of Life
QRS: QRS complex on ECG (ventricular depolarization)
QT: Ventricular depolarization and repolarization time on ECG
QW: Every Week (weekly)
RDI: Relative Dose Intensity
RNA: Ribonucleic acid
RBC: Red blood cell(s)
RDN: Randomization
SABA: Short-Acting Beta Agonist
SAE: Serious Adverse Event
SAS: Statistical analysis software
SC: Subcutaneous
SF36: Short form questionnaire
SMQ: Standardised MedDRA query
SNOT: Sinonasal Outcome Test
SOC: System Organ Class
TARC: Thymus- and activation-regulated chemokine
TEAE: treatment emergent adverse event
TH: T-helper lymphocyte
ULN: upper limit of normal
V: Visit
VAS: Visual Analogue Scale
WBC: White blood cells
WOCBP: Women of childbearing potential
WW: Worldwide
4 INTRODUCTION AND RATIONALE

Nasal polyposis (NP) is a clinical condition characterized by the presence of multiple polyps in the upper nasal cavity, originating from the ostiomeatal complex. The main disease associated with polyp formation is chronic rhinosinusitis (CRS), which is a heterogeneous group of diseases characterized by mucosal inflammation of the nasal cavity and paranasal sinuses with symptoms lasting more than 12 weeks. Clinically symptoms are defined by long-term symptoms of nasal obstruction and congestion, reduction in or loss of sense of smell, anterior and posterior rhinorrhea, and facial pain. These symptoms can impact greatly upon a patient’s quality of life. The presence or absence of polyps is confirmed by performing endoscopy. Coronal computed tomography (CT) scans can confirm the presence and extent of sinus and polyp involvement. The CRS phenotype involving with polyps (CRSwNP) is at the more severe end of the disease severity spectrum than the CRS phenotype without nasal polyps and is the most resistant to treatments. CRSwNP with an estimated prevalence of 2% to 4% (in Europe and US), has a greater burden of symptoms and a higher relapse rate after treatment. Despite the high prevalence and significant morbidity associated with NP, treatment options range from local or systemic corticosteroids to functional endoscopic sinus surgery. Patients with CRSwNP and comorbid asthma (30% of patients with CRSwNP) have a characteristic poor therapeutic response and a high recurrence rate and their disease tends to be more resistant (1) (2).

The pathogenesis of nasal polyps is unknown. Nasal polyps are most commonly thought to be caused by allergy although a significant number are associated with non-allergic adult asthma or no respiratory or allergic trigger that can be demonstrated. Risk factors include genetic susceptibility, anatomic abnormalities, infection, and local immunologic imbalance, some or most of which may play a role in its pathogenesis (3) (4) (5).

Pathophysiologically, NP is an inflammatory process affecting the mucosa of the nose and paranasal sinuses often associated with mucociliary impairment, bacterial infection, allergic disease, and/or anatomical abnormalities (6) (7) (8). NP is a T helper cell-2 (Th-2) driven inflammatory process in which eosinophils are the predominant inflammatory cell found in the sinuses and nasal polyps, and is frequently associated with asthma and aspirin sensitivity (9). More than 80% of patients with chronic sinusitis with nasal polyps have eosinophilic upper airway inflammation. The extent of sinomucosal involvement, the size of the polyps, and the severity of nasal disease correlate with the extent of eosinophilic inflammation (10). Eosinophils and their products are thought to be a hallmark of nasal polyp-associated inflammation as evidenced by the finding of elevated levels of interleukin-5 (promotes eosinophil survival and differentiation), eosinophil cationic protein, and eotaxin (eosinophil chemoattractant), factors that attract and activate eosinophils, in the nasal polyp specimens (11).

4.1 RATIONALE

Recent therapeutic approaches have been focused on trying to control the Th2 response. Dupilumab is under development as a potential novel treatment for Nasal polyposis. Dupilumab is a fully human monoclonal antibody directed against the interleukin-4 receptor alpha (IL-4Ra)
subunit, which is a component of interleukin-4 (IL-4) receptors Type I and Type II, which mediate signaling by IL-4 (both receptors) and by IL-13 (Type II receptor). Dupilumab binds to IL-4Rα, preventing IL-4 and IL-13 binding and activation of their respective receptors. Since both signaling pathways are thought to play key roles in the pathophysiology of inflammatory allergic diseases, dupilumab may provide an effective treatment for NP.

In a proof of concept study designed to investigate dupilumab 300 mg once weekly in patients with moderate to severe asthma with high blood eosinophil levels there was a statistically significant improvement in the SNOT-22 score overall compared to placebo.

4.1.1 Population

The population of ACT12340 is composed of patients with a physician endoscopic diagnosis of bilateral nasal polyposis (nasal poly score of 5 out of a maximum of 8) despite completion of a prior topical INCS treatment for at least 8 weeks and chronic symptoms of sinusitis.

In this study Dupilumab will be administered on top of Mometasone furoate nasal spray (MFNS).

Taking into account the high co-morbidity of NP with asthma, aspirin/ nonsteroidal anti-inflammatory drug (NSAID) hypersensitivity and previous surgeries, these patients will be allowed to enter the study unless they present any of the exclusion criteria described in Section 7.2.

4.1.2 Study Design

ACT12340 is a proof of concept, Ph 2 multinational, multicenter, randomized, double-blind, placebo-controlled, parallel group study evaluating the effect of 300 mg of dupilumab administered QW SC for 16 weeks with a loading dose of 600mg on D1.

The clinical study consists of three periods:

- Screening run in on MFNS for 4 weeks
- Randomized Dupilumab/Placebo Treatment Period (16 weeks)
- Post-treatment Period for PK, immunogenicity, safety and efficacy (16 weeks)

The study is double-blind to avoid the bias incurred by an unblinded design. Both the patient and Investigator are blinded to the assigned treatment group. The study is placebo-controlled to minimize bias- and provide an inactive control group to which differential efficacy and safety can be compared.

4.1.3 Endpoint rationale

The primary endpoint is the change from baseline at Week 16 in bilateral nasal polyp score (NPS).
Bilateral NPS is an objective endpoint (EP) commonly used to evaluate the effect of medications or surgery in NP at the current early stage of clinical development.

Numerous secondary efficacy endpoints including symptom evaluations required as co-primary endpoint in late stage of development are measured to more comprehensively evaluate the efficacy of dupilumab. Also this study will explore improvement of nasal polyposis and associated sinus inflammation in CT scan, improvement in condition specific and general medical questionnaires in order to obtain a better understanding of the impact of severe nasal polyposis on the subject's quality of life (QOL). This approach reflects real-life clinical assessment of nasal polyposis and is in line with increasing focus in the medical field on the effects of medical conditions and treatments on the quality of life of patients (1).

Safety endpoints are typical for investigational drugs at the current stage of clinical development.

These endpoints, together with exploratory sub-group analysis and biomarkers will provide the information on the therapeutic value of Dupilumab to reduce the nasal polyp score and to improve symptoms in NP and its subsets. On top of that, the sustainability of the effect will be also explored through the 4-month post-treatment evaluation period.

4.1.4 Dupilumab dose and regimen rationale

This study will explore the 300 mg QW dose regimen. This dose is anticipated to saturate apparent target mediated clearance level (10-15 mg/L) and has been tested and provided statistically significant and clinically relevant response in two previous proof of concept studies performed with dupilumab in asthma and atopic dermatitis.

The first dose will employ a loading dose of 600 mg in order to achieve faster steady-state concentration. This loading dose range is supported by the acceptable safety profile of the highest loading dose (600 mg) demonstrated in the TDU12265 study conducted in Japanese healthy subjects.

In addition, given that the Cmax after 600 mg loading dose is around 70 mg/L and that the steady state Ctrough of 300 mg QW is around 150 mg/L, the Cmax after the proposed dosing regimen (ie, 600 mg loading dose followed by 300 mg QW) will be below the mean Cmax of 12 mg/kg IV dose (421 mg/L), the highest single dose tested in healthy subjects that was well tolerated, providing additional confidence that this dose regimen should have an acceptable safety profile.

4.1.5 Rationale for biomarkers of drug response

Colonization of the nasal sinuses with Staphylococcus aureus may be a factor in the sustaining chronic sinusitis and progression of nasal polyposis. These microbes produce high-molecular-weight enterotoxins known to function as superantigens that can potently stimulate lymphocytes (12). Coincidental elevations in IgE specific for Staphylococcal enterotoxins have been observed in serum and nasal secretions in patients with nasal polyposis (Bachert) and may participate in chronic inflammation by priming regional immune cells (eg, mast cells and basophils that express high-affinity FceR1 and eosinophils and lymphocytes that express low-affinity FcεRII (CD23) to respond to secreted enterotoxin antigens. In addition, IgE-coated cells sensitized to other airborne
antigens likely participate in chronic sinusitis. IL-4 and IL-13 strongly promote the production of IgE via an immunoglobulin switching mechanism. Dupilumab should in principle suppress nasal production of IgE.

IL-4 and IL-13 also stimulate the airway mucosa, including nasal mucosa, to secrete Thymus- and activation-regulated chemokine (TARC), eotaxin-3 and periostin. TARC is a specific ligand for CC chemokine receptor (CCR) 4 which is highly expressed on Th2 cells. Thus, TARC potently recruits and activates Th2 cells, which further secrete IL-4 and IL-13 to perpetuate Th-2 driven inflammation.

Eotaxin-3 is a specific ligand for CCR3 which is highly expressed on eosinophils, and to a lesser degree on Th2 cells. Thus, this chemotaxin recruits and activates primarily eosinophils, but also Th2 cells, into the mucosa. Notably, pronounced eosinophilic infiltration is a common finding in nasal polyps. Given the extent of eosinophilia in these patients, the production of eosinophil cationic protein (ECP) is likely elevated.

Periostin has emerged as a protein associated with the molecular signature of chronic sinusitis. Periostin is thought to participate in airway remodeling by stimulating the secretion of the growth factor TGFβ. Elevated production of growth factors has been observed in nasal polyps.

Since the secretion of TARC, eotaxin-3 and periostin is dependent, at least in part, on Th2 cytokines and is associated with chronic inflammation of the airway mucosa, including sinus tissue, therapeutic intervention with dupilumab may overall suppress the secretion of these biomarkers into nasal secretions as well as into blood. Quantitation of these biomarkers in nasal secretions, as compared with blood, has the advantage of tissue specificity.

The eosinophilic nature of many, but not all nasal polyps, demonstrates a heterogeneity in phenotype that may have therapeutic consequences. It is possible that the extent of blood eosinophilia or concentrations of ECP and other biomarkers at baseline prior to treatment may have value in predicting clinical responses to dupilumab.

### 4.1.6 Overall benefits and risks assessment

Dupilumab prevents IL-4 and IL-13 binding and activation of their respective receptors involved in signaling pathways that play key roles in the pathophysiology of nasal polyposis. Phase 2a study in asthma demonstrated robust proof of efficacy for the tested product including a statistically significant improvement in the SNOT-22 score overall compared to placebo.

As of the cut-off date 30 November 2012, dupilumab has been administered as a single IV or SC injection to 126 healthy volunteers, as weekly SC injections for 4 weeks to 51 patients with AD and as weekly SC for 12 weeks to 24 patients with AD and 52 patients with asthma. Based upon the current available data for dupilumab and the review of the data by an independent data monitoring committee, no important identified risks have been established. Important potential risks based on the mechanism of action, administration route, or on the risks known with monoclonal antibodies in general, such as: immune-mediated injuries in different body systems, infections (including parasitic infections), severe injection site reactions, hypersensitivity/immunogenicity, malignancy, are being managed through:
• Exclusion of patients with immunosuppressed status or receiving immunosuppressants, and/or having an active viral bacterial, viral or parasitic infection, or are at high risk for developing or reactivating infections

• Monitoring of safety data, including online and periodic blinded safety monitoring team review and unblended IDMC review

The safety data available to date and the potential benefit of Dupilumab in patients with nasal polyposis support development of this compound in NP. The proposed ACT12340 study will provide the basis of a first benefit-risk of Dupilumab in NP.
5 STUDY OBJECTIVES

5.1 PRIMARY

- To evaluate the efficacy of dupilumab in the treatment of bilateral NP by assessment of the endoscopic nasal polyp score in comparison to placebo

5.2 SECONDARY

To evaluate dupilumab in patients with bilateral nasal polyps, with regards to:

- Symptoms of sinusitis
- CT scan changes
- Nasal polyp score in the sub-group of patients with co-morbid asthma
- Safety and tolerability
- Pharmacodynamic responses based on suppression of TH2 biomarkers
- Concentrations of dupilumab in serum
- Immune response to dupilumab (Anti-drug antibodies (ADA))
- Effect of dupilumab in patient reported outcomes and QoL scales
6 STUDY DESIGN

6.1 DESCRIPTION OF THE PROTOCOL

ACT12340 is a randomized, double-blind, phase 2, placebo controlled, 2 arm study to evaluate dupilumab administered QW subcutaneously (SC) for 16 weeks in patients with bilateral nasal polyposis and chronic symptoms of sinusitis.

Approximately 56 patients will be randomized into 2 treatment groups of 28 patients per group.

6.2 DURATION OF STUDY PARTICIPATION

6.2.1 Duration of study participation for each patient

The clinical trial will consist of 3 periods:

- Screening run in up to 4 weeks
- Randomized Dupilumab/Placebo Treatment Period (16 weeks)
- Post-treatment Period for PK, immunogenicity, safety, efficacy (16 weeks)

The total duration of the study participation for each patient is up to 36 weeks.

6.2.2 Determination of end of clinical trial (all patients)

It is planned that recruitment will stop when approximately 56 patients NP are randomized.

To ensure at least 28 patients with co-morbid asthma needed for subgroup analysis:

- Recruitment of NP patient without co-morbid asthma will stop when approximately 28 patients without asthma are randomized

The end of the clinical trial is defined as the last patient’s last visit/contact.

6.3 INTERIM ANALYSIS

An early analysis will be performed at the end of the treatment phase of all patients. This analysis will be the final on-treatment analysis. Procedure to maintain study integrity with respect to the subsequent post-treatment follow up visits, safety visits and analyses are described in Section 11.4.6. A Key Results Summary for the early analysis will be prepared.
6.4 STUDY COMMITTEES

A data monitoring committee (DMC) is commissioned for the dupilumab clinical development program. This committee is comprised of externally-based individuals with expertise in the diseases under study, biostatistics, or clinical research. The primary responsibilities of the DMC are to review and evaluate the safety data during the course of the trial and make appropriate recommendations regarding the conduct of the clinical trial to the Sponsor.

The DMC procedures and safety data to be reviewed by the DMC is described in the DMC charter. In the above capacities, the DMC is advisory to the Sponsor. The Sponsor is responsible for promptly reviewing and for taking into account in a timely manner the recommendations of the DMC in terms of trial continuation with or without alterations or of potential trial termination.
7 SELECTION OF PATIENTS

7.1 INCLUSION CRITERIA

Patients with:

I 01. A minimum bilateral nasal polyp score of 5 out of a maximum score of 8 for both nostrils (with at least a score of 2 for each nostril) despite completion of a prior INCS treatment for at least 8 weeks before screening. (See Section 9.1 for additional information regarding endoscopic nasal polyp score)

I 02. Presence of at least two of the following symptoms prior to screening: nasal blockade/obstruction/congestion or nasal discharge (anterior/posterior nasal drip); facial pain/pressure; reduction or loss of smell

I 03. Signed written informed consent

7.2 EXCLUSION CRITERIA

Patients who have met all the above inclusion criteria listed in Section 7.1 will be screened for the following exclusion criteria which are sorted and numbered in the following 3 subsections:

7.2.1 Exclusion criteria related to study methodology

E 01. Patients <18 or >65 years of age

E 02. Any technical/administrative reason that makes it impossible to randomize the patient in the study

E 03. Patient who has previously participated in any clinical trial of Dupilumab

E 04. SNOT22<7

E 05. Patient who has taken other investigational drugs or prohibited therapy for this study within 2 months before screening or 5 half-lives, whichever is longer:

- who have required a burst of oral corticosteroids (OCS) or intranasal corticosteroid drops within the 2 months before screening or are scheduled to receive OCS during the study period for another condition
- mAB and immunsupressive treatment
- Anti-immunoglobulin E (IgE) therapy (omalizumab) within 130 days of Visit 1
- Leukotriene antagonists / modifiers for patients who were not on a continuous treatment for ≥30 days prior to Visit 1
Initiation of allergen immunotherapy within 3 months prior to Visit 1 or a plan to begin therapy during the Screening Period or the Randomized Treatment Period

E 06. Patients who have undergone any nasal surgery within 6 months before screening or have had more than 2 surgeries for nasal polyps in the past

E 07. Patients with conditions/concomitant diseases making them non evaluable for the primary efficacy endpoint such as:
   - Antrochoanal polyps
   - Nasal septal deviation that would occlude at least one nostril
   - Acute sinusitis, nasal infection or upper respiratory infection at screening or in the 2 weeks before screening
   - Ongoing rhinitis medicamentosa
   - Churg-Strauss syndrome, Young’s syndrome, Kartagener’s syndrome or dyskinetic ciliary syndromes, Cystic fibrosis
   - Signs or a CT scan suggestive of Allergic fungal rhinosinusitis

E 08. Patients with co-morbid asthma are excluded if:
   - Forced expiratory volume (FEV1) is 60% (of predicted normal) or less
   - An exacerbation requiring systemic (oral and/or parenteral) steroid treatment or Hospitalization (>24h) for treatment of asthma, has occurred within 3 months prior screening
   - Are on a dose higher than 1000 μg fluticasone or the equivalent of inhaled corticosteroids (Appendix B)

E 09. Patients with short life expectancy (less than 6 months)

E 10. Patients receiving concomitant treatment prohibited in the study (see Section 8.8.1)

E 11. Patient is the Investigator or any Sub-Investigator, research assistant, pharmacist, study coordinator, other staff or relative thereof directly involved in the conduct of the protocol

E 12. Uncooperative or any condition that could make the patient potentially non-compliant to the study procedures.

7.2.2 Exclusion criteria related to the active comparator and/or mandatory background therapies

E 13. Refer to National Product labeling for all contraindications or warning/precaution of use related to mometasone furoate nasal spray
7.2.3 Exclusion criteria related to the current knowledge of Sanofi compound

E 14. Pregnant or intent to become pregnant during the study, or breast-feeding women

E 15. Women of childbearing potential (pre-menopausal female biologically capable of becoming pregnant) who:

- Do not have a confirmed negative serum β-hCG test at Visit 1
- Who are not protected by one of the following acceptable forms of effective contraception during the study:
  - Established use of oral, injected or implanted hormonal contraceptive
  - "Double barrier" methods (ie, Double Intrauterine device [IUD] with copper or intrauterine system [IUS] with progestogen and barrier contraceptive [condom, diaphragm or cervical/vault caps] used with spermicide [foam, gel, film, cream or suppository])
  - Female sterilization (eg, tubal occlusion, hysterectomy or bilateral salpingectomy)
  - Male sterilization with post-vasectomy documentation of the absence of sperm in the ejaculate; for female patients the study, the vasectomized male partner should be the sole partner for that patient
  - True abstinence; periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) is not an acceptable method of contraception

E 16. Concomitant severe diseases (eg, active and inactive pulmonary tuberculosis, Diabetes mellitus etc.)

E 17. Diagnosed active parasitic infection; suspected or high risk of parasitic infection, unless clinical and (if necessary) laboratory assessments have ruled out active infection before randomization

E 18. History of human immunodeficiency virus (HIV) infection or positive HIV screen (Anti-HIV- and HIV-2 antibodies) at Visit 1

E 19. Evidence of acute or chronic infection. Visit 1 or Visit 2 oral temperature >38° C or a chronic, persistent, or recurring infection requiring active treatment with antibiotics, antivirals, or antifungals within 4 weeks prior to the screening visit or other frequent, recurrent infections per Investigator judgment

E 20. Known or suspected immunosuppression, including history of invasive opportunistic infections (eg, tuberculosis, histoplasmosis, listeriosis, coccidioidomycosis, pneumocystosis, aspergillosis), despite infection resolution

E 21. Live vaccinations within 12 weeks prior to Visit 1 or planned vaccinations during the study (Appendix A)
E 22. Patients with active autoimmune disease or patients using immunosuppressive therapy for autoimmune disease (eg, Hashimoto’s thyroiditis, Graves’ disease, inflammatory bowel disease, primary biliary cirrhosis, systemic lupus erythematosus, multiple sclerosis, psoriasis vulgaris, rheumatoid arthritis)

E 23. Patients with positive or indeterminate hepatitis B surface antigen (HBsAg), hepatitis B core antibody (HBcAb), or hepatitis C antibody at Visit 1.

E 24. Patients with liver injury related criteria:
   - Underlying hepatobiliary disease
   - or ALT>3 ULN
8 STUDY TREATMENTS

8.1 INVESTIGATIONAL MEDICINAL PRODUCT(S)

8.1.1 Dupilumab
Sterile dupilumab will be provided

8.1.2 Placebo
Sterile placebo for dupilumab will be provided

8.1.3 Preparation of investigational product
Instructions for IMP preparation are provided in the pharmacy manual. The IMP should be administered within 3 hours of preparation in the syringe.

8.1.4 Dosing schedule
The IMP is administered every $7 \pm 2$ days (QW). The doses of IMP must be separated by $\geq 5$ days to avoid an overdose. At Visit 2 the Investigator or delegate will perform 2 injections. After V2 one injection of IMP will be performed weekly at the investigational site throughout the randomized treatment period.

The IMP will be administered following clinic procedures and blood collection. Patients should be monitored for at least 1 hour after each study-site administered investigational product administration, for any signs or symptoms of a local site injection or hypersensitivity reaction.

Subcutaneous injection sites should be alternated between the 4 quadrants of the abdomen (avoiding navel and waist areas) or upper thighs so that the same site is not injected for two consecutive times/weeks.

8.2 NON-INVESTIGATIONAL MEDICINAL PRODUCT

8.2.1 Intranasal corticosteroid
On a daily basis throughout the study, the patient will use an electronic diary to record daily use of MFNS. Mometasone furoate (NASONEX®) 50 micrograms/actuation Nasal Spray, is contained in a bottle, that contains 18 g (140 actuations) of product formulation.
8.2.1.1 Screening Period

Prior to screening, patients must be on a stable administration of intranasal corticoids for ≥2 month prior to Visit 1.

If the patient is using an alternative INCS product other than MFNS prior to the screening visit, at V1, the Investigator must switch the patient to MFNS.

After V1 all patients will enter a run-in period of 4 weeks where they will receive MFNS:

- 2 actuations (50 µg/actuation) in each nostril twice daily (total daily dose of 400 µg), unless they’re intolerant to BID regimen of INCS in which case, they can stay on the lower dose (QD) regimen

8.2.1.2 Randomized Treatment Period

During the Randomized Treatment Period, patients continue the stable dose of mometasone furoate:

- MFNS two actuations in each nostril BID or QD (in case patient cannot tolerate the high dose)

8.2.1.3 Post-treatment Period

Upon completing the Randomized Treatment Period (or following early discontinuation of IMP), patients can continue treatment with the stable dose of MFNS maintained over the randomized treatment period, or modify treatment based on medical judgment.

8.2.2 Reliever or background medication

The list of reliever medication or background medication allowed as needed during the study is provided in Section 8.8.2.

8.3 BLINDING PROCEDURES

8.3.1 Methods of blinding

Dupilumab and placebo will be provided in identically matched glass 5 mL vials. To protect the blind, each treatment kit will be prepared such that the treatments are identical and indistinguishable and will be labeled with a treatment kit number. The randomized treatment kit number list will be generated by Sanofi.

In accordance with the double-blind design, study patients, investigators, and study site personnel will remain blinded to study treatment and will not have access to the randomization (treatment codes) except under circumstances described in Section 8.3.2.

Refer to Section 10.5 for suspected unexpected adverse drug reaction unblinding by the Sponsor.
8.3.2 Randomization code breaking during the study

In case of an adverse event (AE), the code should only be broken in circumstances when knowledge of the investigational medicinal product (IMP) is required for treating the patient.

If possible, a contact should be initiated with the Monitoring Team before breaking the code. Code breaking can be performed at any time by using the proper module of the interactive voice response system (IVRS)/interactive web response system (IWRS) and/or by calling any other phone number provided by the Sponsor for that purpose. If the blind is broken, the Investigator should document the date, time of day and reason for code breaking.

If the blind is broken, the patient must be withdrawn from the treatment. Patients who discontinue treatment early are assessed as soon as possible using the procedures normally planned for the End-of-treatment Visit and the four Post-treatment Period Visits.

At the facilities where the pharmacokinetic measurements, anti-drug antibodies and selected biomarkers are determined, the samples will be analyzed prior to data base lock leading to unblinding of responsible bioanalysts. Bioanalysts are excluded from the clinical trial team.

The Data Monitoring Committee will receive blinded by treatment group or unblinded (if necessary) confidential reports from an independent statistician for review, which have to be handled strictly confidentially. None of these reports can be delivered to unauthorized persons.

8.4 METHOD OF ASSIGNING PATIENTS TO TREATMENT GROUP

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

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

Patients who meet the entry criteria will be randomized to receive either dupilumab or placebo.

Patients who fail to meet exclusion criteria may be re-screened once during the open screening period of the study; a different patient identification will be issued. Re-screening is not permitted if the patient fails to meet inclusion criteria. There is no requirement for a waiting period between the screen-failure date and the re-screening date. The IVRS/IWRS report will flag re-screened patients. Patients that are re-screened must sign a new consent form and all Visit 1 procedures must be repeated.

The Investigator obtains treatment kit numbers at randomization and subsequent scheduled visits via an Interactive Voice Response System/Interactive Web Response System (IVRS/IWRS) that will be available 24 hours a day.
Patients will be randomized using a 1:1 randomization ratio for dupilumab 300 mg q week and placebo. Randomization will be stratified by Visit 1 medical history of asthma and by V2 nasal biopsy (details will be specified in the IVRS/IWRS specifications document).

A total of 56 patients shall be randomized and at least 50% of them shall have co-morbid asthma. To ensure at least 28 patients with co-morbid asthma needed for subgroup analysis:

- Recruitment of NP patient without co-morbid asthma will stop when approximately 28 patients without asthma are randomized, and
- Patients with co-morbid asthma will continue to be randomized to complete a total number of 56 randomized NP patients.

A randomized patient is defined as a patient who is registered and assigned with a treatment kit number from the centralized treatment allocation system, as documented from its log file. A patient cannot be randomized more than once in the study.

8.5 PACKAGING AND LABELING

Dupilumab and placebo will be supplied as single vial packed in a box. Both vial and box will be labeled with a single-panel label.

MFNS will be supplied as single bottle packed in a box. Both bottle and box will be labeled with a single-panel label

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

8.6 STORAGE CONDITIONS AND SHELF LIFE

Dupilumab and placebo investigational product should be stored at a temperature between 2°C and 8°C. MFNS storage conditions are specified on the bottle and its box. All IMP and NIMP should be stored in an appropriate, locked room under the responsibility of the Investigator or other authorized persons (eg, pharmacists) in accordance with local regulations, policies and procedures.

Control of storage conditions, especially control of temperature (eg, refrigerated storage) and information on in-use stability and instructions for handling the Sanofi compound should be managed according to the rules provided by the Sponsor.

8.7 RESPONSIBILITIES

The Investigator, the hospital pharmacist, or other personnel allowed to store and dispense the IMP and the NIMP supplied by the Sponsor, will be responsible for ensuring that the IMP and the NIMP supplied by the Sponsor used in the clinical trial is securely maintained as specified by the Sponsor and in accordance with applicable regulatory requirements.
All IMP and the NIMP supplied by the Sponsor will be dispensed in accordance with the Investigator's prescription and it is the Investigator's responsibility to ensure that an accurate record of IMP and NIMP issued and returned is maintained.

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

A potential defect in the quality of IMP and the NIMP supplied by the Sponsor 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 IMP and the NIMP supplied by the Sponsor and eliminate potential hazards.

Under no circumstances will the Investigator supply IMP and the NIMP supplied by the Sponsor to a third party, allows the IMP and the NIMP supplied by the Sponsor to be used other than as directed by this clinical trial protocol, or dispose of IMP and the NIMP supplied by the Sponsor in any other manner.

8.7.1 Treatment accountability and compliance

The Investigator or pharmacist will also keep accurate records of the quantities of the IMP dispensed, used and unused and NIMP dispensed, used, unused, and returned by each patient. The IMP and NIMP dispensation/accountability log is to be updated each time IMP is dispensed and NIMP is dispensed or returned. Any NIMP not returned (even if considered empty) must be accounted for with a comment in the log. The study monitor will periodically check the supplies of the IMP and NIMP held by the Investigator or pharmacist to verify accountability.

Patients will be instructed to return with their used and unused NIMP supplied by the Sponsor to the investigation site. Compliance with IMP and NIMP administration will be reviewed with the patient at each visit. For IMP, compliance will be assessed by inspection of the vial packs and checking the used and unused vials and the remaining volume of solution in each vial, if any. For NIMP compliance with use of the mandatory background therapy (MNFS), is verified based on MFNS use recorded on the patient electronic diary.

8.7.2 Return and/or destruction of treatments

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

A concomitant medication is any treatment received by the patient concomitantly to the IMP.

8.8.1 Prohibited Concomitant Medication

The following concomitant treatments are not permitted during Screening Period and the Randomized treatment period:

- Use of intranasal medication that would interfere with the symptoms of diseases (antihistamines, nasal atropine, ipratropium bromide, nasal cromolyn), except nasal saline
- INCS drops
- Systemic corticosteroid
- Decongestion (topical or systemic) is not allowed, except before endoscopy
- Long term use of systemic antibiotics (for 2 weeks or more)
- Lipoxygenase inhibitors
- Any immunosuppressive treatment including but not limited to methotrexate, cyclosporine, mycophenolate, tacrolimus, gold, penicillamine, sulfasalazine, hydroxychloroquine, azathioprine, cyclophosphamide
- Anti-immunoglobulin E (IgE) therapy (omalizumab)
- Aspirin or NSAID in patients with hypersensitivity to aspirin or NSAID

8.8.2 Permitted Concomitant Medication

The following treatments are allowed:

- MFNS during the screening and throughout the whole study
- Nasal normal saline
- Topical decongestants ex. Oxymetazoline hydrochloride (to reduce the swelling and widen the path for the endoscope), as well as a topical anesthetic ex. Lidocaine are allowed before endoscopy
- Short term use of Antibiotics (<2 weeks) would be allowed during the study
- For patients with asthma:
  - SABA, LABA
  - Methylxanthines (eg, theophylline, aminophyllines)
  - Inhaled corticosteroids on a stable dose ≤1000 µg Fluticasone (or the equivalent dose of another inhaled CS (see Appendix B) only for patients that were on a stable dose ≥30 days prior to Visit 1
- Leukotriene antagonists / modifiers are permitted during the study, only for patients that were on a continuous treatment for ≥30 days prior to Visit 1

- Systemic antihistamines

- Initiation of allergen immunotherapy (allergen immunotherapy in place for ≥3 months prior to Visit 1 is permitted)
9 ASSESSMENT OF INVESTIGATIONAL MEDICINAL PRODUCT

9.1 PRIMARY ENDPOINT

9.1.1 Primary efficacy endpoint

The primary endpoint of the study is the change from baseline at week 16 in bilateral endoscopic Nasal Polyp Score (13). This score (NPS) is the sum of the right and left nostril scores, as evaluated by means of nasal endoscopy. NP is graded based on polyp size described in the Table 1

<table>
<thead>
<tr>
<th>Polyp score</th>
<th>Polyp size</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No polyps</td>
</tr>
<tr>
<td>1</td>
<td>Small polyps in the middle meatus not reaching below the inferior border of the middle turbinate</td>
</tr>
<tr>
<td>2</td>
<td>Polyps reaching below the lower border of the middle turbinate</td>
</tr>
<tr>
<td>3</td>
<td>Large polyps reaching the lower border of the inferior turbinate or polyps medial to the middle turbinate</td>
</tr>
<tr>
<td>4</td>
<td>Large polyps causing complete obstruction of the inferior nasal cavity</td>
</tr>
</tbody>
</table>

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

Standard video sequences will be downloaded or sent to centralized reader. Centralized imaging data assessments and scoring by an independent physician reviewer for the imaging data will be performed for all endoscopies. To confirm eligibility at V2, only the V1 central reading will be made available to the site. The final results of central reading will be made available after the study.

For the analysis of primary endpoint, central reading of V2 will be used for comparison with EOT reading. The sites will remove subject-identifying information from the imaging data header prior to sending the imaging data to the central reader.

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

9.1.2 Secondary efficacy and other exploratory endpoint

Efficacy

Change from baseline at Week 16 in:

- Patient reported symptoms
- 22-item Sinonasal Outcome Test (SNOT-22)
- Subject-assessed nasal congestion/obstruction, anterior rhinorrhea (runny nose), posterior rhinorrhea (post nasal drip), and loss of sense of smell, (daily AM and PM e-diary) month average
- Number of nocturnal awakenings
- Patient-rated rhinosinusitis symptoms severity using a visual analog scale (VAS)
  - Nasal peak inspiratory flow (NPIF)
  - Smell test (UPSIT)
  - In NPS in patients with co-morbid asthma
  - In CT scan assessments

Time to first response (≥1 point improvement) in NPS

**Exploratory endpoints**

- Change from baseline at Week 16 in FEV1 (overall and in sub-group with asthma)
- 5-item Asthma control questionnaire (ACQ-5) in asthma sub-group
- Time to study treatment discontinuation
- Incidence of treatment discontinuation due to need for OCS or nasal surgery

**Quality of life (QoL) endpoints**

Change from baseline at Week 16 in:

- 36-item short form health survey (SF36)
- European quality of life scale (EQ-5D)
- Nasal polyp related resource use questionnaire

**9.1.2.1 Disease-specific tests and assessments**

9.1.2.1.1 *Computed tomography (CT)*

CT of the sinuses should be performed before V2 and at EOT.

For both Lund-Mackay scores and 3D volumetric measurement of the maxillary sinus, the same acquisitions (sequences) will be used for centralized imaging data assessments and scoring by an independent physician reviewer for the imaging data. Central reading of V2 will be used for comparison with EOT. The final results of central reading will be made available after the study. Details on CT will be available in a separate operational manual provided to the sites.
9.1.2.1.1 Lund-Mackay score

Lund-Mackay system is based on localization with points given for degree of opacification: 0 = normal, 1 = partial opacification, 2 = total opacification. These points are then applied to the maxillary, anterior ethmoid, posterior ethmoid, sphenoid, frontal sinus on each side. The osteomeatal complex is graded as 0 = not occluded, or 2 = occluded deriving a maximum score of 12 per side (14). This scoring system has been validated in several studies (15) (16).

For patients in whom the osteomeatal complex (OC) is missing (because of a previous surgery) the reader should consider the location of the former OC and provide a scoring (as if the OC was there).

9.1.2.1.1.2 Three-Dimensional volumetric measurement of the maxillary sinus

This method is used to calculate: (17)
- the volume of the air (mL)
- the volume of mucosa (mL)
- % occupied by disease
- thickness of lateral wall

For the analysis, central reading before V2 will be used for comparison with EOT reading. The sites will remove subject-identifying information from the imaging data header prior to sending the imaging data to the central reader. The % change in opacification from BL to EOT will be calculated.

9.1.2.1.2 Nasal Peak inspiratory flow (NPIF)

Nasal peak flow evaluation represents a physiologic measure of the air flow through both nasal cavities during forced inspiration and/or expiration expressed in liter per minute. The NPIF is the best validated technique for the evaluation of nasal flow through the nose. Nasal inspiration correlates most with the subjective feeling of obstruction and is the best validated technique for monitoring nasal flow in clinical trials.

At screening (Visit 1), patients will be issued an NPIF meter for recording morning (AM) and evening (PM) NPIF. Patients will be instructed on the use of the device, and written instructions on the use of the NPIF meter will be provided to the patients. In addition, the investigator will instruct the patients on how to record the following variables in the e-diary on a daily basis
- AM NPIF performed within 15 minutes after arising (between 6 am and 10 am) prior to taking MFNS
- PM NPIF performed in the evening (between 6 pm and 10 pm) prior to taking MNFS

Three NPIF efforts will be performed by the patient; all 3 values will be recorded by the patient in the e-diary, and the highest value will be used for evaluation. The procedure takes about 5 minutes.
Baseline AM NPIF will be the mean AM measurement recorded for the 28 days prior to the first
dozen of investigational product, and baseline PM NPIF will be the mean PM measurement
recorded for the 28 days prior to the first dose of investigational product.

The nasal flow is expressed in liter per minute, and consecutive measurements are performed.
Taking the best of 3 outcomes with less than 10% variation is considered to be the best means of
expression of the result (18).

9.1.2.1.3 Smell test: University of Pennsylvania Smell Identification Test (UPSIT)

The UPSIT test is a rapid and easy-to-administer method to quantitatively assess human olfactory
function. The UPSIT shows a high test-retest reliability (r: 0.981) and scores on this test are
strongly correlated with the detection threshold for phenyl ethyl alcohol in the same individuals.
When the UPSIT is administered in the standardized manner, clinical subjects show a high degree
of uniformity in UPSIT performance when tested in different laboratories.

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

The 40-odorant UPSIT is used in over 1500 clinics and laboratories throughout the United States,
Canada, South America, and Europe, and has been administered to nearly 200,000 people since its
development in the early 1980s. A particular strength of this test is that it provides an olfactory
diagnosis based on comparing the patient's test score with normative data, providing a percentile
score of an individual relative to his or her age-matched normal group. Furthermore, a clinician
can distinguish patients with a normal sense of smell ("normosmia") from those with different
levels of reduction ("mild, moderate and severe microsmia") or loss ("anosmia") (18).

9.1.2.2 Disease-specific, daily symptom assessments

On a daily basis from V1 and throughout the study, the patient will use an electronic diary to:

- Respond to the morning and evening individual rhinosinusitis symptom questions using a
  0-3 categorical scale (where 0 = no symptoms, 1 = mild symptoms, 2 = moderate
  symptoms and 3 = severe symptoms) (2):
    - congestion and/or obstruction
    - anterior rhinorrhea (runny nose)
    - posterior rhinorrhea (post-nasal drip)
    - loss of sense of smell
- Record the number of nocturnal awakenings
The e-diary is dispensed at Visit 1 and information is downloaded from this device on the other indicated days. The average of the last 7 days before V2 is needed to determine the baseline value. For the BL to EOT analysis, 4 weeks average of total score (sum of all symptoms) or by each symptom will be used.

9.1.3 Safety endpoints

The same safety assessments will be applied across all arms. Adverse events, including serious adverse events (SAEs) and adverse events of special interest (AESI), will be collected at every visit. The Investigator will ask the patient how he/she has felt since the last study visit. The study specific and general safety criteria are detailed in Section 10.4. To assure the continuing safety of patients in this study, an independent DMC will be responsible for reviewing the safety data on a periodic basis throughout the course of the study as outlined in Section 6.4.

Safety Observations

The Investigator should take all appropriate measures to ensure the safety of the patients. Notably, he/she should follow up the outcome of SAEs /AESI until clinical recovery is complete and laboratory results have returned to normal or until progression has been stabilized or death. In all cases, this may imply that observations will continue beyond the last planned visit per protocol, and that additional investigations may be requested by the Sponsor.

When treatment is prematurely discontinued, the patient’s observations will continue until the end of the study as defined by the protocol for that patient.

In case of any SAE/AESI with immediate notification brought to the attention of the Investigator at any time after the end of the study for the patient and considered by him/her to be caused by the investigational product with a reasonable possibility, this should be reported to the Sponsor.

9.1.3.1 Adverse events

Adverse events for each patient will be monitored and documented from the time the patient gives informed consent at Visit 1 until the End-of Study Visit, except for:

SAEs

AEs that are ongoing at database lock.

Adverse events, adverse events with special interest (AESI) and serious adverse events (SAEs) will be reported as described in Section 10.4.1.3

9.1.3.2 Vital signs

Vital signs, including blood pressure (mmHg), heart rate (beats per minute), respiratory rate (breaths per minute), body temperature (degrees Celsius) and body weight (kg) will be measured at every visit. Height (cm) will be measured at screening (Visit 1) only. Vital signs will be
measured in the sitting position using the same arm at each visit, and will be measured prior to receiving investigational product at the clinic visits.

9.1.3.3 Physical Examination

Physical examinations will include an assessment of general appearance, skin, eyes, ear/nose/throat, heart, chest, abdomen, reflexes, lymph nodes, spine, and extremities. All deviations from normal will be recorded, including those attributable to the patient’s disease. Physical examinations will be performed at screening (Visit 1), Week 16 (End-of-Treatment Visit whichever comes first) and End of Study Visit.

9.1.3.4 Electrocardiogram variables

One recording of a standard 12-lead ECG will be performed at screening (Visit 1), Week 8, W12, W16 (or End-of-Treatment Visit whichever comes first) and End of Study Visit. At the post-randomization visits, ECGs will be performed prior to investigational product administration. All ECGs will be performed with the patient in a reclined position. A minimum of 3 complexes in an appropriate lead (lead II) will be averaged to determine the PR-interval, QT/QTc-interval, QRS-complex and heart rate will be measured for each ECG.

All measurements will be made from a single lead: Lead II, or Lead I if Lead II is not possible or lead V5 if Lead II and Lead I are not possible.

9.1.3.5 Laboratory safety variables

The clinical laboratory tests will be conducted by an accredited (College of American Pathologists or equivalent) central laboratory with national and regional clinical licenses as required for diagnostic testing and must provide evidence of participation in proficiency testing, as appropriate. After reviewing the laboratory report and evaluating any results that are outside the normal range, the Investigator must sign and date the laboratory report. Abnormal laboratory values that are considered to be clinically significant by the Investigator must be repeated as soon as possible after receiving the laboratory report to rule out laboratory error. Persistent abnormal laboratory values should be repeated until they return to normal or until an etiology of the persistent abnormality is determined.

Refer to Section 1.2 Study Flow Chart for the description of the clinical laboratory evaluations and the schedule of laboratory evaluations performed throughout this study.

The clinical laboratory parameters that will be measured in safety hematology and chemistry blood samples are:

Hematology: To include hemoglobin, hematocrit, platelet count, total white blood cell count with five-part differential count, and total red blood cell count.

Serum chemistry: To include: creatinine, blood urea nitrogen, glucose, uric acid, total cholesterol, total protein, albumin, total bilirubin, alanine aminotransferase, aspartate aminotransferase,
alkaline phosphatase, electrolytes (sodium, potassium, chloride), bicarbonate, and creatine phosphokinase.

Urine analysis including specific gravity, pH, glucose, ketones, blood, protein, nitrate, leukocyte esterase, urobilinogen and bilirubin (by dipstick). If any parameter on the dipstick is abnormal, a urine sample should be sent to the central laboratory for testing. If positive for proteins, microscopic analysis is performed by central laboratory. Testing is limited to visits at screening, Week 8, Week 16 (EOT), and Week 32 (EOS).

Viral serology testing at Visit 1 includes hepatitis screen (hepatitis B surface antigen (HBsAg), Hepatitis B IgM core antibody (HBcAb-IgM), hepatitis C antibodies (HC Ab), HIV screen (Anti-HIV-1 and HIV-2 antibodies),

Anti-nuclear antibody (ANA): If the titer is ≥1:160 at any time, then the sample will be tested for the presence of anti-ds DNA antibody. If the ANA titer is ≥1:160 at the End of Treatment visit, then it will be rechecked at the End of Study visit.

Decision trees for the management of certain laboratory abnormalities by Sanofi are provided in Appendix D.

9.1.3.6 Pregnancy test

A serum pregnancy test (β-human chorionic gonadotrophin) will be performed at screening (Visit 1) in women of childbearing potential, and a urine pregnancy test will be performed at Visit 2 prior to randomization. A negative result must be obtained at Visit 1 and 2 prior to randomization. Additional urine pregnancy tests will be performed monthly until the End of Study Visit.

9.2 OTHER ENDPOINTS

9.2.1 Pharmacokinetics and anti-drug antibodies

9.2.1.1 Sampling time

Predose blood samples will be collected for determination of serum functional dupilumab and anti-dupilumab antibodies as designated in the study flow chart (see Section 1.2). The date of collection should be recorded in the patient e-CRF. The date and time also will be collected on the central laboratory requisition form and entered into the database through data transfers from the central laboratory.

If an SAE occurs in a patient, blood samples should be collected for determination of functional dupilumab concentration, and anti-dupilumab antibody assessment at or near the onset and completion of the occurrence of the event, if possible. The exact date and time of sample collection must be recorded and entered into the database by the central laboratory. An unscheduled PK page in the e-CRF must be completed as well.
9.2.1.2 Pharmacokinetics and Anti-drug Antibody handling procedure

Special procedures for collection, storage, and shipping of serum are described in separate operational manuals. An overview of handling procedure for samples used in the determination of drug concentration and anti-drug antibodies will be provided to the sites in a separate operational manual.

<table>
<thead>
<tr>
<th>Sample type</th>
<th>dupilumab</th>
<th>Anti-dupilumab antibody</th>
</tr>
</thead>
<tbody>
<tr>
<td>Matrix</td>
<td>Serum</td>
<td>Serum</td>
</tr>
<tr>
<td>Blood sample volume</td>
<td>5 mL</td>
<td>5 mL</td>
</tr>
<tr>
<td>Anticoagulant</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Blood handling procedures</td>
<td>See Operational Manual</td>
<td>See Operational Manual</td>
</tr>
<tr>
<td>Serum aliquot split</td>
<td>Two aliquots</td>
<td>Two aliquots</td>
</tr>
<tr>
<td>Storage conditions</td>
<td>&lt; 6 months: below -20°C</td>
<td>&lt; 6 months: below -20°C</td>
</tr>
<tr>
<td></td>
<td>&lt; 24 months: below -80°C (preferred)</td>
<td>&lt; 24 months: below -80°C (preferred)</td>
</tr>
<tr>
<td>Serum shipment condition</td>
<td>In dry ice</td>
<td>In dry ice</td>
</tr>
</tbody>
</table>

9.2.1.3 Bioanalytical method

Serum samples will be assayed using validated methods as described in Table 3.

<table>
<thead>
<tr>
<th>Analyte</th>
<th>Functional dupilumab</th>
<th>Anti-dupilumab antibody</th>
</tr>
</thead>
<tbody>
<tr>
<td>Matrix</td>
<td>serum</td>
<td>serum</td>
</tr>
<tr>
<td>Analytical technique</td>
<td>ELISA</td>
<td>Electrochemiluminescence</td>
</tr>
<tr>
<td>Lower limit of quantification</td>
<td>0.078 mg/L</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Site of bioanalysis</td>
<td>Regeneron</td>
<td>Regeneron</td>
</tr>
</tbody>
</table>
9.2.1.4 Pharmacokinetics parameters

Predose functional dupilumab concentrations in serum at Visit 2 (Day 1), dupilumab trough concentrations at Week 2, Week 4, Week 8, Week 12, Week 16, and follow-up serum dupilumab at Week 20, Week 24, Week 28 and Week 32 will be provided.

Anti-dupilumab antibody status (negative or titer value) at Visit 2 (Day 1), Week 2, Week 4, Week 8, Week 12, Week 16, and Week 32 will be provided.

Patients with ADA titers ≥1000 at the end of study visit will be scheduled to return approximately 6 months later for an additional assessment of ADA titer. Further follow-up will be considered based on the overall assessment of antibody titers and clinical presentation.

9.2.2 Pharmacodynamics

Several biomarkers related to chronic sinusitis and Th2 polarization will be assessed for their value in predicting therapeutic response (or toxicity, if needed) and/or in documenting the time course of drug response. More detailed information on the collection, handling, transport and preservation of samples will be provided in a separate laboratory manual.

Patients, investigators and site personnel will not have access to assay results for total IgE, ECP, Staphylococcal aureus enterotoxin specific IgEs, TARC, periostin or eotaxin-3 while the study is ongoing, as the related data are not essential for patient care and have the potential for unblinding the study treatments. Assay results for the other tests, designated as “For Research Only”, will not become part of any medical records, but will be reported in the final Clinical Study Report.

Blood eosinophil count will be measured as part of the standard 5-part WBC differential cell count on a hematology autoanalyzer.

9.2.2.1 Serum biomarkers

Sufficient blood should be collected to prepare and store two 1-mL aliquots for each biomarker at each of their specified collection time points.

All blood samples should be allowed to clot in serum separation tubes for 30 minutes at room temperature, then centrifuged at 1500 to 2000 x g for 15 minutes until clot and serum are separated by a well formed polymer barrier. Using a plastic disposable pipette, the serum should be transferred into screw-cap cryovials, appropriately labeled and immediately placed in the upright (cap up) position in a freezer maintained at –20°C or colder (preferably -70 °C) until shipped later on dry ice.

The following assays will be performed on serum as per the study flow charts.

- Total IgE (ImmunoCAP® FEIA method or equivalent): store two 1-mL serum aliquots.
- Staphylococcal enterotoxin A IgE and Staphylococcal enterotoxin B IgE (ImmunoCAP® FEIA method): store two 1-mL serum aliquots.
- Eosinophil cationic protein (ECP) (ImmunoCAP® FEIA method): store two 1-mL serum aliquots.
- Thymus and activation-regulated chemokine (TARC) will be assayed with a validated enzyme immunoassay (Human TARC Quantikine ELISA kit; R&D Systems): store two 1-mL serum aliquots.
- Periostin will be assayed with a validated immunoassay (Human Periostin DuoSet ELISA Development kit; R&D Systems): store two 1-mL serum aliquots.

9.2.2.2 **Allergen-specific IgE panel (region-specific)**

To assess serological atopy at baseline and further assess shifts in serum IgE during treatment, antigen-specific IgE will be quantified using ImmunoCAP assays. Panels of antigen-specific IgE will be customized according to global region for clinical sites to better assure detection of atopy. Two 1-mL serum aliquots will be prepared.

9.2.2.3 **Eotaxin-3 in plasma**

Sufficient blood should be collected into a green tube to prepare and store two 1-mL aliquots of heparinized plasma at each of the specified collection time points. Blood should be centrifuged soon after collection at a minimum of 1500 x g for 15 minutes until cells and plasma are well separated. Using a plastic disposable pipette, the plasma should be transferred into screw-cap cryovials, appropriately labeled and immediately placed in the upright (cap up) position in a freezer maintained at −20°C or colder (preferably -70 °C) until shipped later on dry ice.

9.2.2.4 **Residual serum and plasma**

Prior to use of residual serum and plasma for purposes not previously defined, approval for the intended use will be obtained from the local IRB / Ethics Committee. All residual serum and plasma will be destroyed within 2 years of completion of the last visit for the last patient enrolled in the study.
9.2.2.5 Archival nasal secretions

Nasal secretions will be obtained by inserting nasal swabs bilaterally into the nasal cavity for five minutes. Precise instructions for isolating nasal secretions from the swabs and preserving aliquots will be provided separately. Some of the nasal secretions may be used for validation of assay methodology for this unique biomatrix. The nasal secretions will be preserved for possible analysis of additional biomarkers related to nasal polyposis and responses to dupilumab treatment.

9.2.2.6 Nasal polyp biopsies

At selected clinical site(s) and with specific informed consent, nasal polyp tissue will be optionally obtained by biopsy. A baseline biopsy will be obtained at V2 of the study. After randomization, another biopsy of nasal polyp tissue will be obtained at the end of treatment visit (Week 16).

The complete details on tissue collection and processing will be provided separately.

Briefly, the biopsied polyp tissue will be weighed (mg) and then cut into cubes of approximately 0.5 cm in each dimension. All but one cube will be individually placed into labeled cryotubes and immediately frozen with liquid nitrogen, and then maintained at -70 °C or colder until shipped on dry ice to a central storage site or laboratory. Nasal polyp tissue will be subsequently assessed for various biomarkers of inflammation and disease process or response. Any remaining tissue will be discarded within five years of the completion of the last visit for the last patient in the study.

One cube of tissue will be placed in an equivalence of 5 to 10 volumes of RNAlater® Tissue Collection RNA Stabilization Solution (Ambion) and kept overnight at about 4 °C, not frozen, to allow the preservative time to enter the tissue. On the following day, the preserved tissue will be separated from the stabilizer fluid (by decanting or transfer) and then placed in a freezer at -70 °C or colder. Samples can be thawed subsequently at room temperature and refrozen without significantly affecting the amount or the integrity of the recoverable RNA. RNA will be extracted and used for expression profiling (e.g., microarray, transcriptome sequencing or quantitative RT-PCR). The RNA analyses and conditions of sample storage will be subject to the same restrictions as described for whole blood RNA in the following section, “Pharmacogenomic assessment”.

The Sponsor has included safeguards for protecting patient confidentiality. Genetic samples will be used only for this specific analysis and then the sample and the extracted DNA and RNA will be destroyed upon completion of this analysis and the clinical study report, so no further information can be obtained from it.

9.2.2.7 Optional stored DNA and RNA samples

Pharmacogenomic testing is optional and voluntary. For those patients who signed the optional pharmacogenomic informed consent form, a blood sample will be collected at the study visit as specified in the study flow chart and this sample will be stored for future analysis. Specific procedures for storage and shipping of pharmacogenomic samples will be provided in a lab manual. For DNA, blood will be collected using a 6-mL Vacutainer® (BECTON Dickinson)
containing K2 EDTA with HEMOGARD closure, gently inverted at least 8 times and immediately placed upright at -70 ºC until shipped on dry ice. For RNA, blood will be collected using a 2.5-mL draw PAXgene blood RNA tube (PreAnalytiX/Qiagen), gently inverted at least 8 times and kept upright at room temperature (18ºC-22ºC) or refrigerated (4 ºC) until shipped at room temperature. Special procedures for freezing blood collected in PAXgene tubes may be provided.

Under no circumstances will the DNA and RNA collection tubes be centrifuged.

DNA and RNA samples may be used to determine a possible relationship between genes and response to treatment with dupilumab and possible side effects to dupilumab. Genes that may be studied include those for the IL4R receptor, IL-4, IL-13 and STAT6 and additional genes that may potentially be part of the IL4R signaling pathway, nasal polyposis, or related eosinophilic or atopic indications (e.g., asthma).

This blood sample will be transferred to a contractor that will, on behalf of Sanofi, extract DNA and RNA from the samples; this contractor may be located in a country different than the country of sample origin.

This blood sample, and the DNA or RNA that is extracted from it, will be assigned a second number, a Genetic ID (de-identification code) that is different from the Subject ID. This “double coding” is performed to separate a subject’s medical information and DNA data.

The clinical study data (coded by Subject ID) will be stored in the clinical data management system (CDMS), which is a distinct database in a separate environment from the database containing the pharmacogenomic data (coded by Genetic ID). The key linking Subject ID and Genetic ID will be maintained by a third party, under appropriate access control. The matching of clinical data and pharmacogenomic data, for the purpose of data analysis, will be possible only by using this key, which will be under strict access control. All data will be reported only in coded form in order to maintain confidentiality.

The DNA and RNA will be stored, as applicable, in the US for samples collected in the Americas (e.g., USA, Canada, Latin America, etc), in Switzerland for samples collected in Europe, for up to 15 years from the completion of the clinical study report or as otherwise required by local regulations.

Special procedures for storage and shipping of pharmacogenomic samples will be described in a separate manual.

9.2.3 Quality of life/health economic variables/other endpoints

9.2.3.1 22-item Sinonasal Outcome Test

The SNOT-22 is a validated questionnaire to assess the impact of chronic rhinosinusitis on quality of life (see Appendix E).
Is a 22-item outcome measure on a 5-category scale applicable to sinonasal conditions and surgical treatments. The score range from 0 to 110. Higher total scores on the SNOT-22 imply greater impact of CRS on QoL. The questionnaire was found easy to use (time to completion is 7 minutes) and provided good discriminant validity (Hopkins et al., 2006). The SNOT-22 was validated and recommended for routine clinical practice. A Minimal Clinically Important Difference MCID is available: \( \geq 8.90 \) (19).

9.2.3.2 **Visual analogue scale VAS**

The VAS for rhinosinusitis is used to evaluate the total severity and is only validated in adult CRS to date (2).

The patient is asked to indicate on a VAS the answer to the question: “How troublesome are your symptoms of rhinosinusitis?” The VAS ranks from 0 (Not troublesome) to 10 (Worst thinkable troublesome)

The disease can be divided into MILD, MODERATE and SEVERE based on total severity visual analogue scale (VAS) score (0 10 cm):

MILD = VAS 0-3

MODERATE = VAS >3-7

SEVERE = VAS >7-10

9.2.3.3 **SF-36-Version 2**

Short-Form-36 (SF-36)-Version 2.0: The SF-36 is a generic questionnaire measuring general health status (quality of life) in the last 4 weeks before completing the questionnaire. The SF-36 is a 36 item questionnaire that measures eight multi-item dimensions of health: physical functioning (10 items) social functioning (2 items) role limitations due to physical problems (4 items), role limitations due to emotional problems (3 items), mental health (5 items), energy/vitality (4 items), pain (2 items), and general health perception (5 items).

For each dimension, item scores are coded, summed, and transformed on to a scale from 0 (worst possible health state measured by the questionnaire) to 100 (best possible health state). Two standardised summary scores can also be calculated from the SF-36; the physical component summary (PCS) and the mental health component summary (MCS).

The time for completion is 5-10 minutes.

9.2.3.4 **The Euroqol-5D**

EQ-5D-3L is a standardized health-related quality of life questionnaire developed by the EuroQol Group in order to provide a simple, generic measure of health for clinical and economic appraisal and inter-disease comparisons. (Appendix E). EQ-5D is designed for self-completion by patients and it takes few minutes to complete.
EQ-5D was used to study the impact on QoL for filgrastim administration in CRS patients, the scores improved though they were not statistically significant (20).

The EQ-5D essentially consists of 2 pages – the EQ-5D descriptive system and the EQ VAS (Appendix E). The EQ-5D descriptive system comprises 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 3 levels: no problem, some problems, severe problems. The EQ Visual Analogue Scale (VAS) records the respondent’s self-rated health on a vertical visual analogue scale. The EQ VAS ‘thermometer’ has endpoints of 100 (Best imaginable health state) at the top and 0 (Worst imaginable health state) at the bottom.

9.2.3.5 Nasal polyph related resource use questionnaire

A questionnaire of health care resource utilization for nasal polyposis (specialist visit, emergency care visit, sick leaves, days off etc.) will be completed at monthly visits. (Appendix E)

9.2.3.6 Patient's qualitative self-assessment of the treatment

The patient qualitative self-assessment aims to better understand the patient’s views on their treatment during the trial. One question assessing the patient’s satisfaction would be asked, who will thereafter write the answer on a blank page. This assessment should take between 5-10 minutes, and the text would later be analysed using qualitative data analysis software (Alceste) to perform content analysis.

This is an optional question and the patient will be asked if they want to complete the optional one question on “treatment self-assessment.”

9.2.3.7 ACQ-5 (Asthma Control Questionnaire, 5-question version)

The ACQ-5 was designed to measure both the adequacy of asthma control and change in asthma control which occurs either spontaneously or as a result of treatment.

The ACQ-5 has 5 questions, reflecting the top-scoring five asthma symptoms: woken at night by symptoms, wake in the mornings with symptoms, limitation of daily activities, shortness of breath and wheeze. Patients are asked to recall how their asthma has been during the previous week and to respond to the symptom questions on a 7-point scale (0=no impairment, 6= maximum impairment) (see Appendix E).

A global score is calculated: the questions are equally weighted and the ACQ-5 score is the mean of the 5 questions and, therefore, between 0 (totally controlled) and 6 (severely uncontrolled). Higher score indicates lower asthma control. Patients with a score below 1.0 will have adequately controlled asthma and above 1.0 their asthma will not be well controlled. On the 7-point scale of the ACQ-5, a change or difference in score of 0.5 is the smallest that can be considered clinically important, corresponding to the Minimal Clinically Important Difference (MCID) defined by the developer.

Measurement properties such as reliability, ability to detect change have been documented in the literature (21).
10 STUDY PROCEDURES

10.1 VISIT SCHEDULE

The clinical trial consists of three periods, using an add-on therapy approach to INCS:

- Screening Period (28 days +/- 2 days; Visit 1)
- Randomized Treatment Period (16 weeks; Visits 2-18)
- Post-treatment Period (16 weeks; Visits 19-22)

The study visits occur on the planned dates (relative to the first injection), as scheduled. The visit schedule should be adhered to within the ± 2 day visit window.

If a patient is prematurely discontinued from treatment, all assessments planned at the End of Treatment visit should be performed.

Prior to all screening assessments, after discussion of participation in the study, the written consent form (including voluntary participation in nasal polyp biopsy and pharmacogenomic testing) must be signed and dated.

Although the screening assessments for this study are grouped under the heading of a single visit in this protocol, it is possible for them to be performed over more than 1 site visit if necessary, as long as the screening visit window prior to Day 1 (V2) is respected. Patients that fail screening for exclusion criteria, for example concomitant medications, acute illness (upper respiratory tract infection), required drug-specific discontinuation periods or laboratory tests, may be rescreened for study eligibility 1 additional time.

10.1.1 Visit 1 (D-28): screening run-in

Following a discussion of participation in the clinical trial, signed informed consent must be obtained and documented.

The following procedures will then be performed:

- Call IVRS/IWRS to assign patient number and register screening visit
- Interview to collect patient demographic information, nasal polyposis information, other medical history (including asthma history, number of asthma exacerbations in the previous year, hypersensitivity to aspirin or NSAID), surgical history (including number and dates of previous surgery for nasal polyps), and prior and concomitant medications (including background therapy for NP and asthma)
- Review entry criteria to assess eligibility, with special attention to verify the following:
  - Use of INCS for more than 8 weeks prior to screening
- Presence of at least two of the following symptoms prior to screening: Nasal blockade/obstruction/congestion or nasal discharge (anterior/posterior nasal drip); facial pain/pressure; reduction or loss of smell

Patients have not received any of the prohibited medications described in (Section 8.8.1)

- Measure vital signs [blood pressure, heart rate, respiration rate, body temperature, weight (kg), height (cm)]
- Perform physical examination
- Perform Nasal endoscopy
- Perform CT scan (within the time period between V1 and V2)
- Administer SNOT-22
- Perform spirometry, within the time period between V1 and V2, for all patients and ensure that patients with co-morbid asthma are stable
  - with a FEV\(_1\) ≥60% (of predicted normal) and has not experienced any exacerbation requiring treatment with ≥ 1 systemic (oral or parenteral) steroids bursts for worsening asthma and/or hospitalization or an emergency/urgent medical care visit for worsening asthma in the previous 3 months or are on a dose of inhaled corticosteroids not higher to 1000 μg fluticasone or the equivalent
- Perform 12-lead electrocardiography (ECG)
- Obtain (fasting) blood samples for screening clinical laboratory determinations:
  - Hematology: To include hemoglobin, hematocrit, platelet count, total white blood cell count with five-part differential count, and total red blood cell count.
  - Serum chemistry: To include: creatinine, blood urea nitrogen, glucose, uric acid, total cholesterol, total protein, albumin, total bilirubin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, electrolytes (sodium, potassium, chloride), bicarbonate, and creatine phosphokinase.
- Obtain blood samples for hepatitis screen (hepatitis B surface antigen (HBsAg), Hepatitis B IgM core antibody (HBeAb-IgM), hepatitis C antibodies (HC Ab), HIV screen (Anti-HIV-1 and HIV-2 antibodies), anti-nuclear antibody (ANA)
- Obtain serum β-HCG pregnancy test if female of childbearing potential
- Obtain urine for urinalysis (dipstick)
- Dispense electronic diary/NPIF meter, provide instructions for daily use, and remind patient to bring the device to the next visit
- Dispense MFNS for use as mandatory background therapy throughout the study. Instruct patient to record usage in the electronic diary.
- Commence AE reporting
- Schedule appointment for the next visit
10.1.2 Visit 2 (Week 0): Randomization

- Record all medication use with start date and dose in eCRF; inquire about AEs/SAEs and background therapy tolerability
- Perform nasal endoscopy and for those patients who have signed a specific informed consent form, collect nasal biopsy (prior to administration of investigational product)
- Record symptoms of sinusitis and review results from central reader of V1 nasal endoscopy to confirm entry criteria
- Reconfirm eligibility based on review of Inclusion/Exclusion Criteria and the V2 endoscopy local reading (Section 7).
- Check if CT scan was performed and review local reading assessment
- Obtain spirometry result and record in the e-CRF
- Check compliance with use of the mandatory background therapy (MNFS), as defined as:
  - ≥80% of total number of prescribed “stable dose” sprays taken during the screening period. Compliance is verified based on MFNS use recorded on the patient electronic diary
- Check for use of prohibited medications
- Measure vital signs (blood pressure, heart rate, respiration rate, body temperature, weight)
- Administer SNOT-22

If the patient meets all inclusion and does not meet any exclusion criteria:

- Call IVRS/IWRS to register visit, randomize the patient if entry criteria are met, and receive the first IMP kit number assignment.
- Note: Please screen-fail the patient if entry criteria are not met
- Administer VAS and QoL questionnaires (SF-36, EQ-5D, Nasal polyp related ressource use questionnaire)
- Administer the smell test
- Administer ACQ-5 in patients with asthma
- Perform urine pregnancy test (for women of childbearing potential)
- Perform blood sampling (prior to administration of IMP) for clinical laboratories
- Note: Clinical laboratory testing at Visit 2 is limited to hematology, pharmacokinetics, anti-drug antibodies, biomarkers in serum and plasma, allergen-specific IgE panel sampling
- Perform nasal secretion sampling for biomarkers (as described in Section 9.2.2.4)
- For those patients who have signed a specific informed consent form, collect blood sample for DNA and RNA sampling (prior to administration of investigational product during the Randomized Treatment Period)
- Download electronic diary/NPIF meter and remind patient to bring the device to the next visit

- Dispense IMP and NIMP and administer IMP:
  - At V2 two injections of IMP will be performed. Subcutaneous injection sites should be alternated between the 4 quadrants of the abdomen (avoiding navel and waist areas) or upper thighs so that the same site is not injected for two consecutive times
  - Patients should be monitored for at least 1 hour after the end of administration of IMP for any signs or symptoms of a hypersensitivity reaction.

- Remind patient to continue the stable dose of MFNS and record daily usage in the electronic diary

- Schedule appointment for next visit

10.1.3 Visit 3, 4, 5 (Week 1, Week 2, Week 3)

- Record all medication use with start date and dose in eCRF; inquire about AEs/SAEs and background therapy tolerability

- Call IVRS/IWRS to register visit and obtain next IMP kit number

- At V4 (Week 2) only, perform sampling for pharmacokinetics, anti-drug antibodies, RNA archival, biomarkers in serum and plasma, allergen-specific IgE panel sampling

- Dispense NIMP and administer IMP (one SC injection)

- Patients will be monitored at the study site for a minimum of 1 hour after the injection

- Remind patient to continue the stable dose of MFNS and record daily usage in the electronic diary

- Ensure that the patient has the necessary dose of MFNS up to the next visit (one MFNS device-one bottle-contains sufficient doses for: either 2 weeks of BID treatment/regimen or 4 weeks of QD treatment/regimen) and dispense NIMP if needed

- Schedule appointment for next visit

10.1.4 Visit 6 (Week 4)

- Record all medication use with start date and dose in eCRF; inquire about AEs/SAEs and background therapy tolerability

- Measure vital signs (blood pressure, heart rate, respiration rate, body temperature, weight)

- Perform urine pregnancy test (for women of childbearing potential)

- Download electronic diary/NPIF meter and remind patient to bring the device to the next visit

- Perform nasal endoscopy
- Administer SNOT-22, VAS and QoL questionnaires (SF-36, EQ-5D, Nasal polyp related ressource use questionnaire)
- Administer ACQ-5 in patients with asthma
- Obtain spirometry result and record in the e-CRF
- Perform blood sampling (prior to administration of IMP) for clinical laboratories: hematology, serum chemistry, LFT, pharmacokinetics, anti-drug antibodies, biomarkers in serum and plasma, allergen-specific IgE panel sampling
- Perform nasal secretion sampling
- Call IVRS/IWRS to register visit and obtain next IMP kit number
- Dispense NIMP and administer IMP (one SC injection)
- Patients will be monitored at the study site for a minimum of 1 hour after the injection
- Remind patient to continue the stable dose of MFNS and record daily usage in the electronic diary
- Ensure that the patient has the necessary dose of MFNS up to the next visit (one MFNS device-one bottle-contains sufficient doses for: either 2 weeks of BID treatment/regimen or 4 weeks of QD treatment/regimen) and dispense NIMP if needed
- Schedule appointment for next visit

10.1.5 Visit 7, 8, 9 (Week 5, Week 6, Week 7)
- Record all medication use with start date and dose in eCRF; inquire about AEs/SAEs and background therapy tolerability
- Call IVRS/IWRS to register visit and obtain next IMP kit number
- Dispense NIMP and administer IMP (one SC injection)
- Patients will be monitored at the study site for a minimum of 1 hour after the injection.
- Remind patient to continue the stable dose of MFNS and record daily usage in the electronic diary
- Ensure that the patient has the necessary dose of MFNS up to the next visit (one MFNS device-one bottle-contains sufficient doses for: either 2 weeks of BID treatment/regimen or 4 weeks of QD treatment/regimen) and dispense NIMP if needed
- Schedule appointment for next visit

10.1.6 Visit 10 (Week 8)
- Record all medication use with start date and dose in eCRF; inquire about AEs/SAEs and background therapy tolerability
- Measure vital signs (blood pressure, heart rate, respiration rate, body temperature, weight)
- Perform ECG
Download electronic diary/NPIF meter and remind patient to bring the device to the next visit

Perform urine pregnancy test (for women of childbearing potential)

Perform urinalysis (dipstick)

Perform blood sampling (prior to administration of IMP) for clinical laboratories: hematology, serum chemistry, LFT, pharmacokinetics, anti-drug antibodies, biomarkers in serum and plasma, allergen-specific IgE panel sampling

Perform nasal secretion sampling

Call IVRS/IWRS to register visit and obtain next IMP kit number

Perform nasal endoscopy

Administer smell test

Dispense and administer IMP (one SC injection)
  - Patients will be monitored at the study site for a minimum of 1 hour after the injection

Administer SNOT-22, VAS and QoL questionnaires (SF-36, EQ-5D, Nasal polyp related ressource use questionnaire)

Obtain spirometry result and record in the e-CRF

Administer ACQ-5 (in patients with asthma)

Ensure that the patient has the necessary dose of MFNS up to the next visit (one MFNS device-one bottle-contains sufficient doses for: either 2 weeks of BID treatment/regimen or 4 weeks of QD treatment/regimen) and dispense NIMP if needed

Schedule appointment for next visit

10.1.7 Visit 11, 12, 13 (Week 9, Week 10, Week 11)

Record all medication use with start date and dose in eCRF; inquire about AEs/SAEs and background therapy tolerability

Call IVRS/IWRS to register visit and obtain next treatment kit number

Dispense NIMP and administer IMP (one SC injection)
  - Patients will be monitored at the study site for a minimum of 1 hour after the injection.

Remind patient to continue the stable dose of MFNS and record daily usage in the electronic diary

Ensure that the patient has the necessary dose of MFNS up to the next visit (one MFNS device contains sufficient doses for: 2 weeks of BID treatment/regimen and 1 month of QD treatment/regimen) and dispense NIMP if needed

Schedule appointment for next visit
10.1.8 Visit 14 (Week 12)

- Record all medication use with start date and dose in eCRF; inquire about AEs/SAEs and background therapy tolerability
- Measure vital signs (blood pressure, heart rate, respiration rate, body temperature, weight)
- Perform ECG
- Perform urine pregnancy test (for women of childbearing potential)
- Download electronic diary/NPIF meter and remind patient to bring the device to the next visit
- Perform nasal endoscopy
- Administer SNOT-22, VAS and QoL questionnaires (SF-36, EQ-5D, Nasal polyp related resource use questionnaire)
- Administer ACQ-5 in patients with asthma
- Obtain spirometry result and record in the e-CRF
- Perform blood sampling (prior to administration of IMP) for clinical laboratories: hematology, serum chemistry, LFT, pharmacokinetics, anti-drug antibodies, biomarkers in serum and plasma, allergen-specific IgE panel sampling
- Perform nasal secretion sampling
- Call IVRS/IWRS to register visit and obtain next IMP kit number
- Dispense NIMP and administer IMP (one SC injection)
  - Patients will be monitored at the study site for a minimum of 1 hour after the injection
- Remind patient to continue the stable dose of MFNS and record daily usage in the electronic diary
- Ensure that the patient has the necessary dose of MFNS up to the next visit (one MFNS device—one bottle—contains sufficient doses for: either 2 weeks of BID treatment/regimen or 4 weeks of QD treatment/regimen) and dispense NIMP if needed
- Schedule appointment for next visit

10.1.9 Visit 15, 16, 17 (Week 13, Week 14, Week 15)

- Record all medication use with start date and dose in eCRF; inquire about AEs/SAEs and background therapy tolerability
- Call IVRS/IWRS to register visit and obtain next IMP kit number
- Dispense NIMP and administer IMP (one SC injection)
- Patients will be monitored at the study site for a minimum of 1 hour after the injection.
- Remind patient to continue the stable dose of MFNS and record daily usage in the electronic diary
- Ensure that the patient has the necessary dose of MFNS up to the next visit (one MFNS device-one bottle-contains sufficient doses for: either 2 weeks of BID treatment/regimen or 4 weeks of QD treatment/regimen) and dispense NIMP if needed
- Schedule appointment for EOT visit

10.1.10 EOT visit 18 (Week 16)

- Review patient Home Dosing Diary for content and completeness
- Record all medication use with start date and dose in eCRF; inquire about AEs/SAEs and background therapy tolerability
- Check for use of prohibited medications
- Perform physical examination
- Perform nasal endoscopy
- Perform CT scan (before V19)
- Administer SNOT-22, VAS and QoL questionnaires (SF-36, EQ-5D, Nasal polyp related ressource use questionnaire)
- Administer ACQ-5 in patients with asthma
- Perform spirometry
- Administer smell test (UPSIT)
- Perform urine pregnancy test (for women of childbearing potential)
- Perform urinalysis (dipstick)
- Measure vital signs (blood pressure, heart rate, respiration rate, body temperature, weight)
- Perform ECG
- Perform blood sampling for clinical laboratories hematology, serum biochemistry LFT, pharmacokinetics, anti-drug antibodies, biomarkers in serum and plasma, allergen-specific IgE panel sampling
- Perform RNA sampling
- Perform nasal secretion sampling
- For those patients who have signed a specific informed consent form, collect mucosa sample from nasal biopsy (prior to administration of investigational product during the Randomized Treatment Period)
- Download electronic diary/NPIF meter and remind patient to bring the device to the next visit
- Call IVRS/IWRS to register the EOT date
- Remind patient to continue the stable dose of MFNS and record daily usage in the electronic diary during the post treatment period
- Ensure that the patient has the necessary dose of MFNS up to the next visit (one MFNS device-one bottle-contains sufficient doses for: either 2 weeks of BID treatment/regimen or 4 weeks of QD treatment/regimen) and dispense NIMP if needed
- The optional qualitative self-assessment of the treatment will be proposed to the patient
- Ask patient if they want to complete the optional question on “treatment self-assessment”
- Schedule appointment for next visit.

10.1.11 Visit 19, Visit 20 and Visit 21 (Week 20, Week 24 and Week 28 Post-Treatment Period)
- Record all medication use with start date and dose in eCRF; inquire about AEs/SAEs and background therapy tolerability
- Check for use of prohibited medications
- Measure vital signs (blood pressure, heart rate, respiration rate, body temperature, weight)
- For Visit 20, remind patient to come for visit in fasting state
- PK samples are taken at Visit 19, 20 and 21. No ADA sample is collected at these visits
- At V20 only: Perform blood sampling for clinical laboratories hematology, serum biochemistry, LFT
- Biomarkers and archival serum and nasal secretion sample is collected at Visit 19
- Download electronic diary/NPIF meter and remind patient to bring the device to the next visit
- Remind patient to continue the stable dose of MFNS and record daily usage in the electronic diary during the post treatment period
- Ensure that the patient has the necessary dose of MFNS up to the next visit (one MFNS device-one bottle-contains sufficient doses for: either 2 weeks of BID treatment/regimen or 4 weeks of QD treatment/regimen) and dispense NIMP if needed
- Schedule appointment for next visit

10.1.12 Visit 22 (Week 32 End-of-Study Visit)
- Record all medication use with start date and dose in eCRF; inquire about AEs/SAEs and background therapy tolerability
- Check for use of prohibited medications
- Perform physical examination
• Perform nasal endoscopy
• Administer SNOT-22, VAS and QoL questionnaires (SF-36, EQ-5D, Nasal polyp related ressource use questionnaire)
• Administer ACQ-5 in patients with asthma
• Perform spirometry
• Measure vital signs (blood pressure, heart rate, respiration rate, body temperature, weight)
• Perform urine pregnancy test (for women of childbearing potential)
• Perform urinalysis (dipstick)
• Perform 12-lead electrocardiography (ECG)
• Perform blood sampling for clinical laboratories hematology (including a separate hematology sample obtained for local analysis), serum biochemistry LFT, pharmacokinetics, anti-drug antibodies, biomarkers in serum and plasma, allergen-specific IgE panel sampling
• Perform RNA sampling
• Download electronic diary/NPIF meter
• Call IVRS to register the EOS date

10.2 DEFINITION OF SOURCE DATA

Source data is all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Source documents are original documents, data and records such as hospital records, clinic and office charts, laboratory notes, memoranda, pharmacy dispensing records, recorded data from automated instruments, etc.

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

10.3 HANDLING OF PATIENT TEMPORARY OR PERMANENT TREATMENT DISCONTINUATION AND OF PATIENT STUDY DISCONTINUATION

The IMP and NIMP should be continued whenever possible. Permanent IMP discontinuation should be a last resort. Any IMP discontinuation should be fully documented in the CRF. In any case, the patient should remain in the study as long as possible.

10.3.1 Temporary treatment discontinuation with investigational medicinal product(s)

Temporary treatment discontinuation may be considered by the Investigator because of suspected AEs. Reinitiation of treatment with the IMP will be done under close and appropriate clinical/and
or laboratory monitoring once the Investigator will have considered according to his/her best medical judgment that the responsibility of the IMP(s) in the occurrence of the concerned event was unlikely and if the selection criteria for the study are still met (refer to Section 7.1 and Section 7.2).

For all temporary treatment discontinuations, duration should be recorded by the Investigator in the appropriate pages when considered as confirmed.

10.3.2 Permanent treatment discontinuation with investigational medicinal product(s)

Permanent treatment discontinuation is any treatment discontinuation associated with the definitive decision from the Investigator or the patient not to re-expose the patient to the IMP at any time.

10.3.3 List of criteria for permanent treatment discontinuation

The patients may withdraw from treatment with the IMP if they decide to do so, at any time and irrespective of the reason, or this may be the Investigator’s decision. All efforts should be made to document the reasons for treatment discontinuation and this should be documented in the e-CRF.

Patients must be withdrawn from the study (ie, from any further investigational product or study procedure) 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 patient to the patient’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 patient’s well-being
- If there is need for systemic corticosteroids or surgery to control and/or relief the underlying disease or for the treatment of any other conditions requiring treatment with any of the prohibited concomitant treatment listed in Section 8.8.1.
  - In case of recurrent infectious episodes requiring antibiotics
  - At the specific request of the Sponsor
  - In the event of a protocol deviation, at the discretion of the Investigator or the Sponsor
  - Pregnancy will lead to definitive treatment discontinuation in all cases

Stopping rules described in Appendix D should be applied

Any abnormal laboratory value or ECG parameter will be immediately rechecked for confirmation before making a decision of permanent discontinuation of the IMP for the concerned patient.
10.3.4 Handling of patients after permanent treatment discontinuation

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

If possible, and after the permanent discontinuation of treatment, the patients will be assessed using the procedures normally planned for the End-of-treatment Visit and the four Post-treatment Period Visits.

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

10.3.5 Procedure and consequence for patient withdrawal from study The patients may withdraw from the study before study completion if they decide to do so, at any time and irrespective of the reason:

- If possible, the patients are assessed using the procedure normally planned for the End-of-treatment Visit and the four Post-treatment Period Visits.

For patients who fail to return to the site, the Investigator should make the best effort to recontact the patient (eg, contacting patient’s family or private physician, reviewing available registries or health care databases), and to determine his/her health status, including at least his/her vital status. Attempts to contact such patients must be documented in the patient’s records (eg, times and dates of attempted telephone contact, receipt for sending a registered letter).

Consideration of the analyses for such patients will be prespecified in the SAP.

Patients who have withdrawn from the study cannot be re-randomized (treated) in the study. Their inclusion and treatment numbers must not be reused.

10.4 OBLIGATION OF THE INVESTIGATOR REGARDING SAFETY REPORTING

10.4.1 Definitions of adverse events

10.4.1.1 Adverse event

An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

10.4.1.2 Serious adverse event

A serious adverse event (SAE) is any untoward medical occurrence that at any dose:

- Results in death,
- Is life-threatening, or
  Note: The term “life-threatening” in the definition of “serious” refers to an event in which the patient 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.
- Requires inpatient hospitalization or prolongation of existing hospitalization, or
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect
- Is a medically important event

Medical and scientific judgment should be exercised in deciding whether expedited 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 patient or may require intervention (ie, specific measures or corrective treatment) to prevent one of the other outcomes listed in the definition above.

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

- Intensive treatment in an emergency room or at home for:
  - Allergic bronchospasm
  - Anaphylaxis (refer to Appendix B for Definition of Anaphylaxis)
  - Blood dyscrasias (ie, agranulocytosis, aplastic anemia, bone marrow aplasia, myelodysplasia, pancytopenia, etc),
  - Convulsions (seizures, epilepsy, epileptic fit, absence, etc).
- Development of drug dependency or drug abuse
- ALT >3 x ULN + total bilirubin >2 x ULN or asymptomatic ALT increase >10 x ULN
- Suicide attempt or any event suggestive of suicidality
- Syncope, loss of consciousness (except if documented as a consequence of blood sampling)
- Bullous cutaneous eruptions
- Cancers diagnosed during the study or aggravated during the study
- Chronic neurodegenerative diseases (newly diagnosed) or aggravated during the study (only if judged unusual/significant by the Investigators in studies assessing specifically the effect of a study drug on these diseases).

10.4.1.3 Adverse event of special interest

An adverse event of special interest (AESI) is an AE (serious or non-serious) of scientific and medical concern specific to the Sponsor’s product or program, for which ongoing monitoring and
rapid communication by the Investigator to the Sponsor may be appropriate. Such events may require further investigation in order to characterize and understand them. AESIs may be added or removed during a study by protocol amendment.

10.4.1.3.1 AESI with immediate notification

For these AESIs, the Sponsor will be informed immediately (ie, within 24 hours), per SAE notification described Section 10.4.1.2, even if not fulfilling a seriousness criterion, using the corresponding pages in the CRF (to be sent) or screens in the e-CRF.

Anaphylactic reactions or acute allergic reactions that require immediate treatment (refer to Appendix B for Definition of Anaphylaxis)

- Severe injection site reactions that last longer than 24 hours
- Severe infections include opportunistic infection and parasitic infections
- Significant ALT elevation
  - ALT >5 x the upper limit of normal (ULN) in patients with normal baseline ALT; or
  - ALT >3 x baseline ALT in patients with abnormal baseline ALT
- ALT elevation
  - ALT ≥3 x ULN and ≤5 x ULN plus total bilirubin >2 x ULN in patients with normal baseline ALT; or
  - ALT ≥2 x baseline ALT and ≤3 x baseline ALT plus total bilirubin >2 x ULN in patients with abnormal baseline ALT
- Pregnancy
  - Pregnancy occurring in a female patient included in the clinical trial. Pregnancy will be recorded as a pre-specified AE with immediate notification in all cases. It will be qualified as an SAE only if it fulfills the SAE criteria.
  - In the event of pregnancy, investigational product should be discontinued.
  - The follow-up of the pregnancy will be mandatory until the outcome has been determined.
- Symptomatic overdose with IMP/Non-IMP

An overdose (accidental or intentional) with the IMP is an event suspected by the Investigator or spontaneously notified by the patient and defined as at least twice the 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 Non-IMP is an event suspected by the Investigator or spontaneously notified by the patient and defined as at least twice of the intended dose within the intended therapeutic interval. The circumstances (ie, accidental or intentional) should be clearly specified in the verbatim and symptoms, if any, entered on separate AE forms.
10.4.2 General guidelines for reporting adverse events

- All AEs, regardless of seriousness or relationship to IMP/Non-IMP, spanning from the signature of the informed consent form until the end of the study as defined by the protocol for that patient, are to be recorded on the corresponding page(s) or screen(s) of the CRF.

- When a safety event is categorized as a primary outcome, the event will be reported as an AE but will be waived from reporting to health authorities providing an agreement has been reached with them.

- Whenever possible, diagnosis or single syndrome should be reported instead of symptoms. The Investigator should specify the date of onset, intensity, action taken with respect to IMP, corrective treatment/therapy given, additional investigations performed, outcome, and his/her opinion as to whether there is a reasonable possibility that the AE was caused by the IMP. In studies that require the use of combined/multiple IMPs/Non-IMPs, the Global Safety Officer (GSO) with input from other appropriate study team members must determine if the causal relationship will either be assessed for the combined product as a regimen or as distinct entities. The GSO must communicate this decision to the study team for inclusion in the protocol and AE CRF.

- The Investigator should take appropriate measures to follow all AEs until clinical recovery is complete and laboratory results have returned to normal, or until progression has been stabilized, or until death, in order to ensure the safety of the patients. This may imply that observations will continue beyond the last planned visit per protocol, and that additional investigations may be requested by the monitoring team up to as noticed by the Sponsor. Patients who experience an ongoing SAE or an AESI with immediate notification, at the prespecified study end-date, should be followed until resolution, stabilization, or death and related data will be collected.

- When treatment is prematurely discontinued, the patient’s observations will continue until the end of the study as defined by the protocol for that patient.

- Laboratory, vital signs or ECG abnormalities are to be recorded as AEs only if:
  - Symptomatic, or
  - Requiring either corrective treatment or consultation, or
  - Leading to IMP discontinuation or modification of dosing, or
  - Fulfilling a seriousness criterion, or
  - Defined as an AESI.
The following table summarizes the reporting timelines:

<table>
<thead>
<tr>
<th>Adverse event / laboratory abnormality</th>
<th>Reporting timeline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious adverse event</td>
<td>Within 24 hours</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>Within 24 hours</td>
</tr>
<tr>
<td>Overdose</td>
<td>Within 24 hours</td>
</tr>
<tr>
<td>Symptomatic</td>
<td>Normal</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>Routine</td>
</tr>
<tr>
<td>ALT elevation</td>
<td></td>
</tr>
<tr>
<td>Baseline &lt; ULN</td>
<td></td>
</tr>
<tr>
<td>ALT &gt; 5 ULN</td>
<td>Within 24 hours</td>
</tr>
<tr>
<td>3 ULN ≤ ALT ≤ 5 ULN plus total bilirubin &gt; 2 ULN</td>
<td>Within 24 hours</td>
</tr>
<tr>
<td>Baseline ≥ ULN</td>
<td>Within 24 hours</td>
</tr>
<tr>
<td>ALT &gt; 3x baseline</td>
<td>Within 24 hours</td>
</tr>
<tr>
<td>2 x baseline ≤ ALT ≤ 3x baseline plus total bilirubin &gt; 2 ULN</td>
<td>Within 24 hours</td>
</tr>
<tr>
<td>Anaphylactic reactions or acute allergic reactions that require immediate treatment</td>
<td>Within 24 hours</td>
</tr>
<tr>
<td>Severe injection site reactions that last longer than 24 hours</td>
<td>Within 24 hours</td>
</tr>
<tr>
<td>Severe infections including opportunistic and parasitic infections</td>
<td>Within 24 hours</td>
</tr>
</tbody>
</table>

10.4.3 Instructions for reporting serious adverse events

In the case of occurrence of an SAE, the Investigator must immediately:

- ENTER (within 24 hours) the information related to the SAE in the appropriate screens of the e-CRF; the system will automatically send a notification to the monitoring team after approval of the Investigator within the e-CRF or after a standard delay.

- SEND (preferably by fax or e-mail) a photocopy of all examinations carried out and the dates on which these examinations were performed, to the representative of the monitoring team whose name, fax number, and email address appear on the clinical trial protocol. Care should be taken to ensure that the patient's identity is protected and the patient's identifiers in the clinical trial are properly mentioned on any copy of a source document provided to the Sponsor. For laboratory results, include the laboratory normal ranges.

- All further data updates should be recorded in the e-CRF as appropriate, and further documentation as well as additional information (for laboratory data, concomitant medications, patient status, etc) should be sent (by fax or e-mail) to the monitoring team within 24 hours of knowledge. In addition, every effort should be made to further document any SAE that is fatal or life threatening within a week (7 days) of the initial notification.

- A back-up plan (using a paper CRF process) is available and should be used when the e-CRF system does not work.

Any SAE brought to the attention of the Investigator at any time after the end of the study for the patient and considered by him/her to be caused by the IMP with a reasonable possibility, should be reported to the monitoring team.
10.4.4 Guidelines for management of specific laboratory abnormalities

Decision trees for the management of certain laboratory abnormalities by Sanofi are provided in Appendix D.

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

- Neutropenia
- Thrombocytopenia
- Increase in ALT
- Acute renal insufficiency
- Suspicion of rhabdomyolysis

10.5 OBLIGATIONS OF THE SPONSOR

During the course of the study, the Sponsor will report in an expedited manner all SAEs that are both unexpected and at least reasonably related to the investigational product (SUSAR), to the Health Authorities, IECs/IRBs as appropriate and to the Investigators. In addition, the Sponsor may report in an expedited manner all SAEs that are expected and at least reasonably related to the investigational products to the Authorities, according to local regulations.

Any other adverse event not listed as an expected event in the investigator’s brochure and in this protocol will be considered as unexpected.

The Sponsor will report all safety observations made during the conduct of the trial in the clinical study report.

10.6 SAFETY INSTRUCTIONS

10.6.1 Hypersensitivity

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

Acute allergic reactions may be defined as allergic reaction-mediated signs and symptoms experienced by patients during or shortly after the pharmacologic or biologic agent is given. These reactions may present in a variety of ways, including dizziness, headache, anxiety, dyspnea, hypotension, tachycardia, pruritus, rash, urticaria/angioedema, flushing, nausea, or vomiting. Anaphylaxis may represent the most severe form of infusion reaction, but these events may also occur via non-IgE mediated mechanisms (eg, anaphylactoid reactions), or may occur via other immune-mediated mechanisms (eg, cytokine-mediated). Allergic reactions may begin within a few hours and persist up to 24 hours post dosing. Refer to Appendix B “Definition of Anaphylaxis”, which describes the clinical criteria for the diagnosis of anaphylaxis.

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Patients should be monitored for at least 1 hour after each study-site administered investigational product administration for any signs or symptoms of a hypersensitivity reaction. Any instance of allergic reaction should be reported as an adverse event of special interest (AESI). Any anaphylactic reactions or acute allergic reactions that require immediate treatment will be AESI with immediate reporting (within 24 hours) and study medication should be permanently discontinued. Trained personnel and medications should be available to treat anaphylaxis or any severe allergic reaction if it occurs. Furthermore, the patients will be advised, when the IMP is administered at home, to self-monitor for potential signs and symptoms that may suggest a hypersensitive reaction for 1 hour after administration.

10.6.2 Severe Injection site reactions

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

10.6.3 Infections, including opportunistic infection and parasitic infections

Some biologic therapies have been associated with an increased risk of infection, including opportunistic infection. As a precautionary measure, the Investigator is required to carefully monitor for any signs or symptoms of infection such as, but not limited to, increased body temperature, malaise, weight loss, sweats, cough, dyspnea, pulmonary infiltrates, or serious febrile systemic illness.

Any opportunistic infection requiring parenteral or prolonged (>14 days) antibiotics or antituberculosis medication should be considered serious and be reported as AESI with immediate notification. The study medication should be discontinued in case of suspicion of serious infection and a complete diagnostic work-up should be performed (ie, cultures for fungi and/or mycobacteria other than tuberculosis, histopathological or cytological evaluation, antigen detection and serum antibody titers). Patients should be referred to an infectious disease specialist if deemed necessary for diagnostic work up and appropriate treatment.

Since dupilumab binds to IL-4Rα, preventing IL-4 and IL-13 binding and activation of their respective receptors, it inhibits the T-helper 2 (Th2) cytokines productions. Infections with a diversity of helminthic parasites elicit eosinophilia via stimulation of Th2-like lymphocyte responses. The TH2 response is characterized by production of IL-4 and IL-5, subsequently generating IgG1 and IgE-secreting cells, and eliciting eosinophilia. Eosinophilia is prominent in a number of helminthic parasitic diseases. The eosinophilic response to helminths is determined both by the host's immune response and by the parasite, including its distribution, migration, and development within the infected host. Therefore patient with treatment of dupilumab may potentially have an increased risk of parasitic infection.
In order to minimize this risk, any patient with an active parasitic infection should be excluded from the study. Similarly, patients with suspected parasitic infection, or those at high risk of parasitic infection are also excluded, unless clinical and (if necessary) laboratory assessments have ruled out active infection before randomization. During the study, appearance of signs or symptoms (such as abdominal pain, cough, diarrhea, fever, fatigue hepatosplenomegaly) that could be associated with a parasitic infection should be carefully evaluated, especially if there is a history of parasitic exposure through recent travel to/ or residence in endemic areas, especially when conditions are conducive to infection (e.g., extended stay, rural or slum areas, lack of running water, consumption of uncooked, undercooked, or otherwise potentially contaminated food, close contact with carriers and vectors, etc.). Subsequent medical assessments (e.g., stool exam, blood tests, etc.) must be performed in order to rule out parasitic infection/infestation. Patients with confirmed parasitic infections during the study should be reported as AESI with immediate notification and will be permanently discontinued from the study.

10.6.4 Elevated liver function tests

No pre-clinical and clinical data suggested any hepatic toxicity of anti-IL4 agent; however, as general consideration of clinical development, the administration of immunosuppressant or immunomodulating agents may represent an additional risk factor for hepatotoxicity.

In order to closely follow liver function tests (LFT), assessment of total protein, albumin, total bilirubin, alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase are measured as part of the clinical laboratory testing. Clinical laboratory testing at Visit 1 adds hepatitis screen (hepatitis B surface antigen (HBsAg), Hepatitis B IgM core antibody (HBcAb-IgM), hepatitis C antibodies (HC Ab).

Patients with:

- ALT >3XULN at the V1 and/or V2
- positive or indeterminate hepatitis B surface antigen (HBsAg), hepatitis B core antibody (HBcAb), or hepatitis C antibody at Visit 1

are excluded from the study.

Guidance for the investigation of elevated LFTs is provided in Appendix D

10.7 ADVERSE EVENTS MONITORING

All events will be managed and reported in compliance with all applicable regulations, and included in the final clinical study report.
11 STATISTICAL CONSIDERATIONS

11.1 DETERMINATION OF SAMPLE SIZE

The sample size calculation is based on the primary efficacy variable of NPS change from baseline to week 16 in patients, with the following assumptions:

- A common standard deviation of 1.5, which is assumed based on the paper (*Mepolizumab, a humanized anti-IL-5 mAb, as a treatment option for severe nasal polyposis, by Philippe Gevaert et al.*). (22)
- A 1.3 mean difference between the treatment and placebo in change from baseline in NPS.
- A t-test at a 2-sided 5% significant level with 80% power
- Expected early discontinuation rate of 20%

Based on the above assumptions, 56 patients (28 per group) are needed for this study. Calculations were made using nQuery Advisor 7.0.

When considering patients with co-morbid asthma only, a t-test at a 2-sided 5% significant level and 20% drop out rate, assuming a common standard deviation of 2.0 and a difference of 2.5 (13) between dupilumab and placebo groups in the change of NPS from baseline to Week 16, 14 patients per group will provide 79% power to detect.

11.2 DISPOSITION OF PATIENTS

Screened patients are defined as any patient who met the inclusion criteria and signed the informed consent.

Randomized patients consist of all patients with a treatment kit number allocated and recorded in IVRS database, and regardless of whether the treatment kit was used or not.

Patients treated without being randomized will not be considered as randomized and will not be included in any efficacy population.

For any patient randomized more than once, only the data associated with the first randomization will be used in any analysis population. The safety experience associated with any later randomization will be assessed separately.

The safety experience of patients treated and not randomized will be reported separately, and these patients will not be in the safety population.
11.3 ANALYSIS POPULATIONS

11.3.1 Efficacy populations

11.3.1.1 Intent-to-treat /modified intent-to-treat population

ITT population: all randomized population analyzed according to the treatment group allocated by randomization regardless of whether treatment kit is used or not.

The primary analysis population for the efficacy endpoints will be the double blind randomized ITT population who have been allocated to a randomized treatment regardless of whether the treatment kit was used or not. The efficacy analyses will be conducted according to the treatment to which they are randomized.

11.3.2 Safety population

Safety population: all randomized patients exposed to study medication, regardless of the amount of treatment administered. The safety analyses will be conducted according to the treatment patients actually received.

Treatment emergent period for safety population is defined as the time from the first administration of study medication to the end of the Post-treatment Period.

In addition:

- Nonrandomized but treated patients will not be part of the safety population, but their safety data will be presented separately.
- Randomized patients for whom it is unclear whether they took the study medication will be included in the safety population as randomized.
- For patients receiving more than 1 study treatment during the trial, the treatment group allocation for as-treated analysis will be lowest exposed dupilumab dose / regimen group.

11.3.3 Pharmacokinetics (PK) population

- The PK population will consist of all patients in the safety population with at least one non-missing and eligible plasma concentration data. Patients will be analyzed according to the treatment actually received.

11.3.4 Anti-drug antibody population

- The anti-drug antibody population will consist of all patients in the safety population with at least one post-treatment ADA sample that was assayed successfully using the ADA assay. Patients will be analyzed according to the treatment actually received.
11.4 STATISTICAL METHODS

11.4.1 Extent of study treatment exposure and compliance

The extent of study treatment exposure and compliance will be assessed and summarized by actual treatment received within the safety population.

11.4.1.1 Extent of investigational product exposure

Duration of IMP exposure is defined as: last dose date – first dose date + 7 days, regardless of unplanned intermittent discontinuations

11.4.1.2 Compliance

A given administration will be considered noncompliant if the patient did not take the planned dose of treatment as required by the protocol. No imputation will be made for patients with missing or incomplete data.

Percentage of compliance for a patient will be defined as the number of administrations the patient was compliant divided by the total number of administrations the patient was planned to take during the treatment period (ie, from the 1st to the last administration).

Treatment compliance will be summarized descriptively (N, Mean, SD, Median, Min, and Max). The percentage of patients with compliance <80% will be summarized.

11.4.2 Analyses of efficacy endpoints

The primary efficacy analyses will be based on ITT population.

11.4.2.1 Analyses of primary efficacy endpoint

The change from baseline in NPS at Week 16 in ITT population will be analyzed using a mixed-effect model with repeated measures (MMRM) approach. The model will include change from baseline values up to week 16 as response variables, and factors (fixed effects) for treatment, stratification factor(s), pooled countries / regions, visit, treatment-by-visit interaction, NPS baseline value and baseline-by-visit interaction. An unstructured correlation matrix will be used to model the within-patient errors. Parameters will be estimated using restricted maximum likelihood method with the Newton-Raphson algorithm. Descriptive statistics including number of patients, mean, standard error and LS means will be provided. In addition, difference in LS means, the corresponding 95% CI and the p-value will be provided for comparisons of each dose against placebo. No imputation will be performed for the MMRM model.

Change from baseline at other visits will be summarized using descriptive statistics.
11.4.2.2 Analyses of secondary efficacy endpoints

11.4.2.2.1 Analysis of proportion of patients with binary events

Proportion of patients with:

- $\geq 1$ point improvement (reduction) in NPS at week 16 (as read centrally)
- Drop-out due to oral CS or surgery
- INCS increase after 8 weeks

will be analyzed using a logistic model with the above responses, respectively, as the response variable, and treatment group, pooled countries /regions and the stratification factor(s) prior to the study as covariates.

11.4.2.2.2 Analysis of time to event variables

Time to event (eg, the first response with $\geq 1$ point improvement (reduction) in NPS, study treatment discontinuation, etc) will be analyzed using a Cox regression model with time to event as the dependent variable, and treatment, pooled countries/regions, asthma comorbidity prior to the study as covariates. The Kaplan-Meier method will be used to derive the proportion of patients with an event at Week 4, 8, 12 and 16 specific to each treatment group. For analysis during the treatment period, if a patient has no event before treatment discontinuation/completion, then the patient will be considered as free of event till the end of treatment period (last dose date + 7 days).

11.4.2.2.3 Analysis of change from baseline for continuous variables

The change from baseline at week 16 in:

- In NPS for patients with co-morbid asthma
- % change in maxillary CT opacification
- Lund Mackay score
- 22-item Sinonasal Outcome Test (SNOT-22)
- Subject-assessed congestion and/or obstruction score
- Nasal peak inspiratory flow (NPIF)
- ACQ-5 in patients with co-morbid asthma
- QoL measures (SF36, EQ-5D), VAS

will be analyzed using MMRM same as the primary endpoints. Descriptive statistics including number of patients, mean, standard error and LS means will be provided. In addition, differences in LS means, the corresponding 95% CI and the p-value will be provided for comparisons of each dose against placebo.
11.4.2.2.4 Analysis of efficacy in baseline biomarker of characteristics defined subsets

To examine baseline biomarkers for their potential value to predict treatment response, analyses of change in NPS will also be performed for the following subsets and the entire ITT population by each dose group and selected pooled dose group.

11.4.2.2.5 Subgroup analysis

To assess the consistency treatment effects across the subgroup levels, and to examine baseline biomarkers for their potential value to predict treatment response, exploratory subgroup analyses will be conducted for the change from baseline in NPS with respect to age group, gender, region, race, INCS dose level, baseline NPS, baseline CT scan score, asthma comorbidity, and selected biomarkers prior to the study. The details will be provided in the SAP.

11.4.2.3 Multiplicity considerations

For this two-arm study with a single primary efficacy endpoint, multiplicity adjustment is not considered.

11.4.3 Analyses of safety data

The summary of safety results will be presented by treatment group.

All safety analyses will be performed on the Safety population using the following common rules:

- The baseline value is defined generally as the last available value before randomization.
- Treatment emergent period for safety population is defined as the time from the first administration of study medication to the end of the Post-treatment Period.

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

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

11.4.3.1 Adverse events

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

Proportion of patients with at least one treatment emergent adverse event (TEAE), serious TEAE 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. None treatment emergent serious AE, AE leading to study discontinuation will be summarized separately.

11.4.3.1.1 AESI

The following summaries will be generated:

- Incidence of each AESI will be tabulated by treatment group.

In addition,

- The time-to-first event analyzed using K-M methods and displayed as K-M plots (cumulative incidence (%) versus time based on K-M estimates) will be provided to depict the course of onset over time. When TEAE start date or worsening date is partially available, the maximum of the earliest possible TEAE start date and the treatment start date will be used. When TEAE start date or worsening date is completely missing, the treatment start date will be used.

- An overview summary of the number (%) of patients with
  - any TEAE
  - any serious AE (regardless of treatment-emergent status)
  - any treatment-emergent SAE
  - any AE leading to death
  - any TEAE leading to permanent study drug discontinuation
  - any TEAE by maximum intensity, corrective treatment, and final outcome
  - time to onset of first TEAE
  - cumulative incidence at specified time points (K-M estimates at 1 week, 4 weeks, 12 weeks and 24 weeks)

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

11.4.3.1.2 Death

The following deaths summaries will be generated:

- Number (%) of patients who died by study period (TEAE, on-study) and reasons for death summarized on the safety population by treatment received

- Death in nonrandomized patients or randomized and not treated patients
• TEAE leading to death (death as an outcome on the AE CRF page as reported by the Investigator) by primary SOC, HLGT, HLT and PT showing number (%) of patients sorted by internationally agreed order of SOC and alphabetic order of HLGT, HLT, and PT.

Patient data listings will be provided for all AEs, TEAEs, SAE, AEs leading to study discontinuation, AESIs and deaths.

11.4.3.1.3 Clinical Laboratory Evaluation, Vital Signs and electrocardiogram data

Results and change from baseline for the parameters will be summarized by treatment group for baseline and each post baseline time point, endpoint, minimum and maximum value. Summary statistics will include number of patients, mean, standard deviation, median, q1, q3, minimum and maximum.

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

Listings will be provided with flags indicating clinically out-of range values, as well as PCSA values.

11.4.4 Analyses of pharmacokinetic, anti-drug antibodies and pharmacodynamic variables

11.4.4.1 Pharmacokinetic Descriptive Analysis

Concentrations of functional dupilumab in serum will be summarized using arithmetic and geometric means, SD, standard error of the mean (SEM), coefficient of variation (CV%), minimum, median, and maximum by treatment per visit.

Plasma concentrations of dupilumab will be used for population PK analysis by non-linear mixed effects modeling if warranted. Additional details of the analysis plan and the results will be provided in a separate document.

11.4.4.2 Anti-drug antibody analysis

Listings of anti-DUPILUMAB antibody results (Negative or titer value) will be presented by patient, time point and treatment groups. ADA titer levels will be classified into categories: Low, moderate and high. Low levels of ADA titers are defined as titers below 1000; moderate levels of ADA titers are defined as titers between 1000 and 10,000; high levels of ADA titers are defined as titers >10,000.

Anti-DUPILUMAB antibody assay results will be described categorically. The following summary will be provided for:

• Patients with any positive ADA assay response during the TEAE period.
• Patients with treatment induced positive ADA assay response during the TEAE period.

• Patients with treatment induced positive ADA assay response during the TEAE period will be further described as patients with transient positive response and patients with persistent positive response.

The patients with any positive ADA assay response during the TEAE period is defined as those having at least one sample positive in the ADA assay.

The treatment induced positive ADA assay response is defined as:

• Patients with no positive assay response at baseline but with a positive assay response during the TEAE period or

• Patients with a positive ADA assay response at baseline and also have at least a 4-fold increase in titer during the TEAE period.

A persistent positive response is a treatment induced positive ADA assay response in which at least 2 consecutive post-baseline samples from a patient are positive in the ADA assay or the last post-baseline sample collected is positive in the ADA assay. A transient positive response is defined as any treatment induced positive ADA assay response that is not considered persistent.

ADA variables will be assessed as absolute occurrence (N) and percent (%) of patients grouped by study defined groups and overall study population.

11.4.4.3 Pharmacodynamic analysis

The values to be used as baselines will be those collected on Day 1 (predose assessments). If any of the scheduled assessments on Day 1 are technically disqualified (eg, insufficient sample), then values determined at Screening can be used as baseline.

For all parameters, raw data, absolute changes from baseline and percent changes from baseline will be summarized in descriptive statistics by treatment group and time point.

Summary plots (mean +/- standard error of the mean) on raw data, absolute changes from baseline and percent changes from baseline will be provided by treatment group.

11.4.5 Analyses of quality of life/health economics variables

Change from baseline in the following variables: the ACQ-5 score, the quantitative variables of EQ-5D-3L (single index utility), SF-36 (8 domains, Physical Component Summary (PCS) and Mental Component Summary (MCS) will be analyzed with an MMRM approach described previously for the continuous secondary efficacy variables. Descriptive statistics including number of patients, mean, standard error and LS means will be provided. In addition, difference in LS means, the corresponding 95% CI and the p-value will be provided for comparisons of each dose against placebo.
11.4.6 Interim analysis

An early analysis will be performed at the end of treatment. No decision on the conduct of the study will be made based on this analysis. The assessment of change from baseline in NPS at Week 16 performed will be the final analysis of the primary endpoint. Hence there will be no need for alpha adjustment due to this early analysis.

To maintain study integrity with respect to the subsequent treatment visits, post-treatment follow-up visits, safety visits and analyses, a dissemination plan will be written. This plan will clearly identify the team (including the statistician) that will perform the early analysis and all related activities, restrict other company personnel from access to individual patient treatment allocation and site level analysis results, and ensure that the dedicated team will not participate in the data review or data decisions for the following post treatment analyses. However, the dedicated team can participate in the analysis following the final database lock. A Key Results Summary for the early analysis will be prepared and distributed to limited personnel.


12 ETHICAL AND REGULATORY STANDARDS

12.1 ETHICAL PRINCIPLES

This clinical trial will be conducted in accordance with the principles laid down by the 18th World Medical Assembly (Helsinki, 1964) and all applicable amendments laid down by the World Medical Assemblies, and the ICH guidelines for good clinical practice (GCP).

In compliance with Sanofi public disclosure commitments, this clinical trial will be recorded in the public registry website clinicaltrials.gov before the enrollment of the first patient. The registry will contain basic information about the trial sufficient to inform interested patients (and their healthcare practitioners) how to enroll in the trial.

12.2 LAWS AND REGULATIONS

This clinical trial will be conducted in compliance with all international guidelines, and national laws and regulations of the country(ies) in which the clinical trial is performed, as well as any applicable guidelines. See Section 13.1.

12.3 INFORMED CONSENT

The Investigator (according to applicable regulatory requirements), or a person designated by the Investigator, and under the Investigator's responsibility, should fully inform the patient of all pertinent aspects of the clinical trial including the written information giving approval/favorable opinion by the Ethics Committee (IRB/IEC). All participants should be informed to the fullest extent possible about the study, in language and terms they are able to understand.

Prior to a patient’s participation in the clinical trial, the written informed consent form should be signed, name filled in and personally dated by the patient or by the patient’s legally acceptable representative, and by the person who conducted the informed consent discussion. A copy of the signed and dated written informed consent form will be provided to the patient.

Prior to collection of blood for pharmacogenomics and nasal mucosa biopsy, the optional respective informed consent form (written) should be signed, name filled in, and personally dated by the patient or by the subject’s legally acceptable representative, and by the person who conducted the informed consent discussion. A copy of the signed and dated written optional informed consent form will be provided to the patient.

The informed consent form and the optional pharmacogenomic and nasal biopsy informed consent form used by the Investigator for obtaining the patient's informed consent must be reviewed and approved by the Sponsor prior to submission to the appropriate Ethics Committee (IRB/IEC) for approval/favorable opinion.
If the race/ethnic origin of the patients will be collected in the clinical trial, the scientific justification should be specified.

12.4 INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE (IRB/IEC)

As required by local regulation, the Investigator or the Sponsor must submit this clinical trial protocol to the appropriate Ethics Committee (IRB/IEC), and is required to forward to the respective other party a copy of the written and dated approval/favorable opinion signed by the Chairman with Ethics Committee (IRB/IEC) composition.

The clinical trial (study number, clinical trial protocol title and version number), the documents reviewed (clinical trial protocol, informed consent form, Investigator’s Brochure, Investigator’s curriculum vitae [CV], etc) and the date of the review should be clearly stated on the written (IRB/IEC) approval/favorable opinion.

IMP will not be released at the study site and the Investigator will not start the study before the written and dated approval/favorable opinion is received by the Investigator and the Sponsor.

During the clinical trial, any amendment or modification to the clinical trial protocol should be submitted to the Ethics Committee (IRB/IEC) before implementation, unless the change is necessary to eliminate an immediate hazard to the patients, in which case the IRB/IEC should be informed as soon as possible. It should also be informed of any event likely to affect the safety of patients or the continued conduct of the clinical trial, in particular any change in safety. All updates to the Investigator’s Brochure will be sent to the Ethics Committee (IRB/IEC).

A progress report is sent to the Ethics Committee (IRB/IEC) at least annually and a summary of the clinical trial’s outcome at the end of the clinical trial.
13 STUDY MONITORING

13.1 RESPONSIBILITIES OF THE INVESTIGATOR(S)

The Investigator(s) and delegated Investigator staff undertake(s) to perform the clinical trial in accordance with this clinical trial protocol, ICH guidelines for Good Clinical Practice and the applicable regulatory requirements.

The Investigator is required to ensure compliance with all procedures required by the clinical trial protocol and with all study procedures provided by the Sponsor (including security rules). The Investigator agrees to provide reliable data and all information requested by the clinical trial protocol (with the help of the CRF, Discrepancy Resolution Form [DRF] or other appropriate instrument) in an accurate and legible manner according to the instructions provided and to ensure direct access to source documents by Sponsor representatives.

If any circuit includes transfer of data, particular attention should be paid to the confidentiality of the patient's data to be transferred.

The Investigator may appoint such other individuals as he/she may deem appropriate as Subinvestigators to assist in the conduct of the clinical trial in accordance with the clinical trial protocol. All Subinvestigators shall be appointed and listed in a timely manner. The Subinvestigators will be supervised by and work under the responsibility of the Investigator. The Investigator will provide them with a copy of the clinical trial protocol and all necessary information.

13.2 RESPONSIBILITIES OF THE SPONSOR

The Sponsor of this clinical trial is responsible to health authorities for taking all reasonable steps to ensure the proper conduct of the clinical trial protocol as regards ethics, clinical trial protocol compliance, and integrity and validity of the data recorded on the CRFs. Thus, the main duty of the monitoring team is to help the Investigator and the Sponsor maintain a high level of ethical, scientific, technical and regulatory quality in all aspects of the clinical trial.

At regular intervals during the clinical trial, the site will be contacted, through monitoring visits, letters or telephone calls, by a representative of the monitoring team to review study progress, Investigator and patient compliance with clinical trial protocol requirements and any emergent problems. These monitoring visits will include but not be limited to review of the following aspects: patient informed consent, patient recruitment and follow-up, SAE documentation and reporting, AESI documentation and reporting, AE documentation, IMP allocation, patient compliance with the IMP regimen, IMP accountability, concomitant therapy use and quality of data.
13.3 SOURCE DOCUMENT REQUIREMENTS

According to the ICH guidelines for Good Clinical Practice, the monitoring team must check the CRF entries against the source documents, except for the pre-identified source data directly recorded in the CRF. The informed consent form will include a statement by which the patient allows the Sponsor’s duly authorized personnel, the Ethics Committee (IRB/IEC), and the regulatory authorities to have direct access to original medical records which support the data on the CRFs (eg, patient's medical file, appointment books, original laboratory records, etc). These personnel, bound by professional secrecy, must maintain the confidentiality of all personal identity or personal medical information (according to confidentiality and personal data protection rules).

13.4 USE AND COMPLETION OF CASE REPORT FORMS (CRFS) AND ADDITIONAL REQUEST

It is the responsibility of the Investigator to maintain adequate and accurate CRFs (according to the technology used) designed by the Sponsor to record (according to Sponsor instructions) all observations and other data pertinent to the clinical investigation in a timely manner. All CRFs should be completed in their entirety in a neat, legible manner to ensure accurate interpretation of data.

Should a correction be made, the corrected information will be entered in the e-CRF overwriting the initial information. An audit trail allows identifying the modification.

Data are available within the system to the Sponsor as soon as they are entered in the e-CRF.

The computerized handling of the data by the Sponsor when available in the eCRF may generate additional requests (DRF) to which the Investigator is obliged to respond by confirming or modifying the data questioned. The requests with their responses will be managed through the e-CRF.

13.5 USE OF COMPUTERIZED SYSTEMS

Computerized systems used during the different steps of the study are:

- For screening and randomization activities, IVRS/IWRS
- For data management activities, Oracle RDC
- For statistical activities, SAS, nQuery Advisor 6.01
- For pharmacovigilance activities, AWARE
- For investigational product ordering/tracking, NASCA and CSMS
- For monitoring activities, IMPACT, POLARIS, CTI, I/J review, CSMS
- For medical writing activities, DOMASYS
14 ADMINISTRATIVE EXPECTATIONS

14.1 CURRICULUM VITAE

A current copy of the curriculum vitae describing the experience, qualification and training of each Investigator and Subinvestigator will be signed, dated and provided to the Sponsor prior to the beginning of the clinical trial.

14.2 RECORD RETENTION IN STUDY SITES

The Investigator must maintain confidential all study documentation, and take measures to prevent accidental or premature destruction of these documents.

The Investigator should retain the study documents at least 15 years after the completion or discontinuation of the clinical trial.

However, applicable regulatory requirements should be taken into account in the event that a longer period is required.

The Investigator must notify the Sponsor prior to destroying any study essential documents following the clinical trial completion or discontinuation.

If the Investigator's personal situation is such that archiving can no longer be ensured by him/her, the Investigator shall inform the Sponsor and the relevant records shall be transferred to a mutually agreed upon designee.

14.3 CONFIDENTIALITY

All information disclosed or provided by the Sponsor (or any company/institution acting on their behalf), or produced during the clinical trial, including, but not limited to, the clinical trial protocol, the CRFs, the Investigator's Brochure and the results obtained during the course of the clinical trial, is confidential, prior to the publication of results. The Investigator and any person under his/her authority agree to undertake to keep confidential and not to disclose the information to any third party without the prior written approval of the Sponsor.

However, the submission of this clinical trial protocol and other necessary documentation to the Ethics committee (IRB/IEC) is expressly permitted, the IRB/IEC members having the same obligation of confidentiality.

The Subinvestigators shall be bound by the same obligation as the Investigator. The Investigator shall inform the Subinvestigators of the confidential nature of the clinical trial.
The Investigator and the Subinvestigators shall use the information solely for the purposes of the clinical trial, to the exclusion of any use for their own or for a third party's account.

Furthermore, the Investigator and the Sponsor agree to adhere to the principles of personal data confidentiality in relation to the patients, Investigator and its collaborators involved in the study.

14.4 PROPERTY RIGHTS

All information, documents and IMP provided by the Sponsor or its designee are and remain the sole property of the Sponsor.

14.5 DATA PROTECTION

- The patient's personal data, which are included in the Sponsor database shall be treated in compliance with all applicable laws and regulations;

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

- The Sponsor also collects specific data regarding Investigator as well as personal data from any person involved in the study which may be included in the Sponsor’s databases, shall be treated by both the Sponsor and the Investigator in compliance with all applicable laws and regulations.

Patient race or ethnicity will be collected in this study because these data are frequently required by health authorities.

The data collected in this study will only be used for the purpose(s) of the study and to document the evaluation of the benefit/risk ratio, efficacy and safety of the product(s). They may be further processed if they have been anonymized.
14.7 SPONSOR AUDITS AND INSPECTIONS BY REGULATORY AGENCIES

For the purpose of ensuring compliance with the clinical trial protocol, Good Clinical Practice and applicable regulatory requirements, the Investigator should permit auditing by or on the behalf of the Sponsor and inspection by regulatory authorities.

The Investigator agrees to allow the auditors/inspectors to have direct access to his/her study records for review, being understood that these personnel is bound by professional secrecy, and as such will not disclose any personal identity or personal medical information.

The Investigator will make every effort to help with the performance of the audits and inspections, giving access to all necessary facilities, data, and documents.

As soon as the Investigator is notified of a planned inspection by the authorities, he will inform the Sponsor and authorize the Sponsor to participate in this inspection.

The confidentiality of the data verified and the protection of the patients should be respected during these inspections.

Any result and information arising from the inspections by the regulatory authorities will be immediately communicated by the Investigator to the Sponsor.

The Investigator shall take appropriate measures required by the Sponsor to take corrective actions for all problems found during the audit or inspections.

14.8 PREMATURE DISCONTINUATION OF THE STUDY OR PREMATURE CLOSE-OUT OF A SITE

14.8.1 Decided by the Sponsor

Decided by the Sponsor in the following cases

- If the information on the product leads to doubt as to the benefit/risk ratio;
- If the Investigator has received from the Sponsor all IMP, means and information necessary to perform the clinical trial and has not included any patient after a reasonable period of time mutually agreed upon;
• In the event of breach by the Investigator of a fundamental obligation under this agreement, including but not limited to breach of the clinical trial protocol, breach of the applicable laws and regulations or breach of the ICH guidelines on Good Clinical Practice;

• If the total number of patients are included earlier than expected;

In any case the Sponsor will notify the Investigator of its decision by written notice.

14.8.2 Decided by the Investigator

The Investigator must notify (30 days' prior notice) the Sponsor of his/her decision and give the reason in writing.

In all cases (decided by the Sponsor or by the Investigator), the appropriate Ethics Committee(s) (IRB/IEC) and Health Authorities should be informed according to applicable regulatory requirements.

14.9 CLINICAL TRIAL RESULTS

The Sponsor will be responsible for preparing a clinical study report and to provide a summary of study results to the Investigator.
15 CLINICAL TRIAL PROTOCOL AMENDMENTS

All appendices attached hereto and referred to herein are made part of this clinical trial protocol.

The Investigator should not implement any deviation from, or changes of the clinical trial protocol without agreement by the Sponsor and prior review and documented approval/favorable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to clinical trial Patients, or when the change(s) involves only logistical or administrative aspects of the trial. Any change agreed upon will be recorded in writing, the written amendment will be signed by the Investigator and by the Sponsor and the signed amendment will be filed with this clinical trial protocol.

Any amendment to the clinical trial protocol requires written approval/favorable opinion by the Ethics Committee (IRB/IEC) prior to its implementation, unless there are overriding safety reasons.

In some instances, an amendment may require a change to the informed consent form. The Investigator must receive an IRB/IEC approval/favorable opinion concerning the revised informed consent form prior to implementation of the change and patient signature should be re-collected if necessary.
16 BIBLIOGRAPHIC REFERENCES


17 APPENDICES

Appendix A. List of Prohibited Live, Attenuated Vaccines

Bacillus Chickenpox (Varicella)

Intranasal influenza (FluMist-Influenza); inactive influenza vaccine delivered by injection is permitted

Measles (Rubeola)

Measles-mumps-rubella (MMR) combination

Measles-mumps-rubella-varicella (MMRV) combination

Mumps

Oral polio (Sabin)

Oral typhoid

Rotavirus

Rubella

Smallpox (Vaccinia)

Varicella Zoster (shingles)

Yellow fever
# Appendix B. Equipotent daily doses of Inhaled Glucocorticosteroids for adults

<table>
<thead>
<tr>
<th>Drug</th>
<th>Low Daily dose (μg)</th>
<th>Medium Daily dose (μg)</th>
<th>High Daily dose (μg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beclomethasone dipropionate – CFC</td>
<td>200-500</td>
<td>&gt;500-1000</td>
<td>&gt;1000-2000</td>
</tr>
<tr>
<td>Beclomethasone dipropionate – H FA</td>
<td>100-250</td>
<td>&gt;250-500</td>
<td>&gt;500-1000</td>
</tr>
<tr>
<td>Budesonide</td>
<td>200-400</td>
<td>&gt;400-800</td>
<td>&gt;800-1600</td>
</tr>
<tr>
<td>Ciclesonide</td>
<td>80-160</td>
<td>&gt;160-320</td>
<td>&gt;320-1280</td>
</tr>
<tr>
<td>Flunisolide</td>
<td>500-1000</td>
<td>&gt;1000-2000</td>
<td>&gt;2000</td>
</tr>
<tr>
<td>Fluticasone propionate</td>
<td>100-250</td>
<td>&gt;250-500</td>
<td>&gt;500-1000</td>
</tr>
<tr>
<td>Mometasone furoate</td>
<td>200</td>
<td>≥400</td>
<td>≥800</td>
</tr>
<tr>
<td>Triamcinolone acetonide</td>
<td>400-1000</td>
<td>&gt;1000-2000</td>
<td>2000</td>
</tr>
</tbody>
</table>
Appendix C. Definition of Anaphylaxis

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


Clinical criteria for diagnosing anaphylaxis

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

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula)
   
   AND AT LEAST ONE OF THE FOLLOWING
   
   a. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   b. Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)

2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
   
   a. Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)
   b. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   c. Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)
   d. Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)

3. Reduced BP after exposure to known allergen for that patient (minutes to several hours):
   
   a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP*
   b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person’s baseline

PEF, Peak expiratory flow; BP, blood pressure.

*Low systolic blood pressure for children is defined as less than 70 mm Hg from 1 month to 1 year, less than (70 mm Hg + [2 x age]) from 1 to 10 years, and less than 90 mm Hg from 11 to 17 years.
Appendix D. General Guidance for the follow-up of laboratory abnormalities by Sanofi
**NEUTROPENIA**

Neutrophils < 1500/mm³ or according to ethnic group

- Repeat immediately a full blood count if value close to 1500/mm³

**Neutrophils < 1500/mm³ confirmed with signs of infection**

1. **DISCONTINUE**
   - Investigational Medicinal Product, hospitalization should be considered

2. **PERFORM**
   - biological investigations for infection

**Neutrophils < 1500/mm³ confirmed with no signs of infection**

1. **DISCONTINUE**
   - Investigational Medicinal Product

2. **INVESTIGATE**
   - for infection

In both situations

3. **INFORM**
   - the local monitor

4. **INVESTIGATE**
   - previous treatments particularly long-term, even a long time ago, exposure to toxic agents, e.g., benzene, X-rays, etc.

5. **PERFORM**
   - and collect the following investigations (results):
     - RBC and platelet counts
     - Serology: EBV, (HIV), mumps, measles, rubella

6. **DECISION**
   - for bone marrow aspiration: to be taken in specialized unit

7. **FREEZE**
   - serum (5 mL x 2) on Day 1 (cessation of investigational medicinal product) and Day 5 (for further investigations)

8. **MONITOR**
   - the leukocyte count 3 times per week for at least one week, then twice a month until it returns to normal

**Note:**
- The procedures described in the above flowchart are to be discussed with the patient only in case the event occurs. If applicable (according to local regulations), an additional consent (e.g., for HIV testing) will only be obtained in the case the event actually occurs.
- For individuals of African descent, the relevant value of concern is <1000/mm³

Neutropenia are to be recorded as AE only if they are:
- 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 [in that case, the event (SAE) should be notified within 24 hours to the MT], and/or
- Defined as an Adverse Event of Special Interest (AESI)
THROMBOCYTOPENIA

Platelets < 100 000/mm³ (rule out EDTA – induced pseudo-thrombocytopenia)  

Repeat immediately the count (rule out EDTA anticoagulant in the sample)

Platelets < 100 000/mm³ confirmed with bleeding

1. DISCONTINUE Investigational Medicinal Product
2. HOSPITALIZATION should be considered

Platelets < 100 000/mm³ confirmed with no bleeding

1. DISCONTINUE Investigational Medicinal Product
2. INVESTIGATE for bleeding

In both situations

3. INFORM the local Monitor
4. QUESTION about last intake of quinine (drinks), alcoholism, heparin administration
5. PERFORM or collect the following investigations:
   • Complete blood count, schizocytes, creatinine
   • Bleeding time and coagulation test (fibrinogen, PT, aPTT), Fibrin Degradation Product
   • Viral serology: EBV, HIV, mumps, measles, rubella
6. FREEZE serum (5 mL x 2) on Day 1 (end of treatment) and Day 5 to test for drug-induced antiplatelets antibodies
7. DECISION for bone marrow aspiration: to be taken in specialized unit
   • On Day 1 in the case of associated anemia and/or leukopenia
   • On Day 8 if the Platelets remain < 50 000/mm³
8. MONITOR the platelet count every day for at least one week and then regularly until it returns to normal

Note: the procedures described in the above flowchart are to be discussed with the patient only in case the event occurs. If applicable (according to local regulations), an additional consent (e.g., for HIV testing) will only be obtained in the case the event actually occurs.

Thrombocytopenia are to be recorded as AE only if they are:
• 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 [in that case, the event (SAE) should be notified within 24 hours to the MT], and/or
• Defined as an Adverse Event of Special Interest (AESI)
**INCREASE IN ALT**

ALT ≥ 3 ULN (if baseline ALT < ULN)
Or, ALT ≥ 2 times the baseline value  
(if baseline ALT ≥ ULN)

ALT ≤ 5 ULN  
(if baseline ALT < ULN)
Or, ALT ≤ 3 times the baseline value  
(If baseline ALT ≥ ULN)

ALT > 5 ULN  
(if baseline ALT < ULN)
Or, ALT > 3 times the baseline value  
(if baseline ALT ≥ ULN)

Total bilirubin ≤ 2 ULN

Monitor LFTs every 48 hours  
If Not Possible

Investigational Medicinal Product administration can be continued, as long as – under close monitoring – conditions for stopping are not met

DISCONTINUE ADMINISTRATION OF INVESTIGATIONAL MEDICINAL PRODUCT

**IN ANY CASE, FOLLOW** the instructions #1 to 6 listed in the box below.

1. **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
2. **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, anti-HCV and HCV RNA , anti-CMV IgM and anti-HEV IgM antibodies,
   - Auto-antibodies : anti-nuclear, anti-DNA, anti-smooth muscle, anti-LKM
   - Hepatobiliary ultrasonography (can be completed by other imaging investigations if needed)
3. **CONSIDER** consultation with hepatologist
4. **CONSIDER** patient hospitalisation if INR>2 (or PT<50%) and/or central nervous system disturbances suggesting hepatic encephalopathy.
5. **MONITOR** LFTs
   - If investigational medicinal product is continued: every 48 hours until return to normal (<2ULN) or baseline. If ALT elevation persists beyond 2 weeks then perform LFTs every 2 weeks and 15 to 30 days after the last dose according to the study protocol.
   - If investigational medicinal product is discontinued: as closely as possible to every 48 hours until stabilization then every 2 weeks until return to normal (<2ULN) or baseline or for at least 3 months, whichever comes last.
6. **FREEZE** serum (5 ml X 2)

**Note:** In addition, as soon as a seriousness criterion is met, the event should be notified within 24 hours to the Monitoring Team.
ACUTE RENAL FAILURE

Rapid increase in serum creatinine over 150 μmol/L or rapid decrease in creatinine clearance below 50ml/mn

Can be rapidly reversed:
- By volume repletion
- Or relief of urinary tract obstruction (according to etiology)

Cannot be rapidly reversed:
- Occurrence/aggravation of life threatening symptoms of ARF: anemia, hyperkalemia, hyperuricemia, metabolic acidosis, cardiac insufficiency, pulmonary edema, arrhythmia, DIC, etc.
- And/or predominant elimination of Investigational Medicinal Product by renal route

1. INFORM the local monitor
2. DISCONTINUE Investigational Medicinal Product administration
3. HOSPITALIZATION should be considered and seek for nephrologic advice
4. PERFORM the following examinations:
   - BP, HR, hydration status, ECG
   - Blood count
   - Liver function tests + CPK
   - Biochemistry, including urea
   - Urinalysis
5. FREEZE serum (5mL x 2)
6. MONITOR renal function until return to baseline level (every day at the beginning, then every week)

Acute renal failure is to be recorded as AE only if it is:
- Symptomatic, and/or
- Requiring either corrective treatment or consultation, and/or
- Leading to IMP discontinuation or modification of dosing, and/or
- Fulfilling a seriousness criterion [in that case, the event (SAE) should be notified within 24 hours to the MT], and/or
- Defined as an Adverse Event of Special Interest (AESI)
SUSPICION OF RHABDOMYOLYSIS

Muscular symptoms (myalgia, pain, weakness, dark urines)  Systematic CPK assessment as per protocol

Perform CPK

If Increase in CPK (expressed in ULN)

> 3 ULN

Repeat immediately the count. If confirmed, inform the local monitor and INVESTIGATE for the origin:

- **PERFORM**:
  - ECG
  - CPK-MB -MM
  - Troponin
  - Creatinine
  - Iono (k+, Ca²⁺)
  - Transaminases + Total and conjugated bilirubin
  - Myoglobin (serum and urines)

- **FREEZE** SERUM (5mlx2) for PK
- **INTERVIEW** the patient about a recent intensive muscular effort, trauma, convulsions, electrical injury, injury or stress to the skeletal muscle, multiple intramuscular injections, recent surgery, concomitant medications, consumption of alcohol, morphine, cocaine.
- **SEARCH** for alternative causes to cardiac or muscular toxicity, ie: stroke, pulmonary infarction, dermatomyositis or polymyositis, convulsions, hypothyroidism, delirium tremens, muscular dystrophies.

If either the cardiac origin or the rhabdomyolysis is confirmed or if CPK > 10 ULN:

1. **DISCONTINUE** Investigational Medicinal Product administration
2. **MONITOR** CPK every 3 days for the first week then once weekly until return to normal or for at least 3 months
3. **HOSPITALIZATION** should be considered

If the cardiac origin or the rhabdomyolysis is ruled out and if CPK ≤ 10 ULN:

**MONITOR** CPK every 3 days for the first week then once weekly until return to normal or for at least 3 months

Suspicion of rhabdomyolysis is to be recorded as AE only if it is:

- Symptomatic, and/or
- Requiring either corrective treatment or consultation, and/or
- Leading to IMP discontinuation or modification of dosing, and/or
- Fulfilling a seriousness criterion [in that case, the event (SAE) should be notified within 24 hours to the MT], and/or
- Defined as an Adverse Event of Special Interest (AESI)
Appendix E. QoL, health economic and Patient Reported Outcomes (PRO) questionnaires
**Asthma Control Questionnaire, 5-question Version**

Please answer Questions 1-5.

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

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

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

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

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

5. In general, during the past week, how much of the time did you wheeze?
0  Not at all
1  Hardly any of the time
2  A little of the time
3  A moderate amount of the time
4  A lot of the time
5  Most of the time
6  All the time
Visual Analogue Scale (VAS)
To evaluate the total severity, the patient is asked to indicate on a VAS the answer to the question:

![Visual Analogue Scale Image]
22-item Sinonasal Outcome Test SNOT-22

Below you will find a list of symptoms and social/emotional consequences of your nasal disorder. We would like to know more about these problems and would appreciate you answering the following question to the best of your ability. There are no right or wrong answers, and only you can provide us with this information. Please rate your problems, as they have been over the past two weeks. Thank you for your participation.

<table>
<thead>
<tr>
<th>A: Considering how severe the problem is when you experience it and how frequently it happens, please rate each item below on how 'bad' it is by circling the number that corresponds with how you feel using this scale</th>
<th>No problem</th>
<th>Very mild problem</th>
<th>Mild or slight problem</th>
<th>Moderate problem</th>
<th>Severe problem</th>
<th>Problem as bad as it can be</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Need to blow nose</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>2. Sneezing</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>3. Runny nose</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>4. Cough</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>5. Post nasal discharge (dripping at the back of your nose)</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>6. Thick nasal discharge</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>7. Ear fullness</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>8. Dizziness</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>9. Ear pain/pressure</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>10. Facial pain/pressure</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>11. Difficulty falling asleep</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>12. Waking up at night</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>13. Lack of a good night’s sleep</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>14. Waking up tired</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>15. Fatigue during the day</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>16. Reduced productivity</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>17. Reduced concentration</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>18. Frustrated/restless/irritable</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>19. Sad</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>20. Embarrassed</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>21. Sense of taste/smell</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>22. Blockage/congestion of nose</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>
EQ-5D-3L

By placing a checkmark in one box in each group below, please indicate which statements best describe your own health state today.

**Mobility**
- I have no problems in walking about
- I have some problems in walking about
- I am confined to bed

**Self-Care**
- I have no problems with self-care
- I have some problems washing or dressing myself
- I am unable to wash or dress myself

**Usual Activities (e.g. work, study, housework, family or leisure activities)**
- I have no problems with performing my usual activities
- I have some problems with performing my usual activities
- I am unable to perform my usual activities

**Pain/Discomfort**
- I have no pain or discomfort
- I have moderate pain or discomfort
- I have extreme pain or discomfort

**Anxiety/Depression**
- I am not anxious or depressed
- I am moderately anxious or depressed
- I am extremely anxious or depressed
To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.
SF-36

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. Thank you for completing this survey!

For each of the following questions, please mark an ☐ in the box that best describes your answer.

1. In general, would you say your health is:

<table>
<thead>
<tr>
<th>Excellent</th>
<th>Very good</th>
<th>Good</th>
<th>Fair</th>
<th>Poor</th>
</tr>
</thead>
<tbody>
<tr>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>

2. Compared to one year ago, how would you rate your health in general now?

<table>
<thead>
<tr>
<th>Much better now than one year ago</th>
<th>Somewhat better now than one year ago</th>
<th>About the same as one year ago</th>
<th>Somewhat worse now than one year ago</th>
<th>Much worse now than one year ago</th>
</tr>
</thead>
<tbody>
<tr>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>
3. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

<table>
<thead>
<tr>
<th>Activity</th>
<th>Yes, limited a lot</th>
<th>Yes, limited a little</th>
<th>No, not limited at all</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Lifting or carrying groceries</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Climbing several flights of stairs</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Climbing one flight of stairs</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Bending, kneeling, or stooping</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Walking more than a mile</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Walking several hundred yards</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Walking one hundred yards</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Bathing or dressing yourself</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
</tbody>
</table>
4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

- Cut down on the amount of time you spent on work or other activities
  - None of the time
  - A little of the time
  - Some of the time
  - Most of the time
  - All of the time

5. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

- Cut down on the amount of time you spent on work or other activities
  - None of the time
  - A little of the time
  - Some of the time
  - Most of the time
  - All of the time

- Accomplished less than you would like
  - None of the time
  - A little of the time
  - Some of the time
  - Most of the time
  - All of the time

- Did work or other activities less carefully than usual
  - None of the time
  - A little of the time
  - Some of the time
  - Most of the time
  - All of the time
6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

<table>
<thead>
<tr>
<th>Not at all</th>
<th>Slightly</th>
<th>Moderately</th>
<th>Quite a bit</th>
<th>Extremely</th>
</tr>
</thead>
</table>

7. How much bodily pain have you had during the past 4 weeks?

<table>
<thead>
<tr>
<th>None</th>
<th>Very mild</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Very Severe</th>
</tr>
</thead>
</table>

8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

<table>
<thead>
<tr>
<th>Not at all</th>
<th>A little bit</th>
<th>Moderately</th>
<th>Quite a bit</th>
<th>Extremely</th>
</tr>
</thead>
</table>
9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks...

<table>
<thead>
<tr>
<th>All of the time</th>
<th>Most of the time</th>
<th>Some of the time</th>
<th>A little of the time</th>
<th>None of the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
</tr>
</tbody>
</table>

- Did you feel full of life? ........................................ [ ] ▼ [ ▼ ] [ ▼ ] [ ▼ ] [ ▼ ]
- Have you been very nervous? .................................. [ ▼ ] [ ▼ ] [ ▼ ] [ ▼ ] [ ▼ ]
- Have you felt so down in the dumps that nothing could cheer you up? ........................................ [ ▼ ] [ ▼ ] [ ▼ ] [ ▼ ] [ ▼ ]
- Have you felt calm and peaceful? .......................... [ ▼ ] [ ▼ ] [ ▼ ] [ ▼ ] [ ▼ ]
- Did you have a lot of energy? ...................................... [ ▼ ] [ ▼ ] [ ▼ ] [ ▼ ] [ ▼ ]
- Have you felt downhearted and depressed? ................. [ ▼ ] [ ▼ ] [ ▼ ] [ ▼ ] [ ▼ ]
- Did you feel worn out? .................................................. [ ▼ ] [ ▼ ] [ ▼ ] [ ▼ ] [ ▼ ]
- Have you been happy? .................................................... [ ▼ ] [ ▼ ] [ ▼ ] [ ▼ ] [ ▼ ]
- Did you feel tired? .......................................................... [ ▼ ] [ ▼ ] [ ▼ ] [ ▼ ] [ ▼ ]

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?

<table>
<thead>
<tr>
<th>All of the time</th>
<th>Most of the time</th>
<th>Some of the time</th>
<th>A little of the time</th>
<th>None of the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
</tr>
</tbody>
</table>

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11. How TRUE or FALSE is each of the following statements for you?

<table>
<thead>
<tr>
<th>Definitely true</th>
<th>Mostly true</th>
<th>Don't know</th>
<th>Mostly false</th>
<th>Definitely false</th>
</tr>
</thead>
<tbody>
<tr>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
</tr>
</tbody>
</table>

- I seem to get sick a little easier than other people. □ □ □ □ □
- I am as healthy as anybody I know. □ □ □ □ □
- I expect my health to get worse. □ □ □ □ □
- My health is excellent. □ □ □ □ □

THANK YOU FOR COMPLETING THESE QUESTIONS!
NASAL POLYP RELATED RESOURCE USE Questionnaire

This questionnaire will record information regarding resource use, including healthcare and work related, for nasal polyps.

Employment status
Check one primary category (Excluding charity activity)

Employed:
- Full time
- Part time  Please specify time in %:
  (Example: an half-time = 50%)

Non-Employed:
- Unemployed (Including housewife, student,...)
- Retired

NASAL POLYPS-RELATED RESOURCE USE

Please describe resources associated to nasal polyps that occurred in the past 4 weeks

OUTPATIENT VISITS

In the past 4 weeks, how many outpatient visits did the patient have by a physician or another healthcare professional for his nasal polyps (other than the planned visits of the protocol)?

General Practitioner
Otolaryngologist (ENT specialist)
Allergist
Internist
Nurse
Other  Please specify: ____________________
  ER visit related to NP

SICK LEAVES / DAYS OFF

If the patient is Employed (Full time or Part time), please complete both questions 1 and 2
If the patient is Unemployed or Retired, please complete the question 2 only

1- In the past 4 weeks, if the patient is Employed, how many days did the patient miss from work due to nasal polyps:

__ __ days (1/2 days = 0.5 days)
Please specify the reason(s):
- Breathing difficulties
- Fatigue
- Depression / Anxiety
- Other  Please specify the main reason: ____________________

2- In the past 4 weeks, how many days did the patient approximately miss from his/her usual activities other than work due to nasal polyps:

__ __ days (1/2 days = 0.5 days)
Please specify the reason(s):
- Breathing difficulties
- Fatigue
- Depression / Anxiety
- Other  Please specify the main reason: ____________________
**ACT12340 16.1.1 Protocol**

## ELECTRONIC SIGNATURES

<table>
<thead>
<tr>
<th>Signed by</th>
<th>Meaning of Signature</th>
<th>Server Date (dd-MMM-yyyy HH:mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Approval</td>
<td>01-May-2013 19:50 GMT+0</td>
<td></td>
</tr>
<tr>
<td>Clinical Approval</td>
<td>02-May-2013 13:46 GMT+0</td>
<td></td>
</tr>
</tbody>
</table>
AMENDED CLINICAL TRIAL PROTOCOL NO.3

A randomized, double-blind, phase 2, placebo controlled, 2 arm study to evaluate Dupilumab in patients with bilateral nasal polyposis and chronic symptoms of sinusitis

COMPOUND: dupilumab - SAR231893
STUDY NUMBER: ACT12340
VERSION DATE / STATUS: 16-Dec-2013 /
Approved CLINICAL STUDY DIRECTOR:

Protocol Amendment 3 Version number: 1 Date: 16-Dec-2013
Amended Clinical Trial Protocol 2 Version number 1 Date: 27-Nov-2013
Protocol Amendment 2 Version number 1 Date: 27-Nov-2013
Amended Clinical Trial Protocol 1 Version number 1 Date: 13-Aug-2013
Protocol Amendment 1 Version number: 1 Date: 13-Aug-2013
Clinical Trial Protocol Version number: 1 Date : 30-Apr-2013

EudraCT or IND number :  2013-001803-35 / 105379

Any and all information presented in this document shall be treated as confidential and shall remain the exclusive property of Sanofi (or any of its affiliated companies).
<table>
<thead>
<tr>
<th>NAMES AND ADDRESSES OF</th>
</tr>
</thead>
<tbody>
<tr>
<td>COORDINATING INVESTIGATOR</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>MONITORING TEAM’S REPRESENTATIVE</td>
</tr>
<tr>
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<tr>
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</tr>
<tr>
<td>SPONSOR</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>OTHER EMERGENCY TELEPHONE NUMBERS</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>
## CLINICAL TRIAL SUMMARY

<table>
<thead>
<tr>
<th>COMPOUND: Dupilumab (SAR231893) STUDY No: SAR231893-ACT12340</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TITLE</strong></td>
</tr>
<tr>
<td><strong>INVESTIGATOR/TRIAL LOCATION</strong></td>
</tr>
<tr>
<td><strong>PHASE OF DEVELOPMENT</strong></td>
</tr>
<tr>
<td><strong>STUDY OBJECTIVE(S)</strong></td>
</tr>
<tr>
<td><strong>STUDY DESIGN</strong></td>
</tr>
</tbody>
</table>
### Post-treatment Period for PK, immune response, safety, efficacy (16 weeks)

After completing 16 weeks of treatment with the investigational medicinal product (or following early discontinuation of IMP), patients will be instructed to:

- Return to the study site every 4 weeks during the Post-treatment Period for evaluations of PK and ADA, physical examination, QoL, efficacy, safety and a last endoscopy at the end of study
- Continue to complete e-diary for symptom evaluation
- Continue on MFNS stable dose during post-treatment period
- Contact the Investigator during the Post-treatment Period if the symptoms worsen requiring medical attention
- Report any AE

Patients who discontinue prematurely from treatment are assessed as soon as possible using the procedures normally planned for the End of Treatment Visit and the 4 Post-treatment Period Visits

### STUDY POPULATION

#### Main selection criteria

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with:</td>
</tr>
<tr>
<td>1. A minimum bilateral nasal polyp score of 5 out of a maximum score of 8 for both nostrils (with at least a score of 2 for each nostril) despite completion of a prior INCS treatment for at least 8 weeks before screening</td>
</tr>
<tr>
<td>2. Presence of at least two of the following symptoms prior to screening: nasal blockade/obstruction/congestion or nasal discharge (anterior/posterior nasal drip); facial pain/pressure; reduction or loss of smell</td>
</tr>
</tbody>
</table>

**Main exclusion criteria** (see Section 7.2 for complete list)

- Patients <18 or >65 years of age
- SNOT22<7
- Patient who has taken other investigational drugs or prohibited therapy for this study within 2 months before screening or 5 half-lives, whichever is longer:
  - who have required a burst of systemic corticosteroids (for example oral, intravenous, intramuscular corticosteroids) within the 2 months before screening or are scheduled to receive systemic corticosteroids during the study period for another condition
  - who have required intranasal corticosteroid drops within 1 month prior to screening
  - Monoclonal antibody (mAB) and immunosuppressive treatment
  - Anti-immunoglobulin E (IgE) therapy (omalizumab) within 130 days of Visit 1
  - Leukotriene antagonists / modifiers unless patient is on a continuous treatment for at least 30 days prior to Visit 1
- Patients who have undergone any nasal surgery (including polypectomy) within 6 months before screening or have had more than 5 sinonasal surgeries in the past of which maximal 2 were surgeries changing the lateral wall structure of the nose
**Patients with conditions/concomitant diseases making them non-evaluable for the primary efficacy endpoint such as:**
- Antrochoanal polyps
- Nasal septal deviation that would occlude at least one nostril
- Acute sinusitis, nasal infection or upper respiratory infection at screening or in the 2 weeks before screening
- Ongoing rhinitis medicamentosa
- Churg-Strauss syndrome, Young’s syndrome, Kartagener’s syndrome or dyskinetic ciliary syndromes, concomitant cystic fibrosis
- Signs or a CT scan suggestive of Allergic fungal rhinosinusitis

**Among patients with co-morbid asthma are excluded if one of the following criteria is meet:**
- Patients with FEV1 < 60% (of predicted normal)
- Patients with an asthma exacerbation requiring systemic (oral and/or parenteral) steroid treatment or hospitalization for >24h for treatment of asthma, within 3 month prior to screening or are on a dose of greater than 1000 μg fluticasone or an equivalent inhaled corticosteroids (Appendix B)

<table>
<thead>
<tr>
<th>Total expected number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>A total of 56 NP patients (with or without co-morbid asthma) will be randomized. To ensure at least 28 patients with co-morbid asthma need for subgroup analysis: Recruitment of NP patient without co-morbid asthma will stop when approximately 28 patients without asthma are randomized.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>STUDY TREATMENT(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Investigational medicinal product(s)</strong></td>
</tr>
<tr>
<td><strong>Formulation</strong></td>
</tr>
<tr>
<td>Dupilumab or matching placebo:</td>
</tr>
<tr>
<td>Sterile dupilumab in 5 mL glass vials; each vial will contain a withdrawable volume of 2 mL: 150 mg/mL solution (300 mg dose / 2 mL)</td>
</tr>
<tr>
<td>Sterile placebo in identically matched glass 5 mL vials; each vial contains a withdrawable volume of 2 mL</td>
</tr>
<tr>
<td><strong>Route(s) of administration</strong></td>
</tr>
<tr>
<td>Subcutaneous injection</td>
</tr>
<tr>
<td><strong>Dose regimen</strong></td>
</tr>
<tr>
<td>Dupilumab 600 mg SC on D1 followed by weekly 300 mg SC injection for 15 weeks</td>
</tr>
<tr>
<td>Placebo SC loading dose on D1 followed by weekly SC injection for 15 weeks</td>
</tr>
<tr>
<td><strong>Noninvestigational medicinal product(s) (if applicable)</strong></td>
</tr>
<tr>
<td><strong>Formulation</strong></td>
</tr>
<tr>
<td>Mometasone furoate (NASONEX®) 50 μg/actuation nasal spray, suspension</td>
</tr>
<tr>
<td>Nasal Spray is contained in a bottle, that contains 18 g (140 actuations) of product formulation</td>
</tr>
<tr>
<td>Route(s) of administration</td>
</tr>
<tr>
<td>----------------------------</td>
</tr>
<tr>
<td>Dose regimen</td>
</tr>
</tbody>
</table>

**ENDPOINT(S)**

<table>
<thead>
<tr>
<th>Primary endpoint</th>
<th>Change from baseline at week 16 in endoscopic NPS</th>
</tr>
</thead>
</table>

**Secondary endpoint(s):**

Change from baseline at Week 16 in:
- Patient reported symptoms
  - 22-item Sinonasal Outcome Test (SNOT-22)
  - Subject-assessed nasal congestion/obstruction, anterior rhinorrhea (runny nose), posterior rhinorrhea (post nasal drip), and, loss of sense of smell
  - Daily subject-assessed nasal peak inspiratory flow (NPIF)
  - Patient-rated rhinosinusitis symptoms severity using a visual analog scale (VAS)
- Smell test (UPSIT)
- CT scan assessments
- In NPS in patients with co-morbid asthma

Time to first response (≥1 point improvement) in NPS

**Safety, tolerability and other exploratory endpoints:**

- Spirometry
- 5-item asthma control questionnaire (ACQ-5) in asthma sub-group
- Time to study treatment discontinuation
- Incidence of treatment discontinuation due to need for OCS or nasal surgery
- Adverse events (AE)
- Vital signs
- Physical examination
- Electrocardiogram (ECG)
- Clinical laboratory tests

**Pharmacokinetic and Immune Response to Dupilumab**

- Serum dupilumab concentrations
- Anti-drug antibodies (ADA)

**Biomarkers:**

- Serum: total IgE, Staphylococcal enterotoxin A IgE, Staphylococcal enterotoxin B IgE, ECP, TARC, periostin
- Plasma: Eotaxin-3

**Quality of life (QoL) measurements:**

Change from baseline at Week 16 in:
- 36-item short form health survey (SF36)
- European quality of life scale (EQ-5D)
- Nasal polyp related resource use questionnaire
## Assessment Schedule

<table>
<thead>
<tr>
<th>Period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening period: 4 weeks</td>
</tr>
<tr>
<td>Randomized treatment period: 16 weeks</td>
</tr>
<tr>
<td>Post-treatment period: 16 weeks</td>
</tr>
<tr>
<td>Total of 36 weeks</td>
</tr>
</tbody>
</table>

For detailed assessment schedule across the study report to Section 1.2

## Statistical Considerations

The sample size estimation is based on the comparison between dupilumab 300 mg vs. placebo with regard to the primary endpoint: change from baseline in NPS at week 16.

Assuming a common standard deviation of 1.5, a two-sided and significance level of 0.05, 20% discontinuation rate, 28 patients per group will provide 80% power to detect a difference of 1.3 between dupilumab and placebo groups in the change of NPS from baseline to Week 16.

### Randomization:

Patients will be randomized using a 1:1 randomization ratio for Dupilumab 300 mg QW for 16 weeks, placebo QW for 16 weeks. The randomization will be stratified based on asthma comorbidity status and nasal biopsy sampling.

### Analysis Population:

The primary analysis population for the efficacy endpoints will be the double blind randomized ITT population who have been allocated to a randomized treatment regardless of whether the treatment kit was used or not. The efficacy analyses will be conducted according to the treatment to which they are randomized.

The analysis population for safety endpoints is defined as all randomized patients exposed to study medication, regardless of the amount of treatment administered. The safety analyses will be conducted according to the treatment patients actually received.

The treatment emergent period for the safety population is defined as the time from the first administration of study medication to the end of the Post-treatment Period.

### Primary Analysis:

The change from baseline in NPS will be analyzed using a mixed-effect model with repeated measures (MMRM) approach. The model will include change from baseline values up to Week 16 as response variables, and factors (fixed effects) for treatment, stratification factor, visit, treatment-by-visit interaction, baseline value and baseline-by-visit interaction. An unstructured correlation matrix will be used to model the within-patient errors. Parameters will be estimated using restricted maximum likelihood method with the Newton-Raphson algorithm. Statistical inferences on treatment comparisons for the primary endpoint, change from baseline in NPS at Week 16, will be derived from the mixed-effect model.

### Analysis of secondary endpoints:

Proportion of patients with binary event (eg, improvement in NPS) will be analyzed respectively using a logistic model.

The time to event analysis will be analyzed using Cox regression model.

The change from baseline for continuous endpoints will be analyzed using MMRM same as the primary endpoints.

The safety variables, including AEs, laboratory parameter, vital signs, ECG and physical examinations will be summarized using descriptive statistics.

### Missing data handling
For the primary analysis, no imputation will be done for the MMRM model. Analysis of covariance (ANCOVA) model based on last value carry forward (LOCF) will be used as a sensitivity analysis. For responder analysis, if a patient discontinued the treatment before Week 16, the values measured at the end of treatments will be used to determine whether the patient can be considered as a responder or not. For other endpoints analyzed using MMRM, no imputation will be done.

**Interim Analyses:**

An early analysis will be performed when the last patient completes the end of treatment phase. This analysis will be the final on-treatment analysis. Procedure to maintain study integrity with respect to the subsequent post-treatment follow up visits, safety visits and analyses are described in Section 6.3. A Key Results Summary for the early analysis will be prepared.

**Planned Database lock date:**

A primary database lock will be performed at the end of the treatment phase of all patients. The database will be updated at the end of the study phase of all patients to include the additional post-treatment follow up information and updates for the events previously ongoing at the time of previous lock.

### DURATION OF STUDY PERIOD (per patient)

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Screening period (4 weeks)</strong> + <strong>Randomized Treatment Period (16 weeks)</strong> + <strong>Post-Treatment Period (16 weeks)</strong> = <strong>Approximately 36 weeks</strong></td>
<td></td>
</tr>
</tbody>
</table>
1 FLOW CHARTS

1.1 GRAPHICAL STUDY DESIGN

IMP: Patients will be randomized to one of the following treatments for 16 weeks, receiving QW SC administrations of dupilumab or placebo according to one of the following doses and regimens: Dupilumab 300 mg QW with 600 mg loading dose (LD) at D1 (V2) or Placebo QW (P) with placebo loading dose at D1 (V2). Weekly investigational product administrations must be separated by at least 5 days. At Visit 2 the Investigator or delegate will perform 2 injections. After V2 one injection of IMP will be performed weekly at the investigational site throughout the randomized treatment period. Patients will stay under observation at the study site for a minimum of 1 hour after injections.

NIMP: MFNS will be self-administered by the patient BID or QD (if they cannot tolerate QD). At each visit the investigator must ensure that the patient has the necessary doses up to the next visit, knowing that one MFNS device (1 bottle) contains sufficient doses for: either 2 weeks of BID treatment/regimen or 4 weeks of QD treatment/regimen.
### 1.2 STUDY FLOW CHART

<table>
<thead>
<tr>
<th>Screening period</th>
<th>Randomized treatment period</th>
<th>Post-treatment period</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>VISIT</strong></td>
<td><strong>RDN</strong></td>
<td><strong>EOS</strong></td>
</tr>
<tr>
<td></td>
<td>W-4(D-28)</td>
<td>W0 (D1)</td>
</tr>
<tr>
<td>RDN</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>EOS</td>
<td>19</td>
<td>22</td>
</tr>
<tr>
<td>Inclusion Criteria including Informed Consent (s)</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Patient Demography</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Medical/Surgical History</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Prior Medication History</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Physical Examination</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Spirometry</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Randomization</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>NIMP weekly SC administration</td>
<td>X (loading)</td>
<td>X X X X X X X X X X X X</td>
</tr>
<tr>
<td>Call (IVRS (IWRS))</td>
<td>X X X X X X X X X X X X X X X X X X</td>
<td></td>
</tr>
<tr>
<td>Dispense or download electronic diary/NPIF</td>
<td>X X X X X</td>
<td></td>
</tr>
<tr>
<td>NIMP (MFNS see Section 8.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Record concomitant medication</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Efficacy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nasal endoscopy</td>
<td>X X X X X X</td>
<td></td>
</tr>
<tr>
<td>CT scan</td>
<td>X X X X X</td>
<td></td>
</tr>
<tr>
<td>SNDT 22</td>
<td>X X X X X X</td>
<td></td>
</tr>
<tr>
<td>Visual analogue scale (VAS)</td>
<td>X X X X X X</td>
<td></td>
</tr>
<tr>
<td>QoL (SF-36, EQ-5D)</td>
<td>X X X X X X</td>
<td></td>
</tr>
<tr>
<td>Nasal polyp related resource use questionnaire</td>
<td>X X X X X X</td>
<td></td>
</tr>
<tr>
<td>Self-assessment of the treatment (optional)</td>
<td>X X</td>
<td></td>
</tr>
<tr>
<td>ACQ-5</td>
<td>X X X X X X</td>
<td></td>
</tr>
<tr>
<td>Safety</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AE SAE recording (if any)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vital Signs</td>
<td>X X X X X X X X X X X X</td>
<td></td>
</tr>
<tr>
<td>ECG</td>
<td>X X X X X X X X X X</td>
<td></td>
</tr>
</tbody>
</table>

**Note:** The table above represents the flow chart for the study, detailing the progression of the study phases from screening to post-treatment, with specific criteria and procedures listed for each visit.

**Property of the Sanofi Group - strictly confidential**
### Screening period

- **RDN**
- **EOS**
- **EOS**

<table>
<thead>
<tr>
<th>VISIT</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
<th>12</th>
<th>13</th>
<th>14</th>
<th>15</th>
<th>16</th>
<th>17</th>
<th>18</th>
<th>19</th>
<th>20</th>
<th>21</th>
<th>22</th>
</tr>
</thead>
</table>

#### Laboratory Testing

| Test | VISIT 1 | VISIT 2 | VISIT 3 | VISIT 4 | VISIT 5 | VISIT 6 | VISIT 7 | VISIT 8 | VISIT 9 | VISIT 10 | VISIT 11 | VISIT 12 | VISIT 13 | VISIT 14 | VISIT 15 | VISIT 16 | VISIT 17 | VISIT 18 | VISIT 19 | VISIT 20 | VISIT 21 | VISIT 22 |
|------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|
| Clinical laboratory testing | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Urinalysis (dipstick) | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Pregnancy test (for WOCPB) | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Pk/Wk-drug antibody sampling (PK) | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Serum Biomarker sampling | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Allergen-specific IgE panel sampling | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Plasma sampling for cytokine | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Allergen-specific IgE panel sampling | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Allergen-specific IgE panel sampling | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Polyp biopsy | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Stored DNA sampling | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Stored whole blood RNA sampling | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |

The Screening Period is 28 days in duration to run in any patient on MFNS, and to collect baseline data. V2 will take place 28 days+/-2 day window after V1.

- **a** No IMP administration during this visit. Patients who discontinue treatment early will be assessed as soon as possible using the procedures normally planned for the End-of-treatment Visit and the 4 Post-treatment Period Visits.
- **b** Prior to screening, patients must be on INCS treatment for more than 8 weeks.
- **c** Spirometry: all patients should have the result of FEV1 (% of predicted normal) recorded in e-CRF: anytime during Screening Period (before V2) and at the other scheduled visits during the Randomized treatment period. If a patient’s FEV1 does not qualify, then he/she will not be randomized on that day.
- **d** Weekly IMP administrations starting from V2 at the investigational site must be separated by at least 5 days.
- **e** Electronic diary/NPIF meter is used for daily recording of MFNS use, nocturnal awakenings, morning and evening NPIF and rhinosinusitis symptom scores 1) nasal congestion/obstruction 2) anterior rhinorrhea (runny nose), 3) posterior rhinorrhea (post nasal drip), and 4) loss of sense of smell, scored using a 0-3 categorical scale where 0 = no symptoms, 1 = mild symptoms, 2 = moderate symptoms and 3 = severe symptoms. This device is dispensed at Visit 1 and information is downloaded from this device on the other indicated days. The average of the last 7 days before V2 is needed to determine the baseline value.
- **f** Nasal endoscopy: endoscopy (including use of decongestants before the procedure) will be performed after all other efficacy assessments have been completed for each visit; Standard video sequences will be downloaded by the investigator to the central reader’s secured Internet site. For eligibility central reading of V1 will be used. At V2 investigator review V1 results from central reader to confirm entry criteria and reconfirm eligibility based on review of Inclusion/Exclusion Criteria and the V2 endoscopy local reading.
- **g** CT scan should be performed anytime during Screening Period before a first administration of IMP and at EOT. Central reading will be used for comparison baseline (BL) to EOT.
- **h** Only for patients with co-morbid asthma, ACQ-5 is completed in the patient’s electronic diary during clinic visits.
Hematology: hemoglobin, hematocrit, platelet count, total white blood cell count, differential count, and total red blood cell count. Serum chemistry (Obtain fasting at V1, V6, V10, V14, V18, V20-EOT and V22-EOS): creatinine, blood urea nitrogen, glucose, uric acid, total cholesterol, total protein, albumin, total bilirubin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, electrolytes (sodium, potassium, chloride), bicarbonate, and creatine phosphokinase. Clinical laboratory testing at Visit 1 includes hepatitis screen (hepatitis B surface antigen (HBsAg), Hepatitis B IgM core antibody (HBcAb-IgM), hepatitis C antibodies (HC Ab), HIV screen (Anti-HIV-1 and HIV-2 antibodies), anti-nuclear antibody (ANA). Clinical laboratory testing at Visit 2 is limited to hematology. Note: Anti-ds DNA antibody will be tested if ANA is positive (>1:160 titer).

Serum pregnancy test at Visit 1 and urine pregnancy tests at other visits. A negative result must be obtained at Visits 1 and 2 prior to randomization visits.

Serum pharmacokinetic samples, immune response assessment (ADA) samples and optional whole blood RNA samples will be collected prior to administration of investigational product during the Randomized Treatment Period. During the post-treatment period PK samples will be collected at all visits and ADA samples only at EOS visit. Patients with titers >1000 of the ADA at last visit may be followed after the study.

Biomarkers to be assayed: total IgE, Staphylococcal enterotoxin A IgE, Staphylococcal enterotoxin B IgE, ECP, TARC, periostin.

Nasal secretion samples will be collected and stored for potential future discovery efforts to identify predictors of treatment response.

Optional polyp biopsies will be collected in selected sites.

Samples will be collected prior to administration of investigational product during the Randomized Treatment Period.

Optional sampling for exploratory analysis of DNA and RNA, requiring separate pharmacogenetics informed consent.
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3 LIST OF ABBREVIATIONS

ACQ-5: Asthma Control Questionnaire, 5-question version
ADA: Anti-drug Antibodies
ADI: Actual Dose Intensity
AE: Adverse Event
AESI: Adverse Event of Special Interest
ALT: Alanine aminotransferase
AM: Ante meridiem
ANA: Anti-Nuclear antibody
ANCOVA: Analysis of covariance
AST: Aspartate aminotransferase
β-hCG: Human chorionic gonadotrophin
BID: Two times per day
BP: Blood pressure
CRS: Chronic Rhinosinusitis
CT: Computed Tomography
D: Day
DB: Double-Blind
DMC: Data Monitoring Committee
DNA: Deoxyribonucleic acid
DRF: Discrepancy Resolution Form
EDTA: Ethylene diamine tetra acetic acid
EBV: Epstein-Barr virus
ECG: Electrocardiogram
ECP: Eosinophil cationic protein
EOS: Eosinophils
EOT: End of treatment
EP: End point
EQ-5D: EuroQOL-5D
FEV: Forced expiratory volume
GCP: Good Clinical Practice
GCS: Glucocorticosteroid
GH: General Health
GSO: Global Safety Officer
HBcAb-IgM: Hepatitis B IgM Core Antibody
HBsAg: Hepatitis B Surface Antigen
HC Ab: Hepatitis C Core Antibody
HLGT: High-Level Group Term
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Term</th>
</tr>
</thead>
<tbody>
<tr>
<td>HLT</td>
<td>High-Level Term</td>
</tr>
<tr>
<td>ID</td>
<td>Identification Code</td>
</tr>
<tr>
<td>IC</td>
<td>Informed Consent</td>
</tr>
<tr>
<td>ICH</td>
<td>International Conference on Harmonisation</td>
</tr>
<tr>
<td>IEC</td>
<td>Independent Ethics Committee</td>
</tr>
<tr>
<td>IEP</td>
<td>Immuno-electrophoresis</td>
</tr>
<tr>
<td>Ige</td>
<td>Immunoglobulin E</td>
</tr>
<tr>
<td>INCS</td>
<td>Intranasal Corticosteroid</td>
</tr>
<tr>
<td>IP</td>
<td>Investigational Product</td>
</tr>
<tr>
<td>IMP</td>
<td>Investigational Medicinal Product</td>
</tr>
<tr>
<td>IRB</td>
<td>Institutional Review Board</td>
</tr>
<tr>
<td>ITT</td>
<td>Intent To Treat</td>
</tr>
<tr>
<td>IUD</td>
<td>Intrauterine Device</td>
</tr>
<tr>
<td>IUS</td>
<td>Intrauterine System</td>
</tr>
<tr>
<td>IVRS</td>
<td>Interactive Voice Response System</td>
</tr>
<tr>
<td>IWRS</td>
<td>Interactive Web Response System</td>
</tr>
<tr>
<td>LABA</td>
<td>Long-Acting Beta Agonist</td>
</tr>
<tr>
<td>LD</td>
<td>Loading Dose</td>
</tr>
<tr>
<td>LFT</td>
<td>Liver Function Tests</td>
</tr>
<tr>
<td>LOCF</td>
<td>Last Observation Carry Forward</td>
</tr>
<tr>
<td>mAB</td>
<td>Monoclonal Antibodies</td>
</tr>
<tr>
<td>MFNS</td>
<td>Mometasone Furoate Nasal Spray</td>
</tr>
<tr>
<td>μg</td>
<td>Microgram</td>
</tr>
<tr>
<td>MG</td>
<td>Milligram</td>
</tr>
<tr>
<td>MCID</td>
<td>Minimal Clinically Important Difference</td>
</tr>
<tr>
<td>MMRM</td>
<td>Mixed-effect Model with Repeated Measures</td>
</tr>
<tr>
<td>NPIF</td>
<td>Nasal Peak Inspiratory Flow</td>
</tr>
<tr>
<td>NIMP</td>
<td>Non investigational Medicinal Product</td>
</tr>
<tr>
<td>NP</td>
<td>Nasal Polyposis</td>
</tr>
<tr>
<td>NPS</td>
<td>Nasal Polyp Score</td>
</tr>
<tr>
<td>NSAID</td>
<td>Non-steroidal anti-inflammatory drug</td>
</tr>
<tr>
<td>OCS</td>
<td>Oral Corticosteroid</td>
</tr>
<tr>
<td>PEF</td>
<td>Peak Expiratory Flow</td>
</tr>
<tr>
<td>PCSA</td>
<td>Potentially Clinically Significant Abnormality</td>
</tr>
<tr>
<td>PF</td>
<td>Physical Functioning</td>
</tr>
<tr>
<td>PK</td>
<td>Pharmacokinetics</td>
</tr>
<tr>
<td>PO</td>
<td>Per Os</td>
</tr>
<tr>
<td>PROs</td>
<td>Patient-Reported Outcomes</td>
</tr>
<tr>
<td>PT</td>
<td>Preferred Term</td>
</tr>
<tr>
<td>QD</td>
<td>One time per day</td>
</tr>
</tbody>
</table>
QoL: Quality of Life
QRS: QRS complex on ECG (ventricular depolarization)
QT: Ventricular depolarization and repolarization time on ECG
QW: Every Week (weekly)
RDI: Relative Dose Intensity
RNA: Ribonucleic acid
RBC: Red blood cell(s)
RDN: Randomization
SABA: Short-Acting Beta Agonist
SAE: Serious Adverse Event
SAS: Statistical analysis software
SC: Subcutaneous
SF36: Short form questionnaire
SMQ: Standardised MedDRA query
SNOT: Sinonasal Outcome Test
SOC: System Organ Class
TARC: Thymus- and activation-regulated chemokine
TEAE: treatment emergent adverse event
TH: T-helper lymphocyte
ULN: upper limit of normal
V: Visit
VAS: Visual Analogue Scale
WBC: White blood cells
WOCBP: Women of childbearing potential
WW: Worldwide
4 INTRODUCTION AND RATIONALE

Nasal polyposis (NP) is a clinical condition characterized by the presence of multiple polyps in the upper nasal cavity, originating from the ostiomeatal complex. The main disease associated with polyp formation is chronic rhinosinusitis (CRS), which is a heterogeneous group of diseases characterized by mucosal inflammation of the nasal cavity and paranasal sinuses with symptoms lasting more than 12 weeks. Clinically symptoms are defined by long-term symptoms of nasal obstruction and congestion, reduction in or loss of sense of smell, anterior and posterior rhinorrhea, and facial pain. These symptoms can impact greatly upon a patient's quality of life. The presence or absence of polyps is confirmed by performing endoscopy. Coronal computed tomography (CT) scans can confirm the presence and extent of sinus and polyp involvement. The CRS phenotype involving with polyps (CRSwNP) is at the more severe end of the disease severity spectrum than the CRS phenotype without nasal polyps and is the most resistant to treatments. CRSwNP with an estimated prevalence of 2% to 4% (in Europe and US), has a greater burden of symptoms and a higher relapse rate after treatment. Despite the high prevalence and significant morbidity associated with NP, treatment options range from local or systemic corticosteroids to functional endoscopic sinus surgery. Patients with CRSwNP and comorbid asthma (30% of patients with CRSwNP) have a characteristic poor therapeutic response and a high recurrence rate and their disease tends to be more resistant (1,2).

The pathogenesis of nasal polyps is unknown. Nasal polyps are most commonly thought to be caused by allergy although a significant number are associated with non-allergic adult asthma or no respiratory or allergic trigger that can be demonstrated. Risk factors include genetic susceptibility, anatomic abnormalities, infection, and local immunologic imbalance, some or most of which may play a role in its pathogenesis (3,4,5).

Pathophysiologically, NP is an inflammatory process affecting the mucosa of the nose and paranasal sinuses often associated with mucociliary impairment, bacterial infection, allergic disease, and/or anatomical abnormalities (6,7,8). NP is a T helper cell-2 (Th-2) driven inflammatory process in which eosinophils are the predominant inflammatory cell found in the sinuses and nasal polyps, and is frequently associated with asthma and aspirin sensitivity (9). More than 80% of patients with chronic sinusitis with nasal polyps have eosinophilic upper airway inflammation. The extent of sinomucosal involvement, the size of the polyps, and the severity of nasal disease correlate with the extent of eosinophilic inflammation (10). Eosinophils and their products are thought to be a hallmark of nasal polyp-associated inflammation as evidenced by the finding of elevated levels of interleukin-5 (promotes eosinophil survival and differentiation), eosinophil cationic protein, and eotaxin (eosinophil chemoattractant), factors that attract and activate eosinophils, in the nasal polyp specimens (11).

4.1 RATIONALE

Recent therapeutic approaches have been focused on trying to control the Th2 response. Dupilumab is under development as a potential novel treatment for Nasal polyposis. Dupilumab is a fully human monoclonal antibody directed against the interleukin-4 receptor alpha (IL-4Ra)
subunit, which is a component of interleukin-4 (IL-4) receptors Type I and Type II, which mediate signaling by IL-4 (both receptors) and by IL-13 (Type II receptor). Dupilumab binds to IL-4Rα, preventing IL-4 and IL-13 binding and activation of their respective receptors. Since both signaling pathways are thought to play key roles in the pathophysiology of inflammatory allergic diseases, dupilumab may provide an effective treatment for NP.

In a proof of concept study designed to investigate dupilumab 300 mg once weekly in patients with moderate to severe asthma with high blood eosinophil levels there was a statistically significant improvement in the SNOT-22 score overall compared to placebo.

4.1.1 Population

The population of ACT12340 is composed of patients with a physician endoscopic diagnosis of bilateral nasal polyposis (nasal poly score of 5 out of a maximum of 8) despite completion of a prior topical INCS treatment for at least 8 weeks and chronic symptoms of sinusitis.

In this study Dupilumab will be administered on top of Mometasone furoate nasal spray (MFNS). Taking into account the high co-morbidity of NP with asthma, aspirin/ nonsteroidal anti-inflammatory drug (NSAID) hypersensitivity and previous surgeries, these patients will be allowed to enter the study unless they present any of the exclusion criteria described in Section 7.2

4.1.2 Study Design

ACT12340 is a proof of concept, Ph 2 multinational, multicenter, randomized, double-blind, placebo-controlled, parallel group study evaluating the effect of 300 mg of dupilumab administered QW SC for 16 weeks with a loading dose of 600mg on D1.

The clinical study consists of three periods:
- Screening run in on MFNS for 4 weeks
- Randomized Dupilumab/Placebo Treatment Period (16 weeks)
- Post-treatment Period for PK, immunogenicity, safety and efficacy (16 weeks)

The study is double-blind to avoid the bias incurred by an unblinded design. Both the patient and Investigator are blinded to the assigned treatment group. The study is placebo-controlled to minimize bias and provide an inactive control group to which differential efficacy and safety can be compared.

4.1.3 Endpoint rationale

The primary endpoint is the change from baseline at Week 16 in bilateral nasal polyp score (NPS).
Bilateral NPS is an objective endpoint (EP) commonly used to evaluate the effect of medications or surgery in NP at the current early stage of clinical development.

Numerous secondary efficacy endpoints including symptom evaluations required as co-primary endpoint in late stage of development are measured to more comprehensively evaluate the efficacy of dupilumab. Also this study will explore improvement of nasal polyposis and associated sinus inflammation in CT scan, improvement in condition specific and general medical questionnaires in order to obtain a better understanding of the impact of severe nasal polyposis on the subject's quality of life (QOL). This approach reflects real-life clinical assessment of nasal polyposis and is in line with increasing focus in the medical field on the effects of medical conditions and treatments on the quality of life of patients (1).

Safety endpoints are typical for investigational drugs at the current stage of clinical development.

These endpoints, together with exploratory sub-group analysis and biomarkers will provide the information on the therapeutic value of Dupilumab to reduce the nasal polyp score and to improve symptoms in NP and its subsets. On top of that, the sustainability of the effect will be also explored through the 4-month post-treatment evaluation period.

### 4.1.4 Dupilumab dose and regimen rationale

This study will explore the 300 mg QW dose regimen. This dose is anticipated to saturate apparent target mediated clearance level (10-15 mg/L) and has been tested and provided statistically significant and clinically relevant response in two previous proof of concept studies performed with dupilumab in asthma and atopic dermatitis.

The first dose will employ a loading dose of 600 mg in order to achieve faster steady-state concentration. This loading dose range is supported by the acceptable safety profile of the highest loading dose (600 mg) demonstrated in the TDU12265 study conducted in Japanese healthy subjects.

In addition, given that the Cmax after 600 mg loading dose is around 70 mg/L and that the steady state Ctrough of 300 mg QW is around 150 mg/L, the Cmax after the proposed dosing regimen (ie, 600 mg loading dose followed by 300 mg QW) will be below the mean Cmax of 12 mg/kg IV dose (421 mg/L), the highest single dose tested in healthy subjects that was well tolerated, providing additional confidence that this dose regimen should have an acceptable safety profile.

### 4.1.5 Rationale for biomarkers of drug response

Colonization of the nasal sinuses with Staphylococcus aureus may be a factor in the sustaining chronic sinusitis and progression of nasal polyposis. These microbes produce high-molecular-weight enterotoxins known to function as superantigens that can potently stimulate lymphocytes (12). Coincidental elevations in IgE specific for Staphylococcal enterotoxins have been observed in serum and nasal secretions in patients with nasal polyposis (Bachert) and may participate in chronic inflammation by priming regional immune cells (eg, mast cells and basophils that express high-affinity FceR1 and eosinophils and lymphocytes that express low-affinity FcεRII (CD23) to respond to secreted enterotoxin antigens. In addition, IgE-coated cells sensitized to other airborne
antigens likely participate in chronic sinusitis. IL-4 and IL-13 strongly promote the production of 
IgE via an immunoglobulin switching mechanism. Dupilumab should in principle suppress nasal 
production of IgE.

IL-4 and IL-13 also stimulate the airway mucosa, including nasal mucosa, to secrete Thymus- and 
activation-regulated chemokine (TARC), eotaxin-3 and periostin. TARC is a specific ligand for 
CC chemokine receptor (CCR) 4 which is highly expressed on Th2 cells. Thus, TARC potently 
recruits and activates Th2 cells, which further secrete IL-4 and IL-13 to perpetuate Th-2 driven 
inflammation.

Eotaxin-3 is a specific ligand for CCR3 which is highly expressed on eosinophils, and to a lesser 
degree on Th2 cells. Thus, this chemotaxin recruits and activates primarily eosinophils, but also 
Th2 cells, into the mucosa. Notably, pronounced eosinophilic infiltration is a common finding in 
nasal polyps. Given the extent of eosinophilia in these patients, the production of eosinophil 
cationic protein (ECP) is likely elevated.

Periostin has emerged as a protein associated with the molecular signature of chronic sinusitis. 
Periostin is thought to participate in airway remodeling by stimulating the secretion of the growth 
factor TGFβ. Elevated production of growth factors has been observed in nasal polyps.

Since the secretion of TARC, eotaxin-3 and periostin is dependent, at least in part, on Th2 
cytokines and is associated with chronic inflammation of the airway mucosa, including sinus 
tissue, therapeutic intervention with dupilumab may overall suppress the secretion of these 
biomarkers into nasal secretions as well as into blood. Quantitation of these biomarkers in nasal 
secretions, as compared with blood, has the advantage of tissue specificity.

The eosinophilic nature of many, but not all nasal polyps, demonstrates a heterogeneity in 
phenotype that may have therapeutic consequences. It is possible that the extent of blood 
eosinophilia or concentrations of ECP and other biomarkers at baseline prior to treatment may 
have value in predicting clinical responses to dupilumab.

4.1.6 Overall benefits and risks assessment

Dupilumab prevents IL-4 and IL-13 binding and activation of their respective receptors involved 
in signaling pathways that play key roles in the pathophysiology of nasal polyposis. Phase 2a 
study in asthma demonstrated robust proof of efficacy for the tested product including a 
statistically significant improvement in the SNOT-22 score overall compared to placebo.

As of the cut-off date 30 November 2012, dupilumab has been administered as a single IV or SC 
 injection to 126 healthy volunteers, as weekly SC injections for 4 weeks to 51 patients with AD 
and as weekly SC for 12 weeks to 24 patients with AD and 52 patients with asthma. Based upon 
the current available data for dupilumab and the review of the data by an independent data 
monitoring committee, no important identified risks have been established. Important potential 
risks based on the mechanism of action, administration route, or on the risks known with 
monoclonal antibodies in general, such as: Immune-mediated injuries in different body systems, 
infections (including parasitic infections), severe injection site reactions, hypersensitivity/immunogenicity, malignancy, are being managed through:
• Exclusion of patients with immunosuppressed status or receiving immunosuppressants, and/or having an active viral bacterial, viral or parasitic infection, or are at high risk for developing or reactivating infections

• Monitoring of safety data, including online and periodic blinded safety monitoring team review and unblended IDMC review

The safety data available to date and the potential benefit of Dupilumab in patients with nasal polyposis support development of this compound in NP. The proposed ACT12340 study will provide the basis of a first benefit-risk of Dupilumab in NP.
5 STUDY OBJECTIVES

5.1 PRIMARY

- To evaluate the efficacy of dupilumab in the treatment of bilateral NP by assessment of the endoscopic nasal polyp score in comparison to placebo

5.2 SECONDARY

To evaluate dupilumab in patients with bilateral nasal polyps, with regards to:

- Symptoms of sinusitis
- CT scan changes
- Nasal polyp score in the sub-group of patients with co-morbid asthma
- Safety and tolerability
- Pharmacodynamic responses based on suppression of TH2 biomarkers
- Concentrations of dupilumab in serum
- Immune response to dupilumab (Anti-drug antibodies (ADA))
- Effect of dupilumab in patient reported outcomes and QoL scales
6 STUDY DESIGN

6.1 DESCRIPTION OF THE PROTOCOL

ACT12340 is a randomized, double-blind, phase 2, placebo controlled, 2 arm study to evaluate dupilumab administered QW subcutaneously (SC) for 16 weeks in patients with bilateral nasal polyposis and chronic symptoms of sinusitis.

Approximately 56 patients will be randomized into 2 treatment groups of 28 patients per group.

6.2 DURATION OF STUDY PARTICIPATION

6.2.1 Duration of study participation for each patient

The clinical trial will consist of 3 periods:

- Screening run in up to 4 weeks
- Randomized Dupilumab/Placebo Treatment Period (16 weeks)
- Post-treatment Period for PK, immunogenicity, safety, efficacy (16 weeks)

The total duration of the study participation for each patient is up to 36 weeks.

6.2.2 Determination of end of clinical trial (all patients)

It is planned that recruitment will stop when approximately 56 patients NP are randomized.

To ensure at least 28 patients with co-morbid asthma needed for subgroup analysis:

- Recruitment of NP patient without co-morbid asthma will stop when approximately 28 patients without asthma are randomized.

The end of the clinical trial is defined as the last patient’s last visit/contact.

6.3 INTERIM ANALYSIS

An early analysis will be performed at the end of the treatment phase of all patients. This analysis will be the final on-treatment analysis. Procedure to maintain study integrity with respect to the subsequent post-treatment follow up visits, safety visits and analyses are described in Section 11.4.6. A Key Results Summary for the early analysis will be prepared.
6.4 STUDY COMMITTEES

A data monitoring committee (DMC) is commissioned for the dupilumab clinical development program. This committee is comprised of externally-based individuals with expertise in the diseases under study, biostatistics, or clinical research. The primary responsibilities of the DMC are to review and evaluate the safety data during the course of the trial and make appropriate recommendations regarding the conduct of the clinical trial to the Sponsor.

The DMC procedures and safety data to be reviewed by the DMC is described in the DMC charter. In the above capacities, the DMC is advisory to the Sponsor. The Sponsor is responsible for promptly reviewing and for taking into account in a timely manner the recommendations of the DMC in terms of trial continuation with or without alterations or of potential trial termination.
7 SELECTION OF PATIENTS

7.1 INCLUSION CRITERIA

Patients with:

I 01. A minimum bilateral nasal polyp score of 5 out of a maximum score of 8 for both nostrils (with at least a score of 2 for each nostril) despite completion of a prior INCS treatment for at least 8 weeks before screening. (See Section 9.1 for additional information regarding endoscopic nasal polyp score)

I 02. Presence of at least two of the following symptoms prior to screening: nasal blockade/obstruction/congestion or nasal discharge (anterior/posterior nasal drip); facial pain/pressure; reduction or loss of smell

I 03. Signed written informed consent

7.2 EXCLUSION CRITERIA

Patients who have met all the above inclusion criteria listed in Section 7.1 will be screened for the following exclusion criteria which are sorted and numbered in the following 3 subsections:

7.2.1 Exclusion criteria related to study methodology

E 01. Patients <18 or >65 years of age

E 02. Any technical/administrative reason that makes it impossible to randomize the patient in the study

E 03. Patient who has previously been treated in any clinical trial of Dupilumab

E 04. SNOT22<7

E 05. Patient who has taken other investigational drugs or prohibited therapy for this study within 2 months before screening or 5 half-lives, whichever is longer:

- who have required a burst of systemic corticosteroids (for example oral, intravenous, intramuscular corticosteroids) within the 2 months before screening or are scheduled to receive systemic corticosteroids during the study period for another condition
- who have required intranasal corticosteroid drops within 1 month prior to screening
- mAB and immunosuppressive treatment
- Anti-immunoglobulin E (IgE) therapy (omalizumab) within 130 days of Visit 1
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SAR231893-ACT12340-dupilumab Version number: 1

• Leukotriene antagonists / modifiers for patients who were not on a continuous treatment for ≥30 days prior to Visit 1
  Initiation of allergen immunotherapy within 3 months prior to Visit 1 or a plan to begin therapy during the Screening Period or the Randomized Treatment Period

E 06. Patients who have undergone any nasal surgery (including polypectomy) within 6 months before screening or have had more than 5 sinonasal surgeries in the past of which maximal 2 were surgeries changing the lateral wall structure of the nose

E 07. Patients with conditions/concomitant diseases making them non evaluable for the primary efficacy endpoint such as:
  • Antrochoanal polyps
  • Nasal septal deviation that would occlude at least one nostril
  • Acute sinusitis, nasal infection or upper respiratory infection at screening or in the 2 weeks before screening
  • Ongoing rhinitis medicamentosa
  • Churg-Strauss syndrome, Young’s syndrome, Kartagener’s syndrome or dyskinetic ciliary syndromes, Cystic fibrosis
  • Signs or a CT scan suggestive of Allergic fungal rhinosinusitis

E 08. Patients with co-morbid asthma are excluded if:
  • Forced expiratory volume (FEV1) is 60% (of predicted normal) or less
  • An exacerbation requiring systemic (oral and/or parenteral) steroid treatment or Hospitalization (>24h) for treatment of asthma, has occurred within 3 months prior screening
  • Are on a dose higher than 1000 µg fluticasone or the equivalent of inhaled corticosteroids (Appendix B)

E 09. Patients with short life expectancy (less than 6 months)

E 10. Patients receiving concomitant treatment prohibited in the study (see Section 8.8.1)

E 11. Patient is the Investigator or any Sub-Investigator, research assistant, pharmacist, study coordinator, other staff or relative thereof directly involved in the conduct of the protocol

E 12. Uncooperative or any condition that could make the patient potentially non-compliant to the study procedures.
7.2.2 Exclusion criteria related to the active comparator and/or mandatory background therapies

E 13. Refer to National Product labeling for all contraindications or warning/precaution of use related to mometasone furoate nasal spray

7.2.3 Exclusion criteria related to the current knowledge of Sanofi compound

E 14. Pregnant or intent to become pregnant during the study, or breast-feeding women

E 15. Women of childbearing potential (pre-menopausal female biologically capable of becoming pregnant) who:

- Do not have a confirmed negative serum β-hCG test at Visit 1
- Who are not protected by one of the following acceptable forms of effective contraception during the study:
  - Established use of oral, injected or implanted hormonal contraceptive
  - "Double barrier" methods (ie, Double Intrauterine device [IUD] with copper or intrauterine system [IUS] with progestogen and barrier contraceptive [condom, diaphragm or cervical/vault caps] used with spermicide [foam, gel, film, cream or suppository])
  - Female sterilization (eg, tubal occlusion, hysterectomy or bilateral salpingectomy)
  - Male sterilization with post-vasectomy documentation of the absence of sperm in the ejaculate; for female patients the study, the vasectomized male partner should be the sole partner for that patient
  - True abstinence; periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) is not an acceptable method of contraception

E 16. Concomitant severe diseases (eg, active and inactive pulmonary tuberculosis, Diabetes mellitus etc.)

E 17. Diagnosed active parasitic infection; suspected or high risk of parasitic infection, unless clinical and (if necessary) laboratory assessments have ruled out active infection before randomization

E 18. History of human immunodeficiency virus (HIV) infection or positive HIV screen (Anti-HIV- and HIV-2 antibodies) at Visit 1

E 19. Evidence of acute or chronic infection. Visit 1 or Visit 2 oral temperature >38° C or a chronic, persistent, or recurring infection requiring active treatment with antibiotics, antivirals, or antifungals within 4 weeks prior to the screening visit or other frequent, recurrent infections per Investigator judgment
E 20. Known or suspected immunosuppression, including history of invasive opportunistic infections (eg, tuberculosis, histoplasmosis, listeriosis, coccidioidomycosis, pneumocystosis, aspergillosis), despite infection resolution

E 21. Live vaccinations within 12 weeks prior to Visit 1 or planned vaccinations during the study (Appendix A)

E 22. Patients with active autoimmune disease or patients using immunosuppressive therapy for autoimmune disease (eg, Hashimoto’s thyroiditis, Graves’ disease, inflammatory bowel disease, primary biliary cirrhosis, systemic lupus erythematosus, multiple sclerosis, psoriasis vulgaris, rheumatoid arthritis)

E 23. Patients with positive or indeterminate hepatitis B surface antigen (HBsAg), hepatitis B core antibody (HBcAb), or hepatitis C antibody at Visit 1.

E 24. Patients with liver injury related criteria:
   - Underlying hepatobiliary disease
   - or ALT>3 ULN
8 STUDY TREATMENTS

8.1 INVESTIGATIONAL MEDICINAL PRODUCT(S)

8.1.1 Dupilumab
Sterile dupilumab will be provided

8.1.2 Placebo
Sterile placebo for dupilumab will be provided

8.1.3 Preparation of investigational product
Instructions for IMP preparation are provided in the pharmacy manual. The IMP should be administered within 3 hours of preparation in the syringe.

8.1.4 Dosing schedule
The IMP is administered every 7 ± 2 days (QW). The doses of IMP must be separated by ≥5 days to avoid an overdose. At Visit 2 the Investigator or delegate will perform 2 injections. After V2 one injection of IMP will be performed weekly at the investigational site throughout the randomized treatment period.

The IMP will be administered following clinic procedures and blood collection. Patients should be monitored for at least 1 hour after each dose of study-site administered investigational product, for any signs or symptoms of a local site injection or hypersensitivity reaction.

Subcutaneous injection sites should be alternated between the 4 quadrants of the abdomen (avoiding navel and waist areas) or upper thighs so that the same site is not injected for two consecutive times/weeks.

8.2 NON-INVESTIGATIONAL MEDICINAL PRODUCT

8.2.1 Intranasal corticosteroid
On a daily basis throughout the study, the patient will use an electronic diary to record daily use of MFNS. Mometasone furoate (NASONEX ®) 50 micrograms/actuation Nasal Spray, is contained in a bottle, that contains 18 g (140 actuations) of product formulation.
8.2.1.1 Screening Period

Prior to screening, patients must be on a stable administration of intranasal corticoids for ≥2 month prior to Visit 1.

If the patient is using an alternative INCS product other than MFNS prior to the screening visit, at V1, the Investigator must switch the patient to MFNS.

After V1 all patients will enter a run-in period of 4 weeks where they will receive MFNS:

- 2 actuations (50 μg/actuation) in each nostril twice daily (total daily dose of 400 μg), unless they’re intolerant to BID regimen of INCS in which case, they can stay on the lower dose (QD) regimen.

8.2.1.2 Randomized Treatment Period

During the Randomized Treatment Period, patients continue the stable dose of mometasone furoate:

- MFNS two actuations in each nostril BID or QD (in case patient cannot tolerate the high dose).

8.2.1.3 Post-treatment Period

Upon completing the Randomized Treatment Period (or following early discontinuation of IMP), patients can continue treatment with the stable dose of MFNS maintained over the randomized treatment period, or modify treatment based on medical judgment.

8.2.2 Reliever or background medication

The list of reliever medication or background medication allowed as needed during the study is provided in Section 8.8.2.

8.3 BLINDING PROCEDURES

8.3.1 Methods of blinding

Dupilumab and placebo will be provided in identically matched glass 5 mL vials. To protect the blind, each treatment kit will be prepared such that the treatments are identical and indistinguishable and will be labeled with a treatment kit number. The randomized treatment kit number list will be generated by Sanofi.

In accordance with the double-blind design, study patients, investigators, and study site personnel will remain blinded to study treatment and will not have access to the randomization (treatment codes) except under circumstances described in Section 8.3.2.
Refer to Section 10.5 for suspected unexpected adverse drug reaction unblinding by the Sponsor.

8.3.2 Randomization code breaking during the study

In case of an adverse event (AE), the code should only be broken in circumstances when knowledge of the investigational medicinal product (IMP) is required for treating the patient.

If possible, a contact should be initiated with the Monitoring Team before breaking the code. Code breaking can be performed at any time by using the proper module of the interactive voice response system (IVRS)/interactive web response system (IWRS) and/or by calling any other phone number provided by the Sponsor for that purpose. If the blind is broken, the Investigator should document the date, time of day and reason for code breaking.

If the blind is broken, the patient must be withdrawn from the treatment. Patients who discontinue treatment early are assessed as soon as possible using the procedures normally planned for the End-of-treatment Visit and the four Post-treatment Period Visits.

At the facilities where the pharmacokinetic measurements, anti-drug antibodies and selected biomarkers are determined, the samples will be analyzed prior to data base lock leading to unblinding of responsible bioanalysts. Bioanalysts are excluded from the clinical trial team.

The Data Monitoring Committee will receive blinded by treatment group or unblinded (if necessary) confidential reports from an independent statistician for review, which have to be handled strictly confidentially. None of these reports can be delivered to unauthorized persons.

8.4 METHOD OF ASSIGNING PATIENTS TO TREATMENT GROUP

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

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

Patients who meet the entry criteria will be randomized to receive either dupilumab or placebo.

Patients who fail to meet exclusion criteria may be re-screened once during the open screening period of the study; a different patient identification will be issued. Re-screening is not permitted if the patient fails to meet inclusion criteria. There is no requirement for a waiting period between the screen-failure date and the re-screening date. The IVRS/IWRS report will flag re-screened patients. Patients that are re-screened must sign a new consent form and all Visit 1 procedures must be repeated.

The Investigator obtains treatment kit numbers at randomization and subsequent scheduled visits via an Interactive Voice Response System/Interactive Web Response System (IVRS/IWRS) that will be available 24 hours a day.
Patients will be randomized using a 1:1 randomization ratio for dupilumab 300 mg q week and placebo. Randomization will be stratified by Visit 1 medical history of asthma and by V2 nasal biopsy (details will be specified in the IVRS/IWRS specifications document).

A total of 56 patients shall be randomized and at least 50% of them shall have co-morbid asthma. To ensure at least 28 patients with co-morbid asthma needed for subgroup analysis:

- Recruitment of NP patient without co-morbid asthma will stop when approximately 28 patients without asthma are randomized, and
- Patients with co-morbid asthma will continue to be randomized to complete a total number of 56 randomized NP patients.

A randomized patient is defined as a patient who is registered and assigned with a treatment kit number from the centralized treatment allocation system, as documented from its log file. A patient cannot be randomized more than once in the study.

8.5 PACKAGING AND LABELING

Dupilumab and placebo will be supplied as single vial packed in a box. Both vial and box will be labeled with a single-panel label.

MFNS will be supplied as single bottle packed in a box. Both bottle and box will be labeled with a single-panel label.

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

8.6 STORAGE CONDITIONS AND SHELF LIFE

Dupilumab and placebo investigational product should be stored. MFNS storage conditions are specified on the bottle and its box. All IMP and NIMP should be stored in an appropriate, locked room under the responsibility of the Investigator or other authorized persons (eg, pharmacists) in accordance with local regulations, policies and procedures.

Control of storage conditions, especially control of temperature (eg, refrigerated storage) and information on in-use stability and instructions for handling the Sanofi compound should be managed according to the rules provided by the Sponsor.

8.7 RESPONSIBILITIES

The Investigator, the hospital pharmacist, or other personnel allowed to store and dispense the IMP and the NIMP supplied by the Sponsor, will be responsible for ensuring that the IMP and the NIMP supplied by the Sponsor used in the clinical trial is securely maintained as specified by the Sponsor and in accordance with applicable regulatory requirements.
All IMP and the NIMP supplied by the Sponsor will be dispensed in accordance with the Investigator's prescription and it is the Investigator's responsibility to ensure that an accurate record of IMP and NIMP issued and returned is maintained.

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

A potential defect in the quality of IMP and the NIMP supplied by the Sponsor 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 IMP and the NIMP supplied by the Sponsor and eliminate potential hazards.

Under no circumstances will the Investigator supply IMP and the NIMP supplied by the Sponsor to a third party, allows the IMP and the NIMP supplied by the Sponsor to be used other than as directed by this clinical trial protocol, or dispose of IMP and the NIMP supplied by the Sponsor in any other manner.

**8.7.1 Treatment accountability and compliance**

The Investigator or pharmacist will also keep accurate records of the quantities of the IMP dispensed, used and unused and NIMP dispensed, used, unused, and returned by each patient. The IMP and NIMP dispensation/accountability log is to be updated each time IMP is dispensed and NIMP is dispensed or returned. Any NIMP not returned (even if considered empty) must be accounted for with a comment in the log. The study monitor will periodically check the supplies of the IMP and NIMP held by the Investigator or pharmacist to verify accountability.

Patients will be instructed to return with their used and unused NIMP supplied by the Sponsor to the investigation site. Compliance with IMP and NIMP administration will be reviewed with the patient at each visit. For IMP, compliance will be assessed by inspection of the vial packs and checking the used and unused vials and the remaining volume of solution in each vial, if any. For NIMP compliance with use of the mandatory background therapy (MNFS), is verified based on MFNS use recorded on the patient electronic diary.

**8.7.2 Return and/or destruction of treatments**

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

A concomitant medication is any treatment received by the patient concomitantly to the IMP.

8.8.1 Prohibited Concomitant Medication

The following concomitant treatments are not permitted during Screening Period and the Randomized treatment period:

- Use of intranasal medication that would interfere with the symptoms of diseases (antihistamines, nasal atropine, ipratropium bromide, nasal cromolyn), except nasal saline
- INCS drops
- Systemic corticosteroid
- Decongestion (topical or systemic) is not allowed, except before endoscopy
- Long term use of systemic antibiotics (for 2 weeks or more)
- Lipoxygenase inhibitors
- Any immunosuppressive treatment including but not limited to methotrexate, cyclosporine, mycophenolate, tacrolimus, gold, penicillamine, sulfasalazine, hydroxychloroquine, azathioprine, cyclophosphamide
- Anti-immunoglobulin E (IgE) therapy (omalizumab)
- Aspirin or NSAID in patients with hypersensitivity to aspirin or NSAID
- Initiation of a new allergen immunotherapy (only continuation of allergen immunotherapy in place for ≥3 months prior to visit 1 is permitted)

8.8.2 Permitted Concomitant Medication

- Permitted Concomitant Medication

The following treatments are allowed:

- MFNS during the screening and throughout the whole study
- Nasal normal saline
- Topical decongestants for example Oxymetazoline hydrochloride (to reduce the swelling and widen the path for the endoscope), as well as a topical anesthetic for example Lidocaine are allowed before endoscopy
- Short term use of Antibiotics (<2 weeks) would be allowed during the study
- For patients with asthma:
  - SABA, LABA
- Methylxanthines (for example theophylline, aminophyllines)
- Inhaled corticosteroids on a stable dose ≤1000 µg Fluticasone (or the equivalent dose of another inhaled CS (see Appendix B) only for patients that were on a stable dose ≥30 days prior to Visit 1
- Leukotriene antagonists / modifiers are permitted during the study, only for patients that were on a continuous treatment for ≥30 days prior to Visit 1
  - Systemic antihistamines
  - Allergen immunotherapy in place for ≥3 months prior to Visit 1 is permitted

**CYP substrates**

The impact of dupilumab on CYP enzymes activity has not been studied and the effect on dupilumab on the levels of IL4 and IL13 cytokines has not been fully characterized.

However, literature data of studies in human hepatocytes indicate that the interleukin-4 (IL-4) was able to upregulate cytochrome P450 2E1, 2B6, 3A4 mRNA expression or downregulate Cyp1A2 mRNA (13,14). Another study in human peripheral blood mononuclear cells (PBMC) incubated with various Th2 cytokines, reports that Th2 cytokines IL-4 and IL-13 generally increased the protein expression of CYP2B6 and CYP3A4 (15).

Since the clinical significance of the limited *in vitro* findings for IL-4 and IL-13 involvement in CYP regulation and the impact of dupilumab on CYP enzymes is not fully understood, during the study treatment and at least up to the end of follow-up, caution should be used for drugs with narrow therapeutic index that are metabolized via these CYP450 isoforms.

This means that unless the drug is prohibited (ref. 8.8.1) in the study, close clinical observation and/or laboratory monitoring as applicable are required in order to enable early detection of toxic manifestations or lack of activity/efficacy of these drugs, followed by dose adjustment or their withdrawal if needed.

Some examples of CYP450 substrates with narrow therapeutic index are provided in Appendix F.
9 ASSESSMENT OF INVESTIGATIONAL MEDICINAL PRODUCT

9.1 PRIMARY ENDPOINT

9.1.1 Primary efficacy endpoint

The primary endpoint of the study is the change from baseline at week 16 in bilateral endoscopic Nasal Polyp Score (16). This score (NPS) is the sum of the right and left nostril scores, as evaluated by means of nasal endoscopy. NP is graded based on polyp size described in the Table 1

<table>
<thead>
<tr>
<th>Polyp score</th>
<th>Polyp size</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No polyps</td>
</tr>
<tr>
<td>1</td>
<td>Small polyps in the middle meatus not reaching below the inferior border of the middle turbinate</td>
</tr>
<tr>
<td>2</td>
<td>Polyps reaching below the lower border of the middle turbinate</td>
</tr>
<tr>
<td>3</td>
<td>Large polyps reaching the lower border of the inferior turbinate or polyps medial to the middle turbinate</td>
</tr>
<tr>
<td>4</td>
<td>Large polyps causing complete obstruction of the inferior nasal cavity</td>
</tr>
</tbody>
</table>

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

Standard video sequences will be downloaded or sent to centralized reader. Centralized imaging data assessments and scoring by an independent physician reviewer for the imaging data will be performed for all endoscopies. To confirm eligibility at V2, only the V1 central reading will be made available to the site. The final results of central reading will be made available after the study.

For the analysis of primary endpoint, central reading of V2 will be used for comparison with EOT reading. The sites will remove subject-identifying information from the imaging data header prior to sending the imaging data to the central reader.

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

9.1.2 Secondary efficacy and other exploratory endpoint

Efficacy

Change from baseline at Week 16 in:

- Patient reported symptoms
- 22-item Sinonasal Outcome Test (SNOT-22)
- Subject-assessed nasal congestion/obstruction, anterior rhinorrhea (runny nose), posterior rhinorrhea (post nasal drip), and loss of sense of smell, (daily AM and PM e-diary) month average
- Number of nocturnal awakenings
- Patient-rated rhinosinusitis symptoms severity using a visual analog scale (VAS)
  - Nasal peak inspiratory flow (NPIF)
  - Smell test (UPSIT)
  - In NPS in patients with co-morbid asthma
  - In CT scan assessments

Time to first response (≥1 point improvement) in NPS

**Exploratory endpoints**

- Change from baseline at Week 16 in FEV1 (overall and in sub-group with asthma)
- 5-item Asthma control questionnaire (ACQ-5) in asthma sub-group
- Time to study treatment discontinuation
- Incidence of treatment discontinuation due to need for OCS or nasal surgery

**Quality of life (QoL) endpoints**

Change from baseline at Week 16 in:

- 36-item short form health survey (SF36)
- European quality of life scale (EQ-5D)
- Nasal polyp related resource use questionnaire

**9.1.2.1 Disease-specific tests and assessments**

**9.1.2.1.1 Computed tomography (CT)**

CT of the sinuses should be performed before V2 and at EOT.

For both Lund-Mackay scores and 3D volumetric measurement of the maxillary sinus, the same acquisitions (sequences) will be used for centralized imaging data assessments and scoring by an independent physician reviewer for the imaging data. Central reading of V2 will be used for comparison with EOT. The final results of central reading will be made available after the study. Details on CT will be available in a separate operational manual provided to the sites.
9.1.2.1.1 Lund-Mackay score

Lund-Mackay system is based on localization with points given for degree of opacification: 0 = normal, 1 = partial opacification, 2 = total opacification. These points are then applied to the maxillary, anterior ethmoid, posterior ethmoid, sphenoid, frontal sinus on each side. The osteomeatal complex is graded as 0 = not occluded, or 2 = occluded deriving a maximum score of 12 per side (17). This scoring system has been validated in several studies (18,19).

For patients in whom the osteomeatal complex (OC) is missing (because of a previous surgery) the reader should consider the location of the former OC and provide a scoring (as if the OC was there).

9.1.2.1.1.2 Three-Dimensional volumetric measurement of the maxillary sinus

This method is used to calculate: (20)

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

For the analysis, central reading before V2 will be used for comparison with EOT reading. The sites will remove subject-identifying information from the imaging data header prior to sending the imaging data to the central reader. The % change in opacification from BL to EOT will be calculated.

9.1.2.1.2 Nasal Peak inspiratory flow (NPIF)

Nasal peak flow evaluation represents a physiologic measure of the air flow through both nasal cavities during forced inspiration and/or expiration expressed in liter per minute. The NPIF is the best validated technique for the evaluation of nasal flow through the nose. Nasal inspiration correlates most with the subjective feeling of obstruction and is the best validated technique for monitoring nasal flow in clinical trials.

At screening (Visit 1), patients will be issued an NPIF meter for recording morning (AM) and evening (PM) NPIF. Patients will be instructed on the use of the device, and written instructions on the use of the NPIF meter will be provided to the patients. In addition, the investigator will instruct the patients on how to record the following variables in the e-diary on a daily basis

- AM NPIF performed within 15 minutes after arising (between 5 am and 12 am) prior to taking MFNS
- PM NPIF performed in the evening (between 5 pm and 12 pm) prior to taking MNFS

Three NPIF efforts will be performed by the patient; all 3 values will be recorded by the patient in the e-diary, and the highest value will be used for evaluation. The procedure takes about 5 minutes.
Baseline AM NPIF will be the mean AM measurement recorded for the 28 days prior to the first dose of investigational product, and baseline PM NPIF will be the mean PM measurement recorded for the 28 days prior to the first dose of investigational product.

The nasal flow is expressed in liter per minute, and consecutive measurements are performed. Taking the best of 3 outcomes with less than 10% variation is considered to be the best means of expression of the result (21).

9.1.2.1.3 **Smell test:** *University of Pennsylvania Smell Identification Test (UPSIT)*

The UPSIT test is a rapid and easy-to-administer method to quantitatively assess human olfactory function. The UPSIT shows a high test-retest reliability (r: 0.981) and scores on this test are strongly correlated with the detection threshold for phenyl ethyl alcohol in the same individuals. When the UPSIT is administered in the standardized manner, clinical subjects show a high degree of uniformity in UPSIT performance when tested in different laboratories.

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

The 40-odorant UPSIT is used in over 1500 clinics and laboratories throughout the United States, Canada, South America, and Europe, and has been administered to nearly 200,000 people since its development in the early 1980s. A particular strength of this test is that it provides an olfactory diagnosis based on comparing the patient's test score with normative data, providing a percentile score of an individual relative to his or her age-matched normal group. Furthermore, a clinician can distinguish patients with a normal sense of smell ("normosmia") from those with different levels of reduction ("mild, moderate and severe microsmia") or loss ("anosmia") (21).

9.1.2.2 **Disease-specific, daily symptom assessments**

On a daily basis from V1 and throughout the study, the patient will use an electronic diary to:

- Respond to the morning and evening individual rhinosinusitis symptom questions using a 0-3 categorical scale (where 0 = no symptoms, 1 = mild symptoms, 2 = moderate symptoms and 3 = severe symptoms) (2):
  - congestion and/or obstruction
  - anterior rhinorrhea (runny nose)
  - posterior rhinorrhea (post-nasal drip)
  - loss of sense of smell
- Record the number of nocturnal awakenings
The e-diary is dispensed at Visit 1 and information is downloaded from this device on the other indicated days. The average of the last 7 days before V2 is needed to determine the baseline value. For the BL to EOT analysis, 4 weeks average of total score (sum of all symptoms) or by each symptom will be used.

9.1.3 Safety endpoints

The same safety assessments will be applied across all arms. Adverse events, including serious adverse events (SAEs) and adverse events of special interest (AESI), will be collected at every visit. The Investigator will ask the patient how he/she has felt since the last study visit. The study specific and general safety criteria are detailed in Section 10.4. To assure the continuing safety of patients in this study, an independent DMC will be responsible for reviewing the safety data on a periodic basis throughout the course of the study as outlined in Section 6.4.

Safety Observations

The Investigator should take all appropriate measures to ensure the safety of the patients. Notably, he/she should follow up the outcome of SAEs /AESI until clinical recovery is complete and laboratory results have returned to normal or until progression has been stabilized or death. In all cases, this may imply that observations will continue beyond the last planned visit per protocol, and that additional investigations may be requested by the Sponsor.

When treatment is prematurely discontinued, the patient’s observations will continue until the end of the study as defined by the protocol for that patient.

In case of any SAE/AESI with immediate notification brought to the attention of the Investigator at any time after the end of the study for the patient and considered by him/her to be caused by the investigational product with a reasonable possibility, this should be reported to the Sponsor.

9.1.3.1 Adverse events

Adverse events for each patient will be monitored and documented from the time the patient gives informed consent at Visit 1 until the End-of Study Visit, except for:

SAEs

AEs that are ongoing at database lock.

Adverse events, adverse events with special interest (AESI) and serious adverse events (SAEs) will be reported as described in Section 10.4.1.3.

9.1.3.2 Vital signs

Vital signs, including blood pressure (mmHg), heart rate (beats per minute), respiratory rate (breaths per minute), body temperature (degrees Celsius) and body weight (kg) will be measured at every visit. Height (cm) will be measured at screening (Visit 1) only. Vital signs will be
measured in the sitting position using the same arm at each visit, and will be measured prior to receiving investigational product at the clinic visits.

### 9.1.3.3 Physical Examination

Physical examinations will include an assessment of general appearance, skin, eyes, ear/nose/throat, heart, chest, abdomen, reflexes, lymph nodes, spine, and extremities. All deviations from normal will be recorded, including those attributable to the patient’s disease. Physical examinations will be performed at screening (Visit 1), Week 16 (End-of-Treatment Visit whichever comes first) and End of Study Visit.

### 9.1.3.4 Electrocardiogram variables

One recording of a standard 12-lead ECG will be performed at screening (Visit 1), Week 8, W12, W16 (or End-of-Treatment Visit whichever comes first) and End of Study Visit. At the post-randomization visits, ECGs will be performed prior to investigational product administration. All ECGs will be performed with the patient in a reclined position. A minimum of 3 complexes in an appropriate lead (lead II) will be averaged to determine the PR-interval, QT/QTc-interval, QRS-complex and heart rate will be measured for each ECG.

All measurements will be made from a single lead: Lead II, or Lead I if Lead II is not possible or lead V5 if Lead II and Lead I are not possible.

### 9.1.3.5 Laboratory safety variables

The clinical laboratory tests will be conducted by an accredited (College of American Pathologists or equivalent) central laboratory with national and regional clinical licenses as required for diagnostic testing and must provide evidence of participation in proficiency testing, as appropriate. After reviewing the laboratory report and evaluating any results that are outside the normal range, the Investigator must sign and date the laboratory report. Abnormal laboratory values that are considered to be clinically significant by the Investigator must be repeated as soon as possible after receiving the laboratory report to rule out laboratory error. Persistent abnormal laboratory values should be repeated until they return to normal or until an etiology of the persistent abnormality is determined.

Refer to Section 1.2 Study Flow Chart for the description of the clinical laboratory evaluations and the schedule of laboratory evaluations performed throughout this study.

The clinical laboratory parameters that will be measured in safety hematology and chemistry blood samples are:

**Hematology:** To include hemoglobin, hematocrit, platelet count, total white blood cell count with five-part differential count, and total red blood cell count.

**Serum chemistry:** To include: creatinine, blood urea nitrogen, glucose, uric acid, total cholesterol, total protein, albumin, total bilirubin, alanine aminotransferase, aspartate aminotransferase,
alkaline phosphatase, electrolytes (sodium, potassium, chloride), bicarbonate, and creatine phosphokinase.

Urine analysis including specific gravity, pH, glucose, ketones, blood, protein, nitrate, leukocyte esterase, urobilinogen and bilirubin (by dipstick). If any parameter on the dipstick is abnormal, a urine sample should be sent to the central laboratory for testing. If positive for proteins, microscopic analysis is performed by central laboratory. Testing is limited to visits at screening, Week 8, Week 16 (EOT), and Week 32 (EOS).

Viral serology testing at Visit 1 includes hepatitis screen (hepatitis B surface antigen (HBsAg), Hepatitis B IgM core antibody (HBcAb-IgM), hepatitis C antibodies (HC Ab), HIV screen (Anti-HIV-1 and HIV-2 antibodies),

Anti-nuclear antibody (ANA) : If the titer is ≥1:160 at any time, then the sample will be tested for the presence of anti-ds DNA antibody. If the ANA titer is ≥1:160 at the End of Treatment visit, then it will be rechecked at the End of Study visit.

Decision trees for the management of certain laboratory abnormalities by Sanofi are provided in Appendix D.

### 9.1.3.6 Pregnancy test

A serum pregnancy test (β-human chorionic gonadotrophin) will be performed at screening (Visit 1) in women of childbearing potential, and a urine pregnancy test will be performed at Visit 2 prior to randomization. A negative result must be obtained at Visit 1 and 2 prior to randomization. Additional urine pregnancy tests will be performed monthly until the End of Study Visit.

### 9.2 OTHER ENDPOINTS

#### 9.2.1 Pharmacokinetics and anti-drug antibodies

##### 9.2.1.1 Sampling time

Predose blood samples will be collected for determination of serum functional dupilumab and anti-dupilumab antibodies as designated in the study flow chart (see Section 1.2). The date of collection should be recorded in the patient e-CRF. The date and time also will be collected on the central laboratory requisition form and entered into the database through data transfers from the central laboratory.

If an SAE occurs in a patient, blood samples should be collected for determination of functional dupilumab concentration, and anti-dupilumab antibody assessment at or near the onset and completion of the occurrence of the event, if possible. The exact date and time of sample collection must be recorded and entered into the database by the central laboratory. An unscheduled PK page in the e-CRF must be completed as well.
### 9.2.1.2 Pharmacokinetics and Anti-drug Antibody handling procedure

Special procedures for collection, storage, and shipping of serum are described in separate operational manuals. An overview of handling procedure for samples used in the determination of drug concentration and anti-drug antibodies will be provided to the sites in a separate operational manual.

<table>
<thead>
<tr>
<th>Sample type</th>
<th>dupilumab</th>
<th>Anti-dupilumab antibody</th>
</tr>
</thead>
<tbody>
<tr>
<td>Matrix</td>
<td>Serum</td>
<td>Serum</td>
</tr>
<tr>
<td>Blood sample volume</td>
<td>5 mL</td>
<td>5 mL</td>
</tr>
<tr>
<td>Anticoagulant</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Blood handling procedures</td>
<td>See Operational Manual</td>
<td>See Operational Manual</td>
</tr>
<tr>
<td>Serum aliquot split</td>
<td>Two aliquots</td>
<td>Two aliquots</td>
</tr>
<tr>
<td>Storage conditions</td>
<td>&lt; 6 months: below -20°C</td>
<td>&lt; 6 months: below -20°C</td>
</tr>
<tr>
<td></td>
<td>&lt;24 months: below -80°C (preferred)</td>
<td>&lt;24 months: below -80°C (preferred)</td>
</tr>
<tr>
<td>Serum shipment condition</td>
<td>In dry ice</td>
<td>In dry ice</td>
</tr>
</tbody>
</table>

### 9.2.1.3 Bioanalytical method

Serum samples will be assayed using validated methods as described in Table 3.

<table>
<thead>
<tr>
<th>Analyte</th>
<th>Functional dupilumab</th>
<th>Anti-dupilumab antibody</th>
</tr>
</thead>
<tbody>
<tr>
<td>Matrix</td>
<td>serum</td>
<td>Serum</td>
</tr>
<tr>
<td>Analytical technique</td>
<td>ELISA</td>
<td>Electrochemiluminescence</td>
</tr>
<tr>
<td>Lower limit of quantification</td>
<td>0.078 mg/L</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Site of bioanalysis</td>
<td>Regeneron</td>
<td>Regeneron</td>
</tr>
</tbody>
</table>
9.2.1.4 Pharmacokinetics parameters

Predose functional dupilumab concentrations in serum at Visit 2 (Day 1), dupilumab trough concentrations at Week 2, Week 4, Week 8, Week 12, Week 16, and follow-up serum dupilumab at Week 20, Week 24, Week 28 and Week 32 will be provided.

Anti-dupilumab antibody status (negative or titer value) at Visit 2 (Day 1), Week 2, Week 4, Week 8, Week 12, Week 16, and Week 32 will be provided.

Patients with ADA titers ≥1000 at the end of study visit will be scheduled to return approximately 6 months later for an additional assessment of ADA titer. Further follow-up will be considered based on the overall assessment of antibody titers and clinical presentation.

9.2.2 Pharmacodynamics

Several biomarkers related to chronic sinusitis and Th2 polarization will be assessed for their value in predicting therapeutic response (or toxicity, if needed) and/or in documenting the time course of drug response. More detailed information on the collection, handling, transport and preservation of samples will be provided in a separate laboratory manual.

Patients, investigators and site personnel will not have access to assay results for total IgE, ECP, Staphylococcal aureus enterotoxin specific IgEs, TARC, periostin or eotaxin-3 while the study is ongoing, as the related data are not essential for patient care and have the potential for unblinding the study treatments. Assay results for the other tests, designated as “For Research Only”, will not become part of any medical records, but will be reported in the final Clinical Study Report.

Blood eosinophil count will be measured as part of the standard 5-part WBC differential cell count on a hematology autoanalyzer.

9.2.2.1 Serum biomarkers

Sufficient blood should be collected to prepare and store two 1-mL aliquots for each biomarker at each of their specified collection time points.

All blood samples should be allowed to clot in serum separation tubes for 30 minutes at room temperature, then centrifuged at 1500 to 2000 x g for 15 minutes until clot and serum are separated by a well formed polymer barrier. Using a plastic disposable pipette, the serum should be transferred into screw-cap cryovials, appropriately labeled and immediately placed in the upright (cap up) position in a freezer maintained at –20°C or colder (preferably -70 °C) until shipped later on dry ice.

The following assays will be performed on serum as per the study flow charts.

- **Total IgE (ImmunoCAP® FEIA method or equivalent):** store two 1-mL serum aliquots.
- **Staphylococcal enterotoxin A IgE and Staphylococcal enterotoxin B IgE (ImmunoCAP® FEIA method):** store two 1-mL serum aliquots.
• Eosinophil cationic protein (ECP) (ImmunoCAP® FEIA method): store two 1-mL serum aliquots.

• Thymus and activation-regulated chemokine (TARC) will be assayed with a validated enzyme immunoassay (Human TARC Quantikine ELISA kit; R&D Systems): store two 1-mL serum aliquots.

• Periostin will be assayed with a validated immunoassay (Human Periostin DuoSet ELISA Development kit; R&D Systems): store two 1-mL serum aliquots.

9.2.2.2 Allergen-specific IgE panel (region-specific)

To assess serological atopy at baseline and further assess shifts in serum IgE during treatment, antigen-specific IgE will be quantified using ImmunoCAP assays. Panels of antigen-specific IgE will be customized according to global region for clinical sites to better assure detection of atopy. Two 1-mL serum aliquots will be prepared.

9.2.2.3 Eotaxin-3 in plasma

Sufficient blood should be collected into a green tube to prepare and store two 1-mL aliquots of heparinized plasma at each of the specified collection time points. Blood should be centrifuged soon after collection at a minimum of 1500 x g for 15 minutes until cells and plasma are well separated. Using a plastic disposable pipette, the plasma should be transferred into screw-cap cryovials, appropriately labeled and immediately placed in the upright (cap up) position in a freezer maintained at –20°C or colder (preferably -70 °C) until shipped later on dry ice.

9.2.2.4 Residual serum and plasma

Prior to use of residual serum and plasma for purposes not previously defined, approval for the intended use will be obtained from the local IRB / Ethics Committee. All residual serum and plasma will be destroyed within 2 years of completion of the last visit for the last patient enrolled in the study.
9.2.2.5 Archival nasal secretions

Nasal secretions will be obtained by inserting nasal swabs bilaterally into the nasal cavity for five minutes. Precise instructions for isolating nasal secretions from the swabs and preserving aliquots will be provided separately. Nasal secretions at visit 1 will be used for validation of assay methodology for this unique biomatrix. The nasal secretions collected through visit 2 to visit 19 will be preserved for possible analysis of additional biomarkers related to nasal polyposis and responses to dupilumab treatment.

9.2.2.6 Nasal polyp biopsies

At selected clinical site (s) and with specific informed consent, nasal polyp tissue will be optionally obtained by biopsy. A baseline biopsy will be obtained at V2 of the study. After randomization, another biopsy of nasal polyp tissue will be obtained at the end of treatment visit (Week 16). The complete details on tissue collection and processing will be provided separately in a biopsy collection manual.

Nasal polyp tissue will be subsequently assessed for various biomarkers of inflammation and disease process or response. Any remaining tissue will be discarded within five years of the completion of the last visit for the last patient in the study. RNA will be extracted and used for expression profiling (e.g., microarray, transcriptome sequencing or quantitative RTPCR). The RNA analyses and conditions of sample storage will be subject to the same restrictions as described for whole blood RNA in the following section, “Pharmacogenomic assessment”.

The Sponsor has included safeguards for protecting patient confidentiality. Genetic samples will be used only for this specific analysis and then the sample and the extracted DNA and RNA will be destroyed upon completion of this analysis and the clinical study report, so no further information can be obtained from it.

9.2.2.7 Optional stored DNA and RNA samples

Pharmacogenomic testing is optional and voluntary. For those patients who signed the optional pharmacogenomic informed consent form, a blood sample will be collected at the study visit as specified in the study flow chart and this sample will be stored for future analysis. Specific procedures for storage and shipping of pharmacogenomic samples will be provided in a lab manual. For DNA, blood will be collected using a 6-mL Vacutainer® (BECTON Dickinson) containing K2 EDTA with HEMOGARD closure, gently inverted at least 8 times and immediately placed upright at -70 ºC until shipped on dry ice. For RNA, blood will be collected using a 2.5-mL draw PAXgene blood RNA tube (PreAnalytiX/Qiagen), gently inverted at least 8 times and kept upright at room temperature (18°C-22°C) or refrigerated (4 ºC) until shipped at room temperature. Special procedures for freezing blood collected in PAXgene tubes may be provided.

Under no circumstances will the DNA and RNA collection tubes be centrifuged.
DNA and RNA samples may be used to determine a possible relationship between genes and response to treatment with dupilumab and possible side effects to dupilumab. Genes that may be studied include those for the IL4R receptor, IL-4, IL-13 and STAT6 and additional genes that may potentially be part of the IL4R signaling pathway, nasal polyposis, or related eosinophilic or atopic indications (e.g., asthma).

This blood sample will be transferred to a contractor that will, on behalf of Sanofi, extract DNA and RNA from the samples; this contractor may be located in a country different than the country of sample origin.

This blood sample, and the DNA or RNA that is extracted from it, will be assigned a second number, a Genetic ID (de-identification code) that is different from the Subject ID. This “double coding” is performed to separate a subject’s medical information and DNA data.

The clinical study data (coded by Subject ID) will be stored in the clinical data management system (CDMS), which is a distinct database in a separate environment from the database containing the pharmacogenomic data (coded by Genetic ID). The key linking Subject ID and Genetic ID will be maintained by a third party, under appropriate access control. The matching of clinical data and pharmacogenomic data, for the purpose of data analysis, will be possible only by using this key, which will be under strict access control. All data will be reported only in coded form in order to maintain confidentiality.

The DNA and RNA will be stored, as applicable, in the US for samples collected in the Americas (e.g., USA, Canada, Latin America, etc), in Switzerland for samples collected in Europe, for up to 15 years from the completion of the clinical study report or as otherwise required by local regulations.

Special procedures for storage and shipping of pharmacogenomic samples will be described in a separate manual.

9.2.3 Quality of life/health economic variables/other endpoints

9.2.3.1 22-item Sinonasal Outcome Test

The SNOT-22 is a validated questionnaire to assess the impact of chronic rhinosinusitis on quality of life (see Appendix E).

Is a 22-item outcome measure on a 5- category scale applicable to sinonasal conditions and surgical treatments. The score range from 0 to 110. Higher total scores on the SNOT-22 imply greater impact of CRS on QoL. The questionnaire was found easy to use (time to completion is 7 minutes) and provided good discriminant validity (Hopkins et al., 2006). The SNOT-22 was validated and recommended for routine clinical practice. A Minimal Clinically Important Difference MCID is available: ≥ 8.90 (22).
9.2.3.2 Visual analogue scale VAS

The VAS for rhinosinusitis is used to evaluate the total severity and is only validated in adult CRS to date (2).

The patient is asked to indicate on a VAS the answer to the question: “How troublesome are your symptoms of rhinosinusitis? “ The VAS ranks from 0 (Not troublesome) to 10 (Worst thinkable troublesome)

The disease can be divided into MILD, MODERATE and SEVERE based on total severity visual analogue scale (VAS) score (0 10 cm):

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

9.2.3.3 SF-36-Version 2

Short-Form-36 (SF-36)-Version 2.0: The SF-36 is a generic questionnaire measuring general health status (quality of life) in the last 4 weeks before completing the questionnaire. The SF-36 is a 36 item questionnaire that measures eight multi-item dimensions of health: physical functioning (10 items) social functioning (2 items) role limitations due to physical problems (4 items), role limitations due to emotional problems (3 items), mental health (5 items), energy/vitality (4 items), pain (2 items), and general health perception (5 items).

For each dimension, item scores are coded, summed, and transformed on to a scale from 0 (worst possible health state measured by the questionnaire) to 100 (best possible health state). Two standardised summary scores can also be calculated from the SF-36; the physical component summary (PCS) and the mental health component summary (MCS).

The time for completion is 5-10 minutes.

9.2.3.4 The Euroqol-5D

EQ-5D-3L is a standardized health-related quality of life questionnaire developed by the EuroQol Group in order to provide a simple, generic measure of health for clinical and economic appraisal and inter-disease comparisons. (Appendix E). EQ-5D is designed for self-completion by patients and it takes few minutes to complete.

EQ-5D was used to study the impact on QoL for filgrastim administration in CRS patients, the scores improved though they were not statistically significant (23).

The EQ-5D essentially consists of 2 pages – the EQ-5D descriptive system and the EQ VAS (Appendix E). The EQ-5D descriptive system comprises 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 3 levels: no problem, some
problems, severe problems. The EQ Visual Analogue Scale (VAS) records the respondent’s self-rated health on a vertical visual analogue scale. The EQ VAS ‘thermometer’ has endpoints of 100 (Best imaginable health state) at the top and 0 (Worst imaginable health state) at the bottom.

9.2.3.5 Nasal polyp related ressource use questionnaire

A questionnaire of health care resource utilization for nasal polyposis (specialist visit, emergency care visit, sick leaves, days off etc.) will be completed at monthly visits. (Appendix E)

9.2.3.6 Patient’s qualitative self-assessment of the treatment

The patient qualitative self-assessment aims to better understand the patient’s views on their treatment during the trial. One question assessing the patient’s satisfaction would be asked, who will thereafter write the answer on a blank page. This assessment should take between 5-10 minutes, and the text would later be analysed using qualitative data analysis software (Alceste) to perform content analysis.

This is an optional question and the patient will be asked if they want to complete the optional one question on “treatment self-assessment.” (see Appendix E).

9.2.3.7 ACQ-5 (Asthma Control Questionnaire, 5-question version)

The ACQ-5 was designed to measure both the adequacy of asthma control and change in asthma control which occurs either spontaneously or as a result of treatment.

The ACQ-5 has 5 questions, reflecting the top-scoring five asthma symptoms: woken at night by symptoms, wake in the mornings with symptoms, limitation of daily activities, shortness of breath and wheeze. Patients are asked to recall how their asthma has been during the previous week and to respond to the symptom questions on a 7-point scale (0=no impairment, 6= maximum impairment) (see Appendix E).

A global score is calculated: the questions are equally weighted and the ACQ-5 score is the mean of the 5 questions and, therefore, between 0 (totally controlled) and 6 (severely uncontrolled). Higher score indicates lower asthma control. Patients with a score below 1.0 will have adequately controlled asthma and above 1.0 their asthma will not be well controlled. On the 7-point scale of the ACQ-5, a change or difference in score of 0.5 is the smallest that can be considered clinically important, corresponding to the Minimal Clinically Important Difference (MCID) defined by the developer.

Measurement properties such as reliability, ability to detect change have been documented in the literature (24).
10 STUDY PROCEDURES

10.1 VISIT SCHEDULE

The clinical trial consists of three periods, using an add-on therapy approach to INCS:

- Screening Period (28 days +/- 2 days; Visit 1)
- Randomized Treatment Period (16 weeks; Visits 2-18)
- Post-treatment Period (16 weeks; Visits 19-22)

The study visits occur on the planned dates (relative to the first injection), as scheduled. The visit schedule should be adhered to within the ± 2 day visit window.

If a patient is prematurely discontinued from treatment, all assessments planned at the End of Treatment visit should be performed.

Prior to all screening assessments, after discussion of participation in the study, the written consent form (including voluntary participation in nasal polyp biopsy and pharmacogenomic testing) must be signed and dated.

Although the screening assessments for this study are grouped under the heading of a single visit in this protocol, it is possible for them to be performed over more than 1 site visit if necessary, as long as the screening visit window prior to Day 1 (V2) is respected. Patients that fail screening for exclusion criteria, for example concomitant medications, acute illness (upper respiratory tract infection), required drug-specific discontinuation periods or laboratory tests, may be rescreened for study eligibility 1 additional time.

10.1.1 Visit 1 (D-28): screening run-in

Following a discussion of participation in the clinical trial, signed informed consent must be obtained and documented.

The following procedures will then be performed:

- Call IVRS/IWRS to assign patient number and register screening visit
- Interview to collect patient demographic information, nasal polyposis information, other medical history (including asthma history, number of asthma exacerbations in the previous year, hyper-sensitivity to aspirin or NSAID), surgical history (including number and dates of previous surgery for nasal polyps), and prior and concomitant medications (including background therapy for NP and asthma)
- Review entry criteria to assess eligibility, with special attention to verify the following:
  - Use of INCS for more than 8 weeks prior to screening
- Presence of at least two of the following symptoms prior to screening: Nasal blockade/obstruction/congestion or nasal discharge (anterior/posterior nasal drip); facial pain/pressure; reduction or loss of smell

Patients have not received any of the prohibited medications described in (Section 8.8.1)

- Measure vital signs [blood pressure, heart rate, respiration rate, body temperature, weight (kg), height (cm)]
- Perform physical examination
- Perform Nasal endoscopy
- Perform CT scan (within the time period between V1 and V2)
- Administer SNOT-22
- Perform spirometry, within the time period between V1 and V2, for all patients and ensure that patients with co-morbid asthma are stable
  - with a FEV₁>60% (of predicted normal) and has not experienced any exacerbation requiring treatment with ≥ 1 systemic (oral or parenteral) steroids bursts for worsening asthma and/or hospitalization or an emergency/urgent medical care visit for worsening asthma in the previous 3 months or are on a dose of inhaled corticosteroids not higher to 1000 µg fluticasone or the equivalent
- Perform 12-lead electrocardiography (ECG)
- Obtain (fasting) blood samples for screening clinical laboratory determinations:
  - Hematology: To include hemoglobin, hematocrit, platelet count, total white blood cell count with five-part differential count, and total red blood cell count.
  - Serum chemistry: To include: creatinine, blood urea nitrogen, glucose, uric acid, total cholesterol, total protein, albumin, total bilirubin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, electrolytes (sodium, potassium, chloride), bicarbonate, and creatine phosphokinase.
- Obtain blood samples for hepatitis screen (hepatitis B surface antigen (HBsAg), Hepatitis B IgM core antibody (HBcAb-IgM), hepatitis C antibodies (HC Ab), HIV screen (Anti-HIV-1 and HIV-2 antibodies), anti-nuclear antibody (ANA)
- Perform nasal secretion sampling
- Obtain serum ß-HCG pregnancy test if female of childbearing potential
- Obtain urine for urinalysis (dipstick)
- Dispense electronic diary/NPIF meter, provide instructions for daily use, and remind patient to bring the device to the next visit
- Dispense MFNS for use as mandatory background therapy throughout the study. Instruct patient to record usage in the electronic diary.
- Commence AE reporting
• Schedule appointment for the next visit

10.1.2 Visit 2 (Week 0): Randomization

• Record all medication use with start date and dose in eCRF; inquire about AEs/SAEs and background therapy tolerability
• Perform nasal endoscopy and for those patients who have signed a specific informed consent form, collect nasal biopsy (prior to administration of investigational product)
• Record symptoms of sinusitis and review results from central reader of V1 nasal endoscopy to confirm entry criteria
• Reconfirm eligibility based on review of Inclusion/Exclusion Criteria and the V2 endoscopy local reading (Section 7).
• Check if CT scan was performed and review local reading assessment
• Obtain spirometry result and record in the e-CRF
• Check compliance with use of the mandatory background therapy (MNFS), as defined as:
  - ≥80% of total number of prescribed “stable dose” sprays taken during the screening period. Compliance is verified based on MFNS use recorded on the patient electronic diary
• Check for use of prohibited medications
• Measure vital signs (blood pressure, heart rate, respiration rate, body temperature, weight)
• Administer SNOT-22

If the patient meets all inclusion and does not meet any exclusion criteria:

• Call IVRS/IWRS to register visit, randomize the patient if entry criteria are met, and receive the first IMP kit number assignment.
• Note: Please screen-fail the patient if entry criteria are not met
• Administer VAS and QoL questionnaires (SF-36, EQ-5D, Nasal polyp related resource use questionnaire)
• Administer the smell test
• Administer ACQ-5 in patients with asthma
• Perform urine pregnancy test (for women of childbearing potential)
• Perform blood sampling (prior to administration of IMP) for clinical laboratories
• Note: Clinical laboratory testing at Visit 2 is limited to hematology, pharmacokinetics, anti-drug antibodies, biomarkers in serum and plasma, allergen-specific IgE panel sampling
• Perform nasal secretion sampling for biomarkers (as described in Section 9.2.2.4)
For those patients who have signed a specific informed consent form, collect blood sample for DNA and RNA sampling (prior to administration of investigational product during the Randomized Treatment Period)

Download electronic diary/NPIF meter and remind patient to bring the device to the next visit

Dispense IMP and NIMP and administer IMP:
- At V2 two injections of IMP will be performed. Subcutaneous injection sites should be alternated between the 4 quadrants of the abdomen (avoiding navel and waist areas) or upper thighs so that the same site is not injected for two consecutive times
- Patients should be monitored for at least 1 hour after the end of administration of IMP for any signs or symptoms of a hypersensitivity reaction.

Remind patient to continue the stable dose of MFNS and record daily usage in the electronic diary

Schedule appointment for next visit

10.1.3 Visit 3, 4, 5 (Week 1, Week 2, Week 3)

Record all medication use with start date and dose in eCRF; inquire about AEs/SAEs and background therapy tolerability

Call IVRS/IWRS to register visit and obtain next IMP kit number

At V4 (Week 2) only, perform sampling for pharmacokinetics, anti-drug antibodies, RNA archival, biomarkers in serum and plasma, allergen-specific IgE panel sampling

Dispense NIMP and administer IMP (one SC injection)

Patients will be monitored at the study site for a minimum of 1 hour after the injection

Remind patient to continue the stable dose of MFNS and record daily usage in the electronic diary

Ensure that the patient has the necessary dose of MFNS up to the next visit (one MFNS device-one bottle-contains sufficient doses for: either 2 weeks of BID treatment/regimen or 4 weeks of QD treatment/regimen) and dispense NIMP if needed

Schedule appointment for next visit

At Visit 5: remind the patient to come for Visit 6 in fasting state.

10.1.4 Visit 6 (Week 4)

Record all medication use with start date and dose in eCRF; inquire about AEs/SAEs and background therapy tolerability

Measure vital signs (blood pressure, heart rate, respiration rate, body temperature, weight)

Perform urine pregnancy test (for women of childbearing potential)
• Download electronic diary/NPIF meter and remind patient to bring the device to the next visit
• Perform nasal endoscopy
• Administer SNOT-22, VAS and QoL questionnaires (SF-36, EQ-5D, Nasal polyp related ressource use questionnaire)
• Administer ACQ-5 in patients with asthma
• Obtain spirometry result and record in the e-CRF
• Perform blood sampling (fasting, prior to administration of IMP) for clinical laboratories: hematology, serum chemistry, LFT, pharmacokinetics, anti-drug antibodies, biomarkers in serum and plasma, allergen-specific IgE panel sampling
• Perform nasal secretion sampling
• Call IVRS/IWRS to register visit and obtain next IMP kit number
• Dispense NIMP and administer IMP (one SC injection)
• Patients will be monitored at the study site for a minimum of 1 hour after the injection
• Remind patient to continue the stable dose of MFNS and record daily usage in the electronic diary
• Ensure that the patient has the necessary dose of MFNS up to the next visit (one MFNS device-one bottle-contains sufficient doses for: either 2 weeks of BID treatment/regimen or 4 weeks of QD treatment/regimen) and dispense NIMP if needed
• Schedule appointment for next visit

10.1.5 Visit 7, 8, 9 (Week 5, Week 6, Week 7)
• Record all medication use with start date and dose in eCRF; inquire about AEs/SAEs and background therapy tolerability
• Call IVRS/IWRS to register visit and obtain next IMP kit number
• Dispense NIMP and administer IMP (one SC injection)
• Patients will be monitored at the study site for a minimum of 1 hour after the injection.
• Remind patient to continue the stable dose of MFNS and record daily usage in the electronic diary
• Ensure that the patient has the necessary dose of MFNS up to the next visit (one MFNS device-one bottle-contains sufficient doses for: either 2 weeks of BID treatment/regimen or 4 weeks of QD treatment/regimen) and dispense NIMP if needed
• Schedule appointment for next visit
• At Visit 9: remind the patient to come for Visit 10 in fasting state.
10.1.6 Visit 10 (Week 8)

- Record all medication use with start date and dose in eCRF; inquire about AEs/SAEs and background therapy tolerability
- Measure vital signs (blood pressure, heart rate, respiration rate, body temperature, weight)
- Perform ECG
- Download electronic diary/NPIF meter and remind patient to bring the device to the next visit
- Perform urine pregnancy test (for women of childbearing potential)
- Perform urinalysis (dipstick)
- Perform blood sampling (fasting, prior to administration of IMP) for clinical laboratories: hematology, serum chemistry, LFT, pharmacokinetics, anti-drug antibodies, biomarkers in serum and plasma, allergen-specific IgE panel sampling
- Perform nasal secretion sampling
- Call IVRS/IWRS to register visit and obtain next IMP kit number
- Perform nasal endoscopy
- Administer smell test
- Dispense and administer IMP (one SC injection)
  - Patients will be monitored at the study site for a minimum of 1 hour after the injection
- Administer SNOT-22, VAS and QoL questionnaires (SF-36, EQ-5D, Nasal polyp related resource use questionnaire)
- Obtain spirometry result and record in the e-CRF
- Administer ACQ-5 (in patients with asthma)
- Ensure that the patient has the necessary dose of MFNS up to the next visit (one MFNS device-one bottle-contains sufficient doses for: either 2 weeks of BID treatment/regimen or 4 weeks of QD treatment/regimen) and dispense NIMP if needed
- Schedule appointment for next visit

10.1.7 Visit 11, 12, 13 (Week 9, Week 10, Week 11)

- Record all medication use with start date and dose in eCRF; inquire about AEs/SAEs and background therapy tolerability
- Call IVRS/IWRS to register visit and obtain next treatment kit number
- Dispense NIMP and administer IMP (one SC injection)
  - Patients will be monitored at the study site for a minimum of 1 hour after the injection.
- Remind patient to continue the stable dose of MFNS and record daily usage in the electronic diary
• Ensure that the patient has the necessary dose of MFNS up to the next visit (one MFNS device contains sufficient doses for: 2 weeks of BID treatment/regimen and 1 month of QD treatment/regimen) and dispense NIMP if needed
• Schedule appointment for next visit
• At Visit 13: remind the patient to come for Visit 14 in fasting state.

10.1.8 Visit 14 (Week 12)

• Record all medication use with start date and dose in eCRF; inquire about AEs/SAEs and background therapy tolerability
• Measure vital signs (blood pressure, heart rate, respiration rate, body temperature, weight)
• Perform ECG
• Perform urine pregnancy test (for women of childbearing potential)
• Download electronic diary/NPIF meter and remind patient to bring the device to the next visit
• Perform nasal endoscopy
• Administer SNOT-22, VAS and QoL questionnaires (SF-36, EQ-5D, Nasal polyp related resource use questionnaire)
• Administer ACQ-5 in patients with asthma
• Obtain spirometry result and record in the e-CRF
• Perform blood sampling (fasting, prior to administration of IMP) for clinical laboratories: hematology, serum chemistry, LFT, pharmacokinetics, anti-drug antibodies, biomarkers in serum and plasma, allergen-specific IgE panel sampling
• Perform nasal secretion sampling
• Call IVRS/IWRS to register visit and obtain next IMP kit number
• Dispense NIMP and administer IMP (one SC injection)
  - Patients will be monitored at the study site for a minimum of 1 hour after the injection
• Remind patient to continue the stable dose of MFNS and record daily usage in the electronic diary
• Ensure that the patient has the necessary dose of MFNS up to the next visit (one MFNS device—one bottle—contains sufficient doses for: either 2 weeks of BID treatment/regimen or 4 weeks of QD treatment/regimen) and dispense NIMP if needed
• Schedule appointment for next visit
10.1.9 Visit 15, 16, 17 (Week 13, Week 14, Week 15)

- Record all medication use with start date and dose in eCRF; inquire about AEs/SAEs and background therapy tolerability
- Call IVRS/IWRS to register visit and obtain next IMP kit number
- Dispense NIMP and administer IMP (one SC injection)
- Patients will be monitored at the study site for a minimum of 1 hour after the injection.
- Remind patient to continue the stable dose of MFNS and record daily usage in the electronic diary
- Ensure that the patient has the necessary dose of MFNS up to the next visit (one MFNS device-one bottle-contains sufficient doses for: either 2 weeks of BID treatment/regimen or 4 weeks of QD treatment/regimen) and dispense NIMP if needed
- Schedule appointment for EOT visit
- At Visit 17: remind the patient to come for Visit 18 in fasting state.

10.1.10 EOT visit 18 (Week 16)

- Review patient Home Dosing Diary for content and completeness
- Record all medication use with start date and dose in eCRF; inquire about AEs/SAEs and background therapy tolerability
- Check for use of prohibited medications
- Perform physical examination
- Perform nasal endoscopy
- Perform CT scan (before V19)
- Administer SNOT-22, VAS and QoL questionnaires (SF-36, EQ-5D, Nasal polyp related ressource use questionnaire)
- Administer ACQ-5 in patients with asthma
- Perform spirometry
- Administer smell test (UPSIT)
- Perform urine pregnancy test (for women of childbearing potential)
- Perform urinalysis (dipstick)
- Measure vital signs (blood pressure, heart rate, respiration rate, body temperature, weight)
- Perform ECG
- Perform blood sampling (fasting, prior to administration of IMP) for clinical laboratories: hematology, serum biochemistry LFT, pharmacokinetics, anti-drug antibodies, biomarkers in serum and plasma, allergen-specific IgE panel sampling
• Perform RNA sampling
• Perform nasal secretion sampling
• For those patients who have signed a specific informed consent form, collect mucosa sample from nasal biopsy (prior to administration of investigational product during the Randomized Treatment Period)
• Download electronic diary/NPIF meter and remind patient to bring the device to the next visit
• Call IVRS/IWRS to register the EOT date
• Remind patient to continue the stable dose of MFNS and record daily usage in the electronic diary during the post treatment period
• Ensure that the patient has the necessary dose of MFNS up to the next visit (one MFNS device-one bottle-contains sufficient doses for: either 2 weeks of BID treatment/regimen or 4 weeks of QD treatment/regimen) and dispense NIMP if needed
• The optional qualitative self-assessment of the treatment will be proposed to the patient
• Ask patient if they want to complete the optional question on “treatment self-assessment”
• Schedule appointment for next visit.

10.1.11 Visit 19, Visit 20 and Visit 21 (Week 20, Week 24 and Week 28 Post-Treatment Period)
• Record all medication use with start date and dose in eCRF; inquire about AEs/SAEs and background therapy tolerability
• Check for use of prohibited medications
• Measure vital signs (blood pressure, heart rate, respiration rate, body temperature, weight)
• At Visit 19: remind the patient to come for Visit 20 in fasting state.
• PK samples are taken at Visit 19, 20 and 21. No ADA sample is collected at these visits
• At V20 only: Perform blood sampling (fasting) for clinical laboratories hematology, serum biochemistry, LFT
• Biomarkers and archival serum and nasal secretion sample is collected at Visit 19
• Download electronic diary/NPIF meter and remind patient to bring the device to the next visit
• Remind patient to continue the stable dose of MFNS and record daily usage in the electronic diary during the post treatment period
• Ensure that the patient has the necessary dose of MFNS up to the next visit (one MFNS device-one bottle-contains sufficient doses for: either 2 weeks of BID treatment/regimen or 4 weeks of QD treatment/regimen) and dispense NIMP if needed
Schedule appointment for next visit
At Visit 21: remind the patient to come for Visit 22 in fasting state.

10.1.12 Visit 22 (Week 32 End-of-Study Visit)

- Record all medication use with start date and dose in eCRF; inquire about AEs/SAEs and background therapy tolerability
- Check for use of prohibited medications
- Perform physical examination
- Perform nasal endoscopy
- Administer SNOT-22, VAS and QoL questionnaires (SF-36, EQ-5D, Nasal polyp related ressource use questionnaire)
- Administer ACQ-5 in patients with asthma
- Perform spirometry
- Measure vital signs (blood pressure, heart rate, respiration rate, body temperature, weight)
- Perform urine pregnancy test (for women of childbearing potential)
- Perform urinalysis (dipstick)
- Perform 12-lead electrocardiography (ECG)
- Perform blood sampling (fasting) for clinical laboratories hematology, serum biochemistry LFT, pharmacokinetics, anti-drug antibodies, biomarkers in serum and plasma, allergen-specific IgE panel sampling
- Perform RNA sampling
- Download electronic diary/NPIF meter
- Call IVRS to register the EOS date

10.2 DEFINITION OF SOURCE DATA

Source data is all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Source documents are original documents, data and records such as hospital records, clinic and office charts, laboratory notes, memoranda, pharmacy dispensing records, recorded data from automated instruments, etc.

All the data collected in the e-CRF should be transcribed directly from source documents. Data downloaded from the study-associated central laboratories, endoscopy, CT scan, spirometry, NPIF measurement, ECG, and patient electronic diary will be considered source data.
10.3 HANDLING OF PATIENT TEMPORARY OR PERMANENT TREATMENT DISCONTINUATION AND OF PATIENT STUDY DISCONTINUATION

The IMP and NIMP should be continued whenever possible. Permanent IMP discontinuation should be a last resort. Any IMP discontinuation should be fully documented in the CRF. In any case, the patient should remain in the study as long as possible.

10.3.1 Temporary treatment discontinuation with investigational medicinal product(s)

Temporary treatment discontinuation may be considered by the Investigator because of suspected AEs. Reinitiation of treatment with the IMP will be done under close and appropriate clinical and/or laboratory monitoring once the Investigator will have considered according to his/her best medical judgment that the responsibility of the IMP(s) in the occurrence of the concerned event was unlikely and if the selection criteria for the study are still met (refer to Section 7.1 and Section 7.2).

For all temporary treatment discontinuations, duration should be recorded by the Investigator in the appropriate pages when considered as confirmed.

10.3.2 Permanent treatment discontinuation with investigational medicinal product(s)

Permanent treatment discontinuation is any treatment discontinuation associated with the definitive decision from the Investigator or the patient not to re-expose the patient to the IMP at any time.

10.3.3 List of criteria for permanent treatment discontinuation

The patients may withdraw from treatment with the IMP if they decide to do so, at any time and irrespective of the reason, or this may be the Investigator’s decision. All efforts should be made to document the reasons for treatment discontinuation and this should be documented in the e-CRF.

Patients must be withdrawn from the study (ie, from any further investigational product or study procedure) 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 patient to the patient’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 patient’s well-being

- At the specific request of the Sponsor

- If there is need for systemic corticosteroids or surgery to control and/or relief the underlying disease or for the treatment of any other conditions requiring treatment with any of the prohibited concomitant treatment listed in Section 8.8.1.

- In case of recurrent infectious episodes requiring antibiotics
• In the event of a protocol deviation, at the discretion of the Investigator or the Sponsor
• Pregnancy will lead to definitive treatment discontinuation in all cases

Stopping rules described in Appendix D should be applied

Any abnormal laboratory value or ECG parameter will be immediately rechecked for confirmation before making a decision of permanent discontinuation of the IMP for the concerned patient.

10.3.4 Handling of patients after permanent treatment discontinuation

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

If possible, and after the permanent discontinuation of treatment, the patients will be assessed using the procedures normally planned for the End-of-treatment Visit and the four Post-treatment Period Visits.

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

10.3.5 Procedure and consequence for patient withdrawal from study The patients may withdraw from the study before study completion if they decide to do so, at any time and irrespective of the reason:

• If possible, the patients are assessed using the procedure normally planned for the End-of-treatment Visit and the four Post-treatment Period Visits.

For patients who fail to return to the site, the Investigator should make the best effort to recontact the patient (eg, contacting patient’s family or private physician, reviewing available registries or health care databases), and to determine his/her health status, including at least his/her vital status. Attempts to contact such patients must be documented in the patient’s records (eg, times and dates of attempted telephone contact, receipt for sending a registered letter).

Consideration of the analyses for such patients will be prespecified in the SAP.

Patients who have withdrawn from the study cannot be re-randomized (treated) in the study. Their inclusion and treatment numbers must not be reused.
10.4 OBLIGATION OF THE INVESTIGATOR REGARDING SAFETY REPORTING

10.4.1 Definitions of adverse events

10.4.1.1 Adverse event

An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

10.4.1.2 Serious adverse event

A serious adverse event (SAE) is any untoward medical occurrence that at any dose:

- Results in death, or
- Is life-threatening, or
  Note: The term “life-threatening” in the definition of “serious” refers to an event in which the patient 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.
- Requires inpatient hospitalization or prolongation of existing hospitalization, or
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect
- Is a medically important event

Medical and scientific judgment should be exercised in deciding whether expedited 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 patient or may require intervention (ie, specific measures or corrective treatment) to prevent one of the other outcomes listed in the definition above.

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

- Intensive treatment in an emergency room or at home for:
  - Allergic bronchospasm
  - Anaphylaxis (refer to Appendix B for Definition of Anaphylaxis)
  - Blood dyscrasias (ie, agranulocytosis, aplastic anemia, bone marrow aplasia, myelodysplasia, pancytopenia, etc),
  - Convulsions (seizures, epilepsy, epileptic fit, absence, etc).
- Development of drug dependency or drug abuse
- ALT >3 x ULN + total bilirubin >2 x ULN or asymptomatic ALT increase >10 x ULN


- Suicide attempt or any event suggestive of suicidality
- Syncope, loss of consciousness (except if documented as a consequence of blood sampling)
- Bullous cutaneous eruptions
- Cancers diagnosed during the study or aggravated during the study
- Chronic neurodegenerative diseases (newly diagnosed) or aggravated during the study (only if judged unusual/significant by the Investigators in studies assessing specifically the effect of a study drug on these diseases).

10.4.1.3 Adverse event of special interest

An adverse event of special interest (AESI) is an AE (serious or non-serious) of scientific and medical concern specific to the Sponsor’s product or program, for which ongoing monitoring and rapid communication by the Investigator to the Sponsor may be appropriate. Such events may require further investigation in order to characterize and understand them. AESIs may be added or removed during a study by protocol amendment.

10.4.1.3.1 AESI with immediate notification

For these AESIs, the Sponsor will be informed immediately (ie, within 24 hours), per SAE notification described Section 10.4.1.2, even if not fulfilling a seriousness criterion, using the corresponding pages in the CRF (to be sent) or screens in the e-CRF.

Anaphylactic reactions or acute allergic reactions that require immediate treatment (refer to Appendix B for Definition of Anaphylaxis)

- Severe injection site reactions that last longer than 24 hours
- Severe infections include opportunistic infection and parasitic infections
- Significant ALT elevation
  - ALT >5 x the upper limit of normal (ULN) in patients with normal baseline ALT; or
  - ALT >3 x baseline ALT in patients with abnormal baseline ALT
- ALT elevation
  - ALT ≥3 x ULN and ≤5 x ULN plus total bilirubin >2 x ULN in patients with normal baseline ALT; or
  - ALT ≥2 x baseline ALT and ≤3 x baseline ALT plus total bilirubin >2 x ULN in patients with abnormal baseline ALT
- Pregnancy
  - Pregnancy occurring in a female patient included in the clinical trial. Pregnancy will be recorded as a pre-specified AE with immediate notification in all cases. It will be qualified as an SAE only if it fulfills the SAE criteria.
In the event of pregnancy, investigational product should be discontinued.
- The follow-up of the pregnancy will be mandatory until the outcome has been determined.

- Symptomatic overdose with IMP/Non-IMP

An overdose (accidental or intentional) with the IMP is an event suspected by the Investigator or spontaneously notified by the patient and defined as at least twice the 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 Non-IMP is an event suspected by the Investigator or spontaneously notified by the patient and defined as at least twice of the intended dose within the intended therapeutic interval. The circumstances (ie, accidental or intentional) should be clearly specified in the verbatim and symptoms, if any, entered on separate AE forms.

10.4.2 General guidelines for reporting adverse events

- All AEs, regardless of seriousness or relationship to IMP/Non-IMP, spanning from the signature of the informed consent form until the end of the study as defined by the protocol for that patient, are to be recorded on the corresponding page(s) or screen(s) of the CRF.

- When a safety event is categorized as a primary outcome, the event will be reported as an AE but will be waived from reporting to health authorities providing an agreement has been reached with them.

- Whenever possible, diagnosis or single syndrome should be reported instead of symptoms. The Investigator should specify the date of onset, intensity, action taken with respect to IMP, corrective treatment/therapy given, additional investigations performed, outcome, and his/her opinion as to whether there is a reasonable possibility that the AE was caused by the IMP. In studies that require the use of combined/multiple IMPs/Non-IMPs, the Global Safety Officer (GSO) with input from other appropriate study team members must determine if the causal relationship will either be assessed for the combined product as a regimen or as distinct entities. The GSO must communicate this decision to the study team for inclusion in the protocol and AE CRF.

- The Investigator should take appropriate measures to follow all AEs until clinical recovery is complete and laboratory results have returned to normal, or until progression has been stabilized, or until death, in order to ensure the safety of the patients. This may imply that observations will continue beyond the last planned visit per protocol, and that additional investigations may be requested by the monitoring team up to as noticed by the Sponsor. Patients who experience an ongoing SAE or an AESI with immediate notification, at the prespecified study end-date, should be followed until resolution, stabilization, or death and related data will be collected.

- When treatment is prematurely discontinued, the patient’s observations will continue until the end of the study as defined by the protocol for that patient.
- Laboratory, vital signs or ECG abnormalities are to be recorded as AEs only if:
  - Symptomatic, or
  - Requiring either corrective treatment or consultation, or
  - Leading to IMP discontinuation or modification of dosing, or
  - Fulfilling a seriousness criterion, or
  - Defined as an AESI.

The following table summarizes the reporting timelines:

<table>
<thead>
<tr>
<th>Adverse event / laboratory abnormality</th>
<th>Reporting timeline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious adverse event</td>
<td>Within 24 hours</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>Within 24 hours</td>
</tr>
<tr>
<td>Overdose</td>
<td>Symptomatic</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>Within 24 hours</td>
</tr>
<tr>
<td>ALT elevation</td>
<td>Baseline &lt; ULN</td>
</tr>
<tr>
<td></td>
<td>ALT &gt; 5 ULN</td>
</tr>
<tr>
<td></td>
<td>3 ULN ≤ ALT ≤ 5 ULN plus total bilirubin &gt; 2 ULN</td>
</tr>
<tr>
<td></td>
<td>Baseline ≥ ULN</td>
</tr>
<tr>
<td></td>
<td>ALT &gt; 3x baseline</td>
</tr>
<tr>
<td></td>
<td>2 x baseline ≤ ALT ≤ 3x baseline plus total bilirubin &gt; 2 ULN</td>
</tr>
<tr>
<td>Anaphylactic reactions or acute allergic reactions that require immediate treatment</td>
<td>Within 24 hours</td>
</tr>
<tr>
<td>Severe injection site reactions that last longer than 24 hours</td>
<td>Within 24 hours</td>
</tr>
<tr>
<td>Severe infections including opportunistic and parasitic infections</td>
<td>Within 24 hours</td>
</tr>
</tbody>
</table>

10.4.3 Instructions for reporting serious adverse events

In the case of occurrence of an SAE, the Investigator must immediately:

- ENTER (within 24 hours) the information related to the SAE in the appropriate screens of the e-CRF; the system will automatically send a notification to the monitoring team after approval of the Investigator within the e-CRF or after a standard delay.

- SEND (preferably by fax or e-mail) a photocopy of all examinations carried out and the dates on which these examinations were performed, to the representative of the monitoring team whose name, fax number, and email address appear on the clinical trial protocol. Care should be taken to ensure that the patient's identity is protected and the patient's identifiers in the clinical trial are properly mentioned on any copy of a source document provided to the Sponsor. For laboratory results, include the laboratory normal ranges.

- All further data updates should be recorded in the e-CRF as appropriate, and further documentation as well as additional information (for laboratory data, concomitant medications, patient status, etc) should be sent (by fax or e-mail) to the monitoring team within 24 hours of knowledge. In addition, every effort should be made to further document any SAE that is fatal or life threatening within a week (7 days) of the initial notification.

- A back-up plan (using a paper CRF process) is available and should be used when the e-CRF system does not work.
Any SAE brought to the attention of the Investigator at any time after the end of the study for the patient and considered by him/her to be caused by the IMP with a reasonable possibility, should be reported to the monitoring team.

10.4.4 Guidelines for management of specific laboratory abnormalities

Decision trees for the management of certain laboratory abnormalities by Sanofi are provided in Appendix D.

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

- Neutropenia
- Thrombocytopenia
- Increase in ALT
- Acute renal insufficiency
- Suspicion of rhabdomyolysis

10.5 OBLIGATIONS OF THE SPONSOR

During the course of the study, the Sponsor will report in an expedited manner all SAEs that are both unexpected and at least reasonably related to the investigational product (SUSAR), to the Health Authorities, IECs/IRBs as appropriate and to the Investigators. In addition, the Sponsor may report in an expedited manner all SAEs that are expected and at least reasonably related to the investigational products to the Authorities, according to local regulations.

Any other adverse event not listed as an expected event in the investigator’s brochure and in this protocol will be considered as unexpected.

The Sponsor will report all safety observations made during the conduct of the trial in the clinical study report.

10.6 SAFETY INSTRUCTIONS

10.6.1 Hypersensitivity

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

Acute allergic reactions may be defined as allergic reaction-mediated signs and symptoms experienced by patients during or shortly after the pharmacologic or biologic agent is given. These reactions may present in a variety of ways, including dizziness, headache, anxiety, dyspnea, hypotension, tachycardia, pruritus, rash, urticaria/angioedema, flushing, nausea, or vomiting. Anaphylaxis may represent the most severe form of infusion reaction, but these events may also
occur via non-IgE mediated mechanisms (eg, anaphylactoid reactions), or may occur via other
immune-mediated mechanisms (eg, cytokine-mediated). Allergic reactions may begin within a
few hours and persist up to 24 hours post dosing. Refer to Appendix B “Definition of
Anaphylaxis”, which describes the clinical criteria for the diagnosis of anaphylaxis.

Patients should be monitored for at least 1 hour after each study-site administered investigational
product administration for any signs or symptoms of a hypersensitivity reaction. Any instance of
allergic reaction should be reported as an adverse event of special interest (AESI). Any
anaphylactic reactions or acute allergic reactions that require immediate treatment will be AESI
with immediate reporting (within 24 hours) and study medication should be permanently
discontinued. Trained personnel and medications should be available to treat anaphylaxis or any
severe allergic reaction if it occurs.

10.6.2 Severe Injection site reactions

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

10.6.3 Infections, including opportunistic infection and parasitic infections

Some biologic therapies have been associated with an increased risk of infection, including
opportunistic infection. As a precautionary measure, the Investigator is required to carefully
monitor for any signs or symptoms of infection such as, but not limited to, increased body
temperature, malaise, weight loss, sweats, cough, dyspnea, pulmonary infiltrates, or serious febrile
systemic illness.

Any opportunistic infection requiring parenteral or prolonged (>14 days) antibiotics or
antituberculosis medication should be considered serious and be reported as AESI with immediate
notification. The study medication should be discontinued in case of suspicion of serious infection
and a complete diagnostic work-up should be performed (ie, cultures for fungi and/or
mycobacteria other than tuberculosis, histopathological or cytological evaluation, antigen
detection and serum antibody titers). Patients should be referred to an infectious disease specialist
if deemed necessary for diagnostic work up and appropriate treatment.

Since dupilumab binds to IL-4Rα, preventing IL-4 and IL-13 binding and activation of their
respective receptors, it inhibits the T-helper 2 (Th2) cytokines productions. Infections with a
diversity of helminthic parasites elicit eosinophilia via stimulation of Th2-like lymphocyte
responses. The TH2 response is characterized by production of IL-4 and IL-5, subsequently
generating IgG1 and IgE-secreting cells, and eliciting eosinophilia. Eosinophilia is prominent in a
number of helminthic parasitic diseases. The eosinophilic response to helminths is determined
both by the host's immune response and by the parasite, including its distribution, migration, and
development within the infected host. Therefore patient with treatment of dupilumab may potentially have an increased risk of parasitic infection.

In order to minimize this risk, any patient with an active parasitic infection should be excluded from the study. Similarly, patients with suspected parasitic infection, or those at high risk of parasitic infection are also excluded, unless clinical and (if necessary) laboratory assessments have ruled out active infection before randomization. During the study, appearance of signs or symptoms (such as abdominal pain, cough, diarrhea, fever, fatigue hepatosplenomegaly) that could be associated with a parasitic infection should be carefully evaluated, especially if there is a history of parasitic exposure through recent travel to/ or residence in endemic areas, especially when conditions are conducive to infection (eg, extended stay, rural or slum areas, lack of running water, consumption of uncooked, undercooked, or otherwise potentially contaminated food, close contact with carriers and vectors, etc.). Subsequent medical assessments (eg, stool exam, blood tests, etc.) must be performed in order to rule out parasitic infection/infestation. Patients with confirmed parasitic infections during the study should be reported as AESI with immediate notification and will be permanently discontinued from the study.

10.6.4 Elevated liver function tests

No pre-clinical and clinical data suggested any hepatic toxicity of anti-IL4 agent; however, as general consideration of clinical development, the administration of immunosuppressant or immunomodulating agents may represent an additional risk factor for hepatotoxicity.

In order to closely follow liver function tests (LFT), assessment of total protein, albumin, total bilirubin, alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase are measured as part of the clinical laboratory testing. Clinical laboratory testing at Visit 1 adds hepatitis screen (hepatitis B surface antigen (HBsAg), Hepatitis B IgM core antibody (HBcAb-IgM), hepatitis C antibodies (HC Ab).

Patients with:

- ALT >3XULN at the V1 and/or V2
- positive or indeterminate hepatitis B surface antigen (HBsAg), hepatitis B core antibody (HBcAb), or hepatitis C antibody at Visit 1

are excluded from the study.

Guidance for the investigation of elevated LFTs is provided in Appendix D.

10.7 ADVERSE EVENTS MONITORING

All events will be managed and reported in compliance with all applicable regulations, and included in the final clinical study report.
11 STATISTICAL CONSIDERATIONS

11.1 DETERMINATION OF SAMPLE SIZE

The sample size calculation is based on the primary efficacy variable of NPS change from baseline to week 16 in patients, with the following assumptions:

- A common standard deviation of 1.5, which is assumed based on the paper *(Mepolizumab, a humanized anti-IL-5 mAb, as a treatment option for severe nasal polyposis, by Philippe Gevaert et al.)* (25)
- A 1.3 mean difference between the treatment and placebo in change from baseline in NPS.
- A t-test at a 2-sided 5% significant level with 80% power
- Expected early discontinuation rate of 20%

Based on the above assumptions, 56 patients (28 per group) are needed for this study. Calculations were made using nQuery Advisor 7.0.

When considering patients with co-morbid asthma only, a t-test at a 2-sided 5% significant level and 20% drop out rate, assuming a common standard deviation of 2.0 and a difference of 2.5 (16) between dupilumab and placebo groups in the change of NPS from baseline to Week 16, 14 patients per group will provide 79% power to detect.

11.2 DISPOSITION OF PATIENTS

Screened patients are defined as any patient who met the inclusion criteria and signed the informed consent.

Randomized patients consist of all patients with a treatment kit number allocated and recorded in IVRS database, and regardless of whether the treatment kit was used or not.

Patients treated without being randomized will not be considered as randomized and will not be included in any efficacy population.

For any patient randomized more than once, only the data associated with the first randomization will be used in any analysis population. The safety experience associated with any later randomization will be assessed separately.

The safety experience of patients treated and not randomized will be reported separately, and these patients will not be in the safety population.
11.3 ANALYSIS POPULATIONS

11.3.1 Efficacy populations

11.3.1.1 Intent–to-treat /modified intent-to-treat population

ITT population: all randomized population analyzed according to the treatment group allocated by randomization regardless of whether treatment kit is used or not.

The primary analysis population for the efficacy endpoints will be the double blind randomized ITT population who have been allocated to a randomized treatment regardless of whether the treatment kit was used or not. The efficacy analyses will be conducted according to the treatment to which they are randomized.

11.3.2 Safety population

Safety population: all randomized patients exposed to study medication, regardless of the amount of treatment administered. The safety analyses will be conducted according to the treatment patients actually received.

Treatment emergent period for safety population is defined as the time from the first administration of study medication to the end of the Post-treatment Period.

In addition:

- Nonrandomized but treated patients will not be part of the safety population, but their safety data will be presented separately.
- Randomized patients for whom it is unclear whether they took the study medication will be included in the safety population as randomized.
- For patients receiving more than 1 study treatment during the trial, the treatment group allocation for as-treated analysis will be lowest exposed dupilumab dose / regimen group.

11.3.3 Pharmacokinetics (PK) population

- The PK population will consist of all patients in the safety population with at least one non-missing and eligible plasma concentration data. Patients will be analyzed according to the treatment actually received.

11.3.4 Anti-drug antibody population

- The anti-drug antibody population will consist of all patients in the safety population with at least one post-treatment ADA sample that was assayed successfully using the ADA assay. Patients will be analyzed according to the treatment actually received.
11.4 STATISTICAL METHODS

11.4.1 Extent of study treatment exposure and compliance

The extent of study treatment exposure and compliance will be assessed and summarized by actual treatment received within the safety population.

11.4.1.1 Extent of investigational product exposure

Duration of IMP exposure is defined as: last dose date – first dose date + 7 days, regardless of unplanned intermittent discontinuations

11.4.1.2 Compliance

A given administration will be considered noncompliant if the patient did not take the planned dose of treatment as required by the protocol. No imputation will be made for patients with missing or incomplete data.

Percentage of compliance for a patient will be defined as the number of administrations the patient was compliant divided by the total number of administrations the patient was planned to take during the treatment period (ie, from the 1st to the last administration).

Treatment compliance will be summarized descriptively (N, Mean, SD, Median, Min, and Max). The percentage of patients with compliance <80% will be summarized.

11.4.2 Analyses of efficacy endpoints

The primary efficacy analyses will be based on ITT population.

11.4.2.1 Analyses of primary efficacy endpoint

The change from baseline in NPS at Week 16 in ITT population will be analyzed using a mixed-effect model with repeated measures (MMRM) approach. The model will include change from baseline values up to week 16 as response variables, and factors (fixed effects) for treatment, stratification factor(s), pooled countries / regions, visit, treatment-by-visit interaction, NPS baseline value and baseline-by-visit interaction. An unstructured correlation matrix will be used to model the within-patient errors. Parameters will be estimated using restricted maximum likelihood method with the Newton-Raphson algorithm. Descriptive statistics including number of patients, mean, standard error and LS means will be provided. In addition, difference in LS means, the corresponding 95% CI and the p-value will be provided for comparisons of each dose against placebo. No imputation will be performed for the MMRM model.

Change from baseline at other visits will be summarized using descriptive statistics.
11.4.2.2 Analyses of secondary efficacy endpoints

11.4.2.2.1 Analysis of proportion of patients with binary events

Proportion of patients with:

- $\geq 1$ point improvement (reduction) in NPS at week 16 (as read centrally)
- Drop-out due to oral CS or surgery
- INCS increase after 8 weeks

will be analyzed using a logistic model with the above responses, respectively, as the response variable, and treatment group, pooled countries /regions and the stratification factor(s) prior to the study as covariates.

11.4.2.2.2 Analysis of time to event variables

Time to event (eg, the first response with $\geq 1$ point improvement (reduction) in NPS, study treatment discontinuation, etc) will be analyzed using a Cox regression model with time to event as the dependent variable, and treatment, pooled countries/regions, asthma comorbidity prior to the study as covariates. The Kaplan-Meier method will be used to derive the proportion of patients with an event at Week 4, 8, 12 and 16 specific to each treatment group. For analysis during the treatment period, if a patient has no event before treatment discontinuation/completion, then the patient will be considered as free of event till the end of treatment period (last dose date + 7 days).

11.4.2.2.3 Analysis of change from baseline for continuous variables

The change from baseline at week 16 in:

- In NPS for patients with co-morbid asthma
- % change in maxillary CT opacification
- Lund Mackay score
- 22-item Sinonasal Outcome Test (SNOT-22)
- Subject-assessed congestion and/or obstruction score
- Nasal peak inspiratory flow (NPIF)
- ACQ-5 in patients with co-morbid asthma
- QoL measures (SF36, EQ-5D), VAS

will be analyzed using MMRM same as the primary endpoints. Descriptive statistics including number of patients, mean, standard error and LS means will be provided. In addition, differences in LS means, the corresponding 95% CI and the p-value will be provided for comparisons of each dose against placebo.
11.4.2.2.4 Analysis of efficacy in baseline biomarker of characteristics defined subsets

To examine baseline biomarkers for their potential value to predict treatment response, analyses of change in NPS will also be performed for the following subsets and the entire ITT population by each dose group and selected pooled dose group.

11.4.2.2.5 Subgroup analysis

To assess the consistency treatment effects across the subgroup levels, and to examine baseline biomarkers for their potential value to predict treatment response, exploratory subgroup analyses will be conducted for the change from baseline in NPS with respect to age group, gender, region, race, INCS dose level, baseline NPS, baseline CT scan score, asthma comorbidity, and selected biomarkers prior to the study. The details will be provided in the SAP.

11.4.2.3 Multiplicity considerations

For this two-arm study with a single primary efficacy endpoint, multiplicity adjustment is not considered.

11.4.3 Analyses of safety data

The summary of safety results will be presented by treatment group.

All safety analyses will be performed on the Safety population using the following common rules:

- The baseline value is defined generally as the last available value before randomization.
- Treatment emergent period for safety population is defined as the time from the first administration of study medication to the end of the Post-treatment Period.

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

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

11.4.3.1 Adverse events

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

Proportion of patients with at least one treatment emergent adverse event (TEAE), serious TEAE 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. None treatment emergent serious AE, AE leading to study discontinuation will be summarized separately.

11.4.3.1.1 AESI

The following summaries will be generated:

- Incidence of each AESI will be tabulated by treatment group.

In addition,

- The time-to-first event analyzed using K-M methods and displayed as K-M plots (cumulative incidence (%) versus time based on K-M estimates) will be provided to depict the course of onset over time. When TEAE start date or worsening date is partially available, the maximum of the earliest possible TEAE start date and the treatment start date will be used. When TEAE start date or worsening date is completely missing, the treatment start date will be used.

- An overview summary of the number (%) of patients with
  - any TEAE
  - any serious AE (regardless of treatment-emergent status)
  - any treatment-emergent SAE
  - any AE leading to death
  - any TEAE leading to permanent study drug discontinuation
  - any TEAE by maximum intensity, corrective treatment, and final outcome
  - time to onset of first TEAE
  - cumulative incidence at specified time points (K-M estimates at 1 week, 4 weeks, 12 weeks and 24 weeks)

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

11.4.3.1.2 Death

The following deaths summaries will be generated:

- Number (%) of patients who died by study period (TEAE, on-study) and reasons for death summarized on the safety population by treatment received

- Death in nonrandomized patients or randomized and not treated patients
• TEAE leading to death (death as an outcome on the AE CRF page as reported by the Investigator) by primary SOC, HLGT, HLT and PT showing number (%) of patients sorted by internationally agreed order of SOC and alphabetic order of HLGT, HLT, and PT.

Patient data listings will be provided for all AEs, TEAEs, SAE, AEs leading to study discontinuation, AESIs and deaths.

11.4.3.1.3 Clinical Laboratory Evaluation, Vital Signs and electrocardiogram data

Results and change from baseline for the parameters will be summarized by treatment group for baseline and each post baseline time point, endpoint, minimum and maximum value. Summary statistics will include number of patients, mean, standard deviation, median, q1, q3, minimum and maximum.

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

Listings will be provided with flags indicating clinically out-of-range values, as well as PCSA values.

11.4.4 Analyses of pharmacokinetic, anti-drug antibodies and pharmacodynamic variables

11.4.4.1 Pharmacokinetic Descriptive Analysis

Concentrations of functional dupilumab in serum will be summarized using arithmetic and geometric means, SD, standard error of the mean (SEM), coefficient of variation (CV%), minimum, median, and maximum by treatment per visit.

Plasma concentrations of dupilumab will be used for population PK analysis by non-linear mixed effects modeling if warranted. Additional details of the analysis plan and the results will be provided in a separate document.

11.4.4.2 Anti-drug antibody analysis

Listings of anti-DUPILUMAB antibody results (Negative or titer value) will be presented by patient, time point and treatment groups. ADA titer levels will be classified into categories: Low, moderate and high. Low levels of ADA titers are defined as titers below 1000; moderate levels of ADA titers are defined as titers between 1000 and 10,000; high levels of ADA titers are defined as titers >10,000.

Anti-DUPILUMAB antibody assay results will be described categorically. The following summary will be provided for:

• Patients with any positive ADA assay response during the TEAE period.
- Patients with treatment induced positive ADA assay response during the TEAE period.
- Patients with treatment induced positive ADA assay response during the TEAE period will be further described as patients with transient positive response and patients with persistent positive response.

The patients with any positive ADA assay response during the TEAE period is defined as those having at least one sample positive in the ADA assay.

The treatment induced positive ADA assay response is defined as:
- Patients with no positive assay response at baseline but with a positive assay response during the TEAE period or
- Patients with a positive ADA assay response at baseline and also have at least a 4-fold increase in titer during the TEAE period.

A persistent positive response is a treatment induced positive ADA assay response in which at least 2 consecutive post-baseline samples from a patient are positive in the ADA assay or the last post-baseline sample collected is positive in the ADA assay. A transient positive response is defined as any treatment induced positive ADA assay response that is not considered persistent.

ADA variables will be assessed as absolute occurrence (N) and percent (%) of patients grouped by study defined groups and overall study population.

11.4.4.3 Pharmacodynamic analysis

The values to be used as baselines will be those collected on Day 1 (predose assessments). If any of the scheduled assessments on Day 1 are technically disqualified (eg, insufficient sample), then values determined at Screening can be used as baseline.

For all parameters, raw data, absolute changes from baseline and percent changes from baseline will be summarized in descriptive statistics by treatment group and time point.

Summary plots (mean +/- standard error of the mean) on raw data, absolute changes from baseline and percent changes from baseline will be provided by treatment group.

11.4.5 Analyses of quality of life/health economics variables

Change from baseline in the following variables: the ACQ-5 score, the quantitative variables of EQ-5D-3L (single index utility), SF-36 (8 domains, Physical Component Summary (PCS) and Mental Component Summary (MCS) will be analyzed with an MMRM approach described previously for the continuous secondary efficacy variables. Descriptive statistics including number of patients, mean, standard error and LS means will be provided. In addition, difference in LS means, the corresponding 95% CI and the p-value will be provided for comparisons of each dose against placebo.
11.4.6 Interim analysis

An early analysis will be performed at the end of treatment. No decision on the conduct of the study will be made based on this analysis. The assessment of change from baseline in NPS at Week 16 performed will be the final analysis of the primary endpoint. Hence there will be no need for alpha adjustment due to this early analysis.

To maintain study integrity with respect to the subsequent treatment visits, post-treatment follow-up visits, safety visits and analyses, a dissemination plan will be written. This plan will clearly identify the team (including the statistician) that will perform the early analysis and all related activities, restrict other company personnel from access to individual patient treatment allocation and site level analysis results, and ensure that the dedicated team will not participate in the data review or data decisions for the following post treatment analyses. However, the dedicated team can participate in the analysis following the final database lock. A Key Results Summary for the early analysis will be prepared and distributed to limited personnel.
12 ETHICAL AND REGULATORY STANDARDS

12.1 ETHICAL PRINCIPLES

This clinical trial will be conducted in accordance with the principles laid down by the 18th World Medical Assembly (Helsinki, 1964) and all applicable amendments laid down by the World Medical Assemblies, and the ICH guidelines for good clinical practice (GCP).

In compliance with Sanofi public disclosure commitments, this clinical trial will be recorded in the public registry website clinicaltrials.gov before the enrollment of the first patient. The registry will contain basic information about the trial sufficient to inform interested patients (and their healthcare practitioners) how to enroll in the trial.

12.2 LAWS AND REGULATIONS

This clinical trial will be conducted in compliance with all international guidelines, and national laws and regulations of the country(ies) in which the clinical trial is performed, as well as any applicable guidelines. See Section 13.1.

12.3 INFORMED CONSENT

The Investigator (according to applicable regulatory requirements), or a person designated by the Investigator, and under the Investigator's responsibility, should fully inform the patient of all pertinent aspects of the clinical trial including the written information giving approval/favorable opinion by the Ethics Committee (IRB/IEC). All participants should be informed to the fullest extent possible about the study, in language and terms they are able to understand.

Prior to a patient’s participation in the clinical trial, the written informed consent form should be signed, name filled in and personally dated by the patient or by the patient’s legally acceptable representative, and by the person who conducted the informed consent discussion. A copy of the signed and dated written informed consent form will be provided to the patient.

Prior to collection of blood for pharmacogenomics and nasal mucosa biopsy, the optional respective informed consent form (written) should be signed, name filled in, and personally dated by the patient or by the subject’s legally acceptable representative, and by the person who conducted the informed consent discussion. A copy of the signed and dated written optional informed consent form will be provided to the patient.

The informed consent form and the optional pharmacogenomic and nasal biopsy informed consent form used by the Investigator for obtaining the patient's informed consent must be reviewed and approved by the Sponsor prior to submission to the appropriate Ethics Committee (IRB/IEC) for approval/favorable opinion.
If the race/ethnic origin of the patients will be collected in the clinical trial, the scientific justification should be specified.

12.4 INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE (IRB/IEC)

As required by local regulation, the Investigator or the Sponsor must submit this clinical trial protocol to the appropriate Ethics Committee (IRB/IEC), and is required to forward to the respective other party a copy of the written and dated approval/favorable opinion signed by the Chairman with Ethics Committee (IRB/IEC) composition.

The clinical trial (study number, clinical trial protocol title and version number), the documents reviewed (clinical trial protocol, informed consent form, Investigator’s Brochure, Investigator’s curriculum vitae [CV], etc) and the date of the review should be clearly stated on the written (IRB/IEC) approval/favorable opinion.

IMP will not be released at the study site and the Investigator will not start the study before the written and dated approval/favorable opinion is received by the Investigator and the Sponsor.

During the clinical trial, any amendment or modification to the clinical trial protocol should be submitted to the Ethics Committee (IRB/IEC) before implementation, unless the change is necessary to eliminate an immediate hazard to the patients, in which case the IRB/IEC should be informed as soon as possible. It should also be informed of any event likely to affect the safety of patients or the continued conduct of the clinical trial, in particular any change in safety. All updates to the Investigator’s Brochure will be sent to the Ethics Committee (IRB/IEC).

A progress report is sent to the Ethics Committee (IRB/IEC) at least annually and a summary of the clinical trial’s outcome at the end of the clinical trial.
13 STUDY MONITORING

13.1 RESPONSIBILITIES OF THE INVESTIGATOR(S)

The Investigator(s) and delegated Investigator staff undertake(s) to perform the clinical trial in accordance with this clinical trial protocol, ICH guidelines for Good Clinical Practice and the applicable regulatory requirements.

The Investigator is required to ensure compliance with all procedures required by the clinical trial protocol and with all study procedures provided by the Sponsor (including security rules). The Investigator agrees to provide reliable data and all information requested by the clinical trial protocol (with the help of the CRF, Discrepancy Resolution Form [DRF] or other appropriate instrument) in an accurate and legible manner according to the instructions provided and to ensure direct access to source documents by Sponsor representatives.

If any circuit includes transfer of data, particular attention should be paid to the confidentiality of the patient's data to be transferred.

The Investigator may appoint such other individuals as he/she may deem appropriate as Subinvestigators to assist in the conduct of the clinical trial in accordance with the clinical trial protocol. All Subinvestigators shall be appointed and listed in a timely manner. The Subinvestigators will be supervised by and work under the responsibility of the Investigator. The Investigator will provide them with a copy of the clinical trial protocol and all necessary information.

13.2 RESPONSIBILITIES OF THE SPONSOR

The Sponsor of this clinical trial is responsible to health authorities for taking all reasonable steps to ensure the proper conduct of the clinical trial protocol as regards ethics, clinical trial protocol compliance, and integrity and validity of the data recorded on the CRFs. Thus, the main duty of the monitoring team is to help the Investigator and the Sponsor maintain a high level of ethical, scientific, technical and regulatory quality in all aspects of the clinical trial.

At regular intervals during the clinical trial, the site will be contacted, through monitoring visits, letters or telephone calls, by a representative of the monitoring team to review study progress, Investigator and patient compliance with clinical trial protocol requirements and any emergent problems. These monitoring visits will include but not be limited to review of the following aspects: patient informed consent, patient recruitment and follow-up, SAE documentation and reporting, AESI documentation and reporting, AE documentation, IMP allocation, patient compliance with the IMP regimen, IMP accountability, concomitant therapy use and quality of data.
13.3 SOURCE DOCUMENT REQUIREMENTS

According to the ICH guidelines for Good Clinical Practice, the monitoring team must check the CRF entries against the source documents, except for the pre-identified source data directly recorded in the CRF. The informed consent form will include a statement by which the patient allows the Sponsor’s duly authorized personnel, the Ethics Committee (IRB/IEC), and the regulatory authorities to have direct access to original medical records which support the data on the CRFs (e.g., patient's medical file, appointment books, original laboratory records, etc). These personnel, bound by professional secrecy, must maintain the confidentiality of all personal identity or personal medical information (according to confidentiality and personal data protection rules).

13.4 USE AND COMPLETION OF CASE REPORT FORMS (CRFS) AND ADDITIONAL REQUEST

It is the responsibility of the Investigator to maintain adequate and accurate CRFs (according to the technology used) designed by the Sponsor to record (according to Sponsor instructions) all observations and other data pertinent to the clinical investigation in a timely manner. All CRFs should be completed in their entirety in a neat, legible manner to ensure accurate interpretation of data.

Should a correction be made, the corrected information will be entered in the e-CRF overwriting the initial information. An audit trail allows identifying the modification.

Data are available within the system to the Sponsor as soon as they are entered in the e-CRF.

The computerized handling of the data by the Sponsor when available in the eCRF may generate additional requests (DRF) to which the Investigator is obliged to respond by confirming or modifying the data questioned. The requests with their responses will be managed through the e-CRF.
13.5 USE OF COMPUTERIZED SYSTEMS

Computerized systems used during the different steps of the study are:

- For screening and randomization activities, IVRS/IWRS
- For data management activities, Oracle RDC
- For statistical activities, SAS, nQuery Advisor 6.01
- For pharmacovigilance activities, AWARE
- For investigational product ordering/tracking, NASCA and CSMS
- For monitoring activities, IMPACT, POLARIS, CTI, I/J review, CSMS
- For medical writing activities, DOMASYS
- External data loading is planned for this clinical trial

For medical writing activities, DOMASYS
14 ADMINISTRATIVE EXPECTATIONS

14.1 CURRICULUM VITAE

A current copy of the curriculum vitae describing the experience, qualification and training of each Investigator and Subinvestigator will be signed, dated and provided to the Sponsor prior to the beginning of the clinical trial.

14.2 RECORD RETENTION IN STUDY SITES

The Investigator must maintain confidential all study documentation, and take measures to prevent accidental or premature destruction of these documents.

The Investigator should retain the study documents at least 15 years after the completion or discontinuation of the clinical trial.

However, applicable regulatory requirements should be taken into account in the event that a longer period is required.

The Investigator must notify the Sponsor prior to destroying any study essential documents following the clinical trial completion or discontinuation.

If the Investigator's personal situation is such that archiving can no longer be ensured by him/her, the Investigator shall inform the Sponsor and the relevant records shall be transferred to a mutually agreed upon designee.

14.3 CONFIDENTIALITY

All information disclosed or provided by the Sponsor (or any company/institution acting on their behalf), or produced during the clinical trial, including, but not limited to, the clinical trial protocol, the CRFs, the Investigator's Brochure and the results obtained during the course of the clinical trial, is confidential, prior to the publication of results. The Investigator and any person under his/her authority agree to undertake to keep confidential and not to disclose the information to any third party without the prior written approval of the Sponsor.

However, the submission of this clinical trial protocol and other necessary documentation to the Ethics committee (IRB/IEC) is expressly permitted, the IRB/IEC members having the same obligation of confidentiality.

The Subinvestigators shall be bound by the same obligation as the Investigator. The Investigator shall inform the Subinvestigators of the confidential nature of the clinical trial.

The Investigator and the Subinvestigators shall use the information solely for the purposes of the clinical trial, to the exclusion of any use for their own or for a third party's account.
Furthermore, the Investigator and the Sponsor agree to adhere to the principles of personal data confidentiality in relation to the patients, Investigator and its collaborators involved in the study.

14.4 PROPERTY RIGHTS

All information, documents and IMP provided by the Sponsor or its designee are and remain the sole property of the Sponsor.

14.5 DATA PROTECTION

- The patient's personal data, which are included in the Sponsor database shall be treated in compliance with all applicable laws and regulations;
- When archiving or processing personal data pertaining to the Investigator and/or to the patients, the Sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.
- The Sponsor also collects specific data regarding Investigator as well as personal data from any person involved in the study which may be included in the Sponsor’s databases, shall be treated by both the Sponsor and the Investigator in compliance with all applicable laws and regulations.

Patient race or ethnicity will be collected in this study because these data are frequently required by health authorities.

The data collected in this study will only be used for the purpose(s) of the study and to document the evaluation of the benefit/ risk ratio, efficacy and safety of the product(s). They may be further processed if they have been anonymized.
14.7 SPONSOR AUDITS AND INSPECTIONS BY REGULATORY AGENCIES

For the purpose of ensuring compliance with the clinical trial protocol, Good Clinical Practice and applicable regulatory requirements, the Investigator should permit auditing by or on the behalf of the Sponsor and inspection by regulatory authorities.

The Investigator agrees to allow the auditors/inspectors to have direct access to his/her study records for review, being understood that these personnel is bound by professional secrecy, and as such will not disclose any personal identity or personal medical information.

The Investigator will make every effort to help with the performance of the audits and inspections, giving access to all necessary facilities, data, and documents.

As soon as the Investigator is notified of a planned inspection by the authorities, he will inform the Sponsor and authorize the Sponsor to participate in this inspection.

The confidentiality of the data verified and the protection of the patients should be respected during these inspections.

Any result and information arising from the inspections by the regulatory authorities will be immediately communicated by the Investigator to the Sponsor.

The Investigator shall take appropriate measures required by the Sponsor to take corrective actions for all problems found during the audit or inspections.

14.8 PREMATURE DISCONTINUATION OF THE STUDY OR PREMATURE CLOSE-OUT OF A SITE

14.8.1 Decided by the Sponsor

Decided by the Sponsor in the following cases

- If the information on the product leads to doubt as to the benefit/risk ratio;
- If the Investigator has received from the Sponsor all IMP, means and information necessary to perform the clinical trial and has not included any patient after a reasonable period of time mutually agreed upon;
- In the event of breach by the Investigator of a fundamental obligation under this agreement, including but not limited to breach of the clinical trial protocol, breach of the applicable laws and regulations or breach of the ICH guidelines on Good Clinical Practice;
- If the total number of patients are included earlier than expected;
In any case the Sponsor will notify the Investigator of its decision by written notice.

14.8.2 Decided by the Investigator

The Investigator must notify (30 days' prior notice) the Sponsor of his/her decision and give the reason in writing.

In all cases (decided by the Sponsor or by the Investigator), the appropriate Ethics Committee(s) (IRB/IEC) and Health Authorities should be informed according to applicable regulatory requirements.

14.9 CLINICAL TRIAL RESULTS

The Sponsor will be responsible for preparing a clinical study report and to provide a summary of study results to the Investigator.
15 CLINICAL TRIAL PROTOCOL AMENDMENTS

All appendices attached hereto and referred to herein are made part of this clinical trial protocol.

The Investigator should not implement any deviation from, or changes of the clinical trial protocol without agreement by the Sponsor and prior review and documented approval/favorable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to clinical trial Patients, or when the change(s) involves only logistical or administrative aspects of the trial. Any change agreed upon will be recorded in writing, the written amendment will be signed by the Investigator and by the Sponsor and the signed amendment will be filed with this clinical trial protocol.

Any amendment to the clinical trial protocol requires written approval/favorable opinion by the Ethics Committee (IRB/IEC) prior to its implementation, unless there are overriding safety reasons.

In some instances, an amendment may require a change to the informed consent form. The Investigator must receive an IRB/IEC approval/favorable opinion concerning the revised informed consent form prior to implementation of the change and patient signature should be re-collected if necessary.
16 BIBLIOGRAPHIC REFERENCES


17 APPENDICES

Appendix A. List of Prohibited Live, Attenuated Vaccines

Bacillus Chickenpox (Varicella)

Intranasal influenza (FluMist-Influenza); inactive influenza vaccine delivered by injection is permitted

Measles (Rubeola)

Measles-mumps-rubella (MMR) combination

Measles-mumps-rubella-varicella (MMRV) combination

Mumps

Oral polio (Sabin)

Oral typhoid

Rotavirus

Rubella

Smallpox (Vaccinia)

Varicella Zoster (shingles)

Yellow fever
Appendix B. Equipotent daily doses of Inhaled Glucocorticosteroids for adults

<table>
<thead>
<tr>
<th>Drug</th>
<th>Low Daily dose (μg)</th>
<th>Medium Daily dose (μg)</th>
<th>High Daily dose (μg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beclomethasone dipropionate – CFC</td>
<td>200-500</td>
<td>&gt;500-1000</td>
<td>&gt;1000-2000</td>
</tr>
<tr>
<td>Beclomethasone dipropionate – H FA</td>
<td>100-250</td>
<td>&gt;250-500</td>
<td>&gt;500-1000</td>
</tr>
<tr>
<td>Budesonide</td>
<td>200-400</td>
<td>&gt;400-800</td>
<td>&gt;800-1600</td>
</tr>
<tr>
<td>Ciclesonide</td>
<td>80-160</td>
<td>&gt;160-320</td>
<td>&gt;320-1280</td>
</tr>
<tr>
<td>Flunisolide</td>
<td>500-1000</td>
<td>&gt;1000-2000</td>
<td>&gt;2000</td>
</tr>
<tr>
<td>Fluticasone propionate</td>
<td>100-250</td>
<td>&gt;250-500</td>
<td>&gt;500-1000</td>
</tr>
<tr>
<td>Mometasone furoate</td>
<td>200</td>
<td>≥400</td>
<td>≥800</td>
</tr>
<tr>
<td>Triamcinolone acetonide</td>
<td>400-1000</td>
<td>&gt;1000-2000</td>
<td>2000</td>
</tr>
</tbody>
</table>
Appendix C. Definition of Anaphylaxis

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


Clinical criteria for diagnosing anaphylaxis

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

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips-tongue-uvula)

   AND AT LEAST ONE OF THE FOLLOWING
   a. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   b. Reduced BP or associated symptoms of end-organ dysfunction (e.g., 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 (e.g., generalized hives, itch-flush, swollen lips-tongue-uvula)
   b. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   c. Reduced BP or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence)
   d. Persistent gastrointestinal symptoms (e.g., 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 x age]) from 1 to 10 years, and less than 90 mm Hg from 11 to 17 years.
Appendix D. General Guidance for the follow-up of laboratory abnormalities by Sanofi
**NEUTROPENIA**

Neutrophils < 1500/mm³ or according to ethnic group

Repeat immediately a full blood count if value close to 1500/mm³

- Neutrophils < 1500/mm³ confirmed with signs of infection
  1. **DISCONTINUE** Investigational Medicinal Product, hospitalization should be considered
  2. **PERFORM** biological investigations for infection

- Neutrophils < 1500/mm³ confirmed with no signs of infection
  1. **DISCONTINUE** Investigational Medicinal Product
  2. **INVESTIGATE** for infection

In both situations

3. **INFORM** the local monitor
4. **INVESTIGATE** previous treatments particularly long-term, even a long time ago, exposure to toxic agents, e.g., benzene, X-rays, etc.
5. **PERFORM** and collect the following investigations (results):
   - RBC and platelet counts
   - Serology: EBV, (HIV), mumps, measles, rubella
6. **DECISION** for bone marrow aspiration: to be taken in specialized unit
7. **FREEZE** serum (5 mL x 2) on Day 1 (cessation of investigational medicinal product) and Day 5 (for further investigations)
8. **MONITOR** the leukocyte count 3 times per week for at least one week, then twice a month until it returns to normal

**Note:**
- The procedures described in the above flowchart are to be discussed with the patient only in case the event occurs. If applicable (according to local regulations), an additional consent (e.g., for HIV testing) will only be obtained in the case the event actually occurs.
- For individuals of African descent, the relevant value of concern is <1000/mm³

Neutropenia are to be recorded as AE only if they are:
- 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 [in that case, the event (SAE) should be notified within 24 hours to the MT], and/or
- Defined as an Adverse Event of Special Interest (AESI)
THROMBOCYTOPENIA

Platelets < 100 000/mm³ (rule out EDTA – induced pseudo-thrombocytopenia)

 Repeat immediately the count (rule out EDTA anticoagulant in the sample)

Platelets < 100 000/mm³ confirmed with bleeding

1. DISCONTINUE
   Investigational Medicinal Product
2. HOSPITALIZATION should be considered

Platelets < 100 000/mm³ confirmed with no bleeding

1. DISCONTINUE
   Investigational Medicinal Product
2. INVESTIGATE for bleeding

In both situations

3. INFORM the local Monitor
4. QUESTION about last intake of quinine (drinks), alcoholism, heparin administration
5. PERFORM or collect the following investigations:
   • Complete blood count, schizocytes, creatinine
   • Bleeding time and coagulation test (fibrinogen, PT, aPTT), Fibrin Degradation Product
   • Viral serology: EBV, HIV, mumps, measles, rubella
6. FREEZE serum (5 mL x 2) on Day 1 (end of treatment) and Day 5 to test for drug-induced antiplatelets antibodies
7. DECISION for bone marrow aspiration: to be taken in specialized unit
   • On Day 1 in the case of associated anemia and/or leukopenia
   • On Day 8 if the Platelets remain < 50 000/mm³
8. MONITOR the platelet count every day for at least one week and then regularly until it returns to normal

Note:
the procedures described in the above flowchart are to be discussed with the patient only in case the event occurs. If applicable (according to local regulations), an additional consent (e.g., for HIV testing) will only be obtained in the case the event actually occurs.

Thrombocytopenia are to be recorded as AE only if they are:
• 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 [in that case, the event (SAE) should be notified within 24 hours to the MT], and/or
• Defined as an Adverse Event of Special Interest (AESI)
**INCREASE IN ALT**

**ALT ≥ 3 ULN (if baseline ALT < ULN)**
Or, **ALT ≥ 2 times the baseline value**
(if baseline ALT ≥ ULN)

**ALT ≤ 5 ULN**
(if baseline ALT < ULN)
Or, **ALT ≤ 3 times the baseline value**
(If baseline ALT ≥ ULN)

**ALT > 5 ULN**
(if baseline ALT < ULN)
Or, **ALT > 3 times the baseline value**
(If baseline ALT ≥ ULN)

**Total bilirubin ≤ 2 ULN**

**Total bilirubin > 2 ULN**

**Monitor LFTs every 48 hours**

If Not Possible**

**DISCONTINUE ADMINISTRATION OF INVESTIGATIONAL MEDICINAL PRODUCT**

**Investigational Medicinal Product administration can be continued, as long as – under close monitoring – conditions for stopping are not met**

In **ANY CASE**, FOLLOW the instructions #1 to 6 listed in the box below.

1. **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
2. **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-HBe IgM, anti-HCV and HCV RNA, anti-CMV IgM and anti-HEV IgM antibodies,
   - Auto-antibodies: anti-nuclear, anti-DNA, anti-smooth muscle, anti-LKM
   - Depending on the clinical context, check for recent infection with EBV, Herpes viruses and toxoplasma
   - Hepatobiliary ultrasonography (can be completed by other imaging investigations if needed)
3. **CONSIDER** consultation with hepatologist
4. **CONSIDER** patient hospitalisation if INR>2 (or PT<50%) and/or central nervous system disturbances suggesting hepatic encephalopathy.
5. **MONITOR LFTs**
   - **If investigational medicinal product is continued:** every 48 hours until return to normal (<2ULN) or baseline. If ALT elevation persists beyond 2 weeks then perform LFTs every 2 weeks and 15 to 30 days after the last dose according to the study protocol.
   - **If investigational medicinal product is discontinued:** as closely as possible to every 48 hours until stabilization then every 2 weeks until return to normal (<2ULN) or baseline or for at least 3 months, whichever comes last.
6. **FREEZE** serum (5 ml X 2)

Note: In addition, as soon as a seriousness criterion is met, the event should be notified within 24 hours to the Monitoring Team.
**ACUTE RENAL FAILURE**

Rapid increase in serum creatinine over 150 \( \mu \text{mol/L} \) or rapid decrease in creatinine clearance below 50ml/mn

Can be rapidly reversed:
- By volume repletion
- Or relief of urinary tract obstruction (according to etiology)

Cannot be rapidly reversed:
- Occurrence/aggravation of life threatening symptoms of ARF: anemia, hyperkalemia, hyperuricemia, metabolic acidosis, cardiac insufficiency, pulmonary edema, arrhythmia, DIC, etc.
- And/or predominant elimination of Investigational Medicinal Product by renal route

1. **INFORM** the local monitor
2. **DISCONTINUE** Investigational Medicinal Product administration
3. **HOSPITALIZATION** should be considered and seek for nephrologic advice
4. **PERFORM** the following examinations:
   - BP, HR, hydration status, ECG
   - Blood count
   - Liver function tests + CPK
   - Biochemistry, including urea
   - Urinalysis
5. **FREEZE** serum (5mL x 2)
6. **MONITOR** renal function until return to baseline level (every day at the beginning, then every week)

Acute renal failure is to be recorded as AE only if it is:
- Symptomatic, and/or
- Requiring either corrective treatment or consultation, and/or
- Leading to IMP discontinuation or modification of dosing, and/or
- Fulfilling a seriousness criterion [in that case, the event (SAE) should be notified within 24 hours to the MT], and/or
- Defined as an Adverse Event of Special Interest (AESI)
If Increase in CPK (expressed in ULN)

> 3 ULN

- INVESTIGATE for the origin:
  - PERFORM:
    - ECG
    - CPK-MB -MM
    - Troponin
    - Creatinine
    - Iono (k+, Ca2+)
    - Transaminases + Total and conjugated bilirubin
    - Myoglobin (serum and urines)
  - FREEZE SERUM (5mlx2) for PK
  - INTERVIEW the patient about a recent intensive muscular effort, trauma, convulsions, electrical injury, injury or stress to the skeletal muscle, multiple intramuscular injections, recent surgery, concomitant medications, consumption of alcohol, morphine, cocaine.
  - SEARCH for alternative causes to cardiac or muscular toxicity, ie: stroke, pulmonary infarction, dermatomyositis or polymyositis, convulsions, hypothyroidism, delirium tremens, muscular dystrophies.

If either the cardiac origin or the rhabdomyolysis is confirmed or if CPK > 10 ULN:

1. DISCONTINUE Investigational Medicinal Product administration
2. MONITOR CPK every 3 days for the first week then once weekly until return to normal or for at least 3 months
3. HOSPITALIZATION should be considered

If the cardiac origin or the rhabdomyolysis is ruled out and if CPK ≤ 10 ULN:

MONITOR CPK every 3 days for the first week then once weekly until return to normal or for at least 3 months

Suspicion of rhabdomyolysis is to be recorded as AE only if it is:
- Symptomatic, and/or
- Requiring either corrective treatment or consultation, and/or
- Leading to IMP discontinuation or modification of dosing, and/or
- Fulfilling a seriousness criterion [in that case, the event (SAE) should be notified within 24 hours to the MT], and/or
- Defined as an Adverse Event of Special Interest (AESI)
Appendix E. QoL, health economic and Patient Reported Outcomes (PRO) questionnaires

Asthma Control Questionnaire, 5-question Version

Please answer Questions 1-5.

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

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

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

3. In general, during the past week, how limited were you in your activities because of your asthma?
   0 Not limited at all
   1 Very slightly limited
   2 Slightly limited
   3 Moderately limited
   4 Very limited
   5 Extremely limited
   6 Totally limited
4. In general, during the past week, how much shortness of breath did you experience because of your asthma?
   
   0  None
   1  A very little
   2  A little
   3  A moderate amount
   4  Quite a lot
   5  A great deal
   6  A very great deal

5. In general, during the past week, how much of the time did you wheeze?

   0  Not at all
   1  Hardly any of the time
   2  A little of the time
   3  A moderate amount of the time
   4  A lot of the time
   5  Most of the time
   6  All the time

**Visual Annalogue Scale (VAS)**

To evaluate the total severity, the patient is asked to indicate on a VAS the answer to the question:

![Visual Analogue Scale](image)
### 22-item Sinonasal Outcome Test SNOT-22

Below you will find a list of symptoms and social/emotional consequences of your nasal disorder. We would like to know more about these problems and would appreciate you answering the following question to the best of your ability. There are no right or wrong answers, and only you can provide us with this information. Please rate your problems, as they have been over the past two weeks. Thank you for your participation.

<table>
<thead>
<tr>
<th>Item Description</th>
<th>No problem</th>
<th>Very mild problem</th>
<th>Mild or slight problem</th>
<th>Moderate problem</th>
<th>Severe problem</th>
<th>Problem as bad as it can be</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Need to blow nose</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>2. Sneezing</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>3. Runny nose</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>4. Cough</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>5. Post nasal discharge (ripping at the back of your nose)</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>6. Thick nasal discharge</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>7. Ear fullness</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>8. Dizziness</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>9. Ear pain/pressure</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>10. Facial pain/pressure</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>11. Difficulty falling asleep</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>12. Waking up at night</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>13. Lack of a good night’s sleep</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>14. Waking up tired</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>15. Fatigue during the day</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>16. Reduced productivity</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>17. Reduced concentration</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>18. Frustrated/restless/impatient</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>19. Sad</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>20. Embarrassed</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>21. Sense of taste/smell</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>22. Blockage/congestion of nose</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>
EQ-5D-3L

By placing a check mark in one box in each group below, please indicate which statements best describe your own health state today.

**Mobility**
- I have no problems in walking about
- I have some problems in walking about
- I am confined to bed

**Self-Care**
- I have no problems with self-care
- I have some problems washing or dressing myself
- I am unable to wash or dress myself

**Usual Activities (e.g. work, study, housework, family or leisure activities)**
- I have no problems with performing my usual activities
- I have some problems with performing my usual activities
- I am unable to perform my usual activities

**Pain/Discomfort**
- I have no pain or discomfort
- I have moderate pain or discomfort
- I have extreme pain or discomfort

**Anxiety/Depression**
- I am not anxious or depressed
- I am moderately anxious or depressed
- I am extremely anxious or depressed
To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.
SF-36

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. Thank you for completing this survey!

For each of the following questions, please mark an ☑ in the one box that best describes your answer.

1. In general, would you say your health is:

<table>
<thead>
<tr>
<th>Excellent</th>
<th>Very good</th>
<th>Good</th>
<th>Fair</th>
<th>Poor</th>
</tr>
</thead>
<tbody>
<tr>
<td>☑</td>
<td>☑</td>
<td>☑</td>
<td>☑</td>
<td>☑</td>
</tr>
</tbody>
</table>

2. Compared to one year ago, how would you rate your health in general now?

<table>
<thead>
<tr>
<th>Much better now than one year ago</th>
<th>Somewhat better now than one year ago</th>
<th>About the same as one year ago</th>
<th>Somewhat worse now than one year ago</th>
<th>Much worse now than one year ago</th>
</tr>
</thead>
<tbody>
<tr>
<td>☑</td>
<td>☑</td>
<td>☑</td>
<td>☑</td>
<td>☑</td>
</tr>
</tbody>
</table>

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(SF-36/C Standard, U7 Version 2.0)
3. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

<table>
<thead>
<tr>
<th>Yes, limited a lot</th>
<th>Yes, limited a little</th>
<th>No, not limited at all</th>
</tr>
</thead>
<tbody>
<tr>
<td>▼</td>
<td>▼</td>
<td>▼</td>
</tr>
</tbody>
</table>

- Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports
- Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf
- Lifting or carrying groceries
- Climbing several flights of stairs
- Climbing one flight of stairs
- Bending, kneeling, or stooping
- Walking more than a mile
- Walking several hundred yards
- Walking one hundred yards
- Bathing or dressing yourself

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(SF-36® Standard, US Version 2.0)
4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

<table>
<thead>
<tr>
<th></th>
<th>All of the time</th>
<th>Most of the time</th>
<th>Some of the time</th>
<th>A little of the time</th>
<th>None of the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cut down on the amount of time you spent on work or other activities</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
</tr>
<tr>
<td>Accomplished less than you would like</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Were limited in the kind of work or other activities</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Had difficulty performing the work or other activities (for example, it took extra effort)</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
</tbody>
</table>

5. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

<table>
<thead>
<tr>
<th></th>
<th>All of the time</th>
<th>Most of the time</th>
<th>Some of the time</th>
<th>A little of the time</th>
<th>None of the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cut down on the amount of time you spent on work or other activities</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
</tr>
<tr>
<td>Accomplished less than you would like</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Did work or other activities less carefully than usual</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
</tbody>
</table>

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(SF-36v2 Standard, US Version 2.0)
6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

<table>
<thead>
<tr>
<th>Not at all</th>
<th>Slightly</th>
<th>Moderately</th>
<th>Quite a bit</th>
<th>Extremely</th>
</tr>
</thead>
<tbody>
<tr>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
</tbody>
</table>

7. How much bodily pain have you had during the past 4 weeks?

<table>
<thead>
<tr>
<th>None</th>
<th>Very mild</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Very Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
</tbody>
</table>

8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

<table>
<thead>
<tr>
<th>Not at all</th>
<th>A little bit</th>
<th>Moderately</th>
<th>Quite a bit</th>
<th>Extremely</th>
</tr>
</thead>
<tbody>
<tr>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
</tbody>
</table>
9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks...

<table>
<thead>
<tr>
<th>All of the time</th>
<th>Most of the time</th>
<th>Some of the time</th>
<th>A little of the time</th>
<th>None of the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
</tr>
</tbody>
</table>

- Did you feel full of life?  
- Have you been very nervous?  
- Have you felt so down in the dumps that nothing could cheer you up?  
- Have you felt calm and peaceful?  
- Did you have a lot of energy?  
- Have you felt downhearted and depressed?  
- Did you feel worn out?  
- Have you been happy?  
- Did you feel tired?

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?

<table>
<thead>
<tr>
<th>All of the time</th>
<th>Most of the time</th>
<th>Some of the time</th>
<th>A little of the time</th>
<th>None of the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
</tr>
</tbody>
</table>
11. How TRUE or FALSE is each of the following statements for you?

<table>
<thead>
<tr>
<th>Definitely true</th>
<th>Mostly true</th>
<th>Don't know</th>
<th>Mostly false</th>
<th>Definitely false</th>
</tr>
</thead>
<tbody>
<tr>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
</tr>
</tbody>
</table>

1. I seem to get sick a little easier than other people. □ □ □ □ □

2. I am as healthy as anybody I know. □ □ □ □ □

3. I expect my health to get worse. □ □ □ □ □

4. My health is excellent. □ □ □ □ □

THANK YOU FOR COMPLETING THESE QUESTIONS!
NASAL POLYP RELATED RESOURCE USE Questionnaire

This questionnaire will record information regarding resource use, including healthcare and work related, for nasal polyps.

Employment status
Check one primary category (Excluding charity activity)

Employed:
- [ ] Full time
- [ ] Part time  Please specify time in %:   (Example: an half-time = 50%)

Non-Employed:
- [ ] Unemployed (Including housewife, student,...)
- [ ] Retired

NASAL POLYPS-RELATED RESOURCE USE

Please describe resources associated to nasal polyps that occurred in the past 4 weeks

OUTPATIENT VISITS

In the past 4 weeks, how many outpatient visits did the patient have by a physician or another healthcare professional for his nasal polyps (other than the planned visits of the protocol)?

[ ] General Practitioner
[ ] Otolaryngologist (ENT specialist)
[ ] Allergist
[ ] Internist
[ ] Nurse
[ ] Other  Please specify: ____________________

ER visit related to NP  ____________________

SICK LEAVES / DAYS OFF

If the patient is Employed (Full time or Part time), please complete both questions 1 and 2
If the patient is Unemployed or Retired, please complete the question 2 only

1- In the past 4 weeks, if the patient is Employed, how many days did the patient miss from work due to nasal polyps:

_______ days (1/2 days = 0.5 days)

Please specify the reason(s):
- [ ] Breathing difficulties
- [ ] Fatigue
- [ ] Depression / Anxiety
- [ ] Other  Please specify the main reason: ____________________

2- In the past 4 weeks, how many days did the patient approximately miss from his/her usual activities other than work due to nasal polyps:

_______ days (1/2 days = 0.5 days)

Please specify the reason(s):
- [ ] Breathing difficulties
- [ ] Fatigue
- [ ] Depression / Anxiety
- [ ] Other  Please specify the main reason: ____________________
Self-assessment of the treatment (optional)

We would like to better understand your opinion on the treatment you received during the trial. Please, answer the following question. Thank you for your cooperation.

*Could you tell us about your opinion regarding the treatment you had during the trial? What did you like or dislike about the treatment?*

________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________________
### Appendix F. Examples\(^{(1)}\) of CYP Substrates with Narrow Therapeutic Range

<table>
<thead>
<tr>
<th>CYP Enzymes</th>
<th>Substrates with narrow therapeutic range(^{(2)})</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP1A2</td>
<td>Theophylline, tizanidine</td>
</tr>
<tr>
<td>CYP2C8</td>
<td>Paclitaxel</td>
</tr>
<tr>
<td>CYP2C9</td>
<td>Warfarin, phenytoin</td>
</tr>
<tr>
<td>CYP2C19</td>
<td>S-mephenytoin</td>
</tr>
<tr>
<td>CYP3A(^{(3)})</td>
<td>Alfentanil, astemizole(^{(4)}), cisapride(^{(4)}), cyclosporine (^{(5)}), dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus (^{(5)}), terfenadine(^{(4)})</td>
</tr>
<tr>
<td>CYP2D6</td>
<td>Thioridazine</td>
</tr>
</tbody>
</table>

\(^{(1)}\) Note that this is not an exhaustive list. For an updated list, see the following link: [http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm](http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm).

\(^{(2)}\) CYP substrates with narrow therapeutic range refers to drugs whose exposure-response relationship indicates that small changes in their exposure levels by the concomitant use of CYP inhibitors or inducers may lead to either serious safety concerns (e.g., Torsades de Pointes) or loss of therapeutic effect.

\(^{(3)}\) Because a number of CYP3A substrates (e.g., darunavir, maraviroc) are also substrates of P-gp, the observed increase in exposure could be due to inhibition of both CYP3A and P-gp.

\(^{(4)}\) Withdrawn from the United States market because of safety reasons

\(^{(5)}\) Prohibited medication during the study
### Electronic Signatures

<table>
<thead>
<tr>
<th>Signed by</th>
<th>Meaning of Signature</th>
<th>Server Date (dd-MMM-yyyy HH:mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Approval</td>
<td>Clinical Approval</td>
<td>16-Dec-2013 16:52 GMT+01</td>
</tr>
<tr>
<td>Clinical Approval</td>
<td>Clinical Approval</td>
<td>16-Dec-2013 20:28 GMT+01</td>
</tr>
</tbody>
</table>
Changes in the conduct of the study

The protocol was amended 3 times during the study. The changes introduced by these amendments are summarized below.

Table - Summary of protocol amendments

<table>
<thead>
<tr>
<th>No.</th>
<th>Date</th>
<th>Changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>13 August 2013</td>
<td>- Nasal secretion samplings were added at screening visit for the purpose of assay validation of the biomarker in this unique biomatrix</td>
</tr>
<tr>
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<td>- Change to permitted concomitant medication, to:</td>
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<td>- Provide more information on the potential effect of dupilumab on CYP450</td>
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<td>- Provide a list of CYP450 substrates with a narrow therapeutic index (Appendix F)</td>
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<td>- Ensure monitoring and, if needed, dose adjustment following the initiation and stopping of dupilumab</td>
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<td>- Change of Clinical Study Director</td>
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<tr>
<td>2</td>
<td>27 November 2013</td>
<td>- Simplification of the protocol concerning tissue collection and processing of nasal polyp biopsies. Details were provided separately</td>
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<tr>
<td></td>
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<td>in a biopsy collection manual</td>
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<td>3</td>
<td>12 December 2013</td>
<td>- Changed exclusion criteria:</td>
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<td>- <strong>E 03.</strong> Patient who has previously participated in any clinical trial of Dupilumab was replaced with:</td>
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<tr>
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<td>Patient who has previously been treated in any clinical trial of Dupilumab</td>
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<td>- <strong>E 05.</strong> Patient who has taken other investigational drugs or prohibited therapy for this study within 2 months before screening or 5 half-lives, whichever is longer:</td>
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<tr>
<td></td>
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<td>1. who have required a burst of oral corticosteroids (OCS) or intranasal corticosteroid drops within the 2 months before screening or are scheduled to receive OCS during the study period for another condition was replaced with:</td>
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<tr>
<td></td>
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<td>Patient who has taken other investigational drugs or prohibited therapy for this study within 2 months before screening or 5 half-lives, whichever is longer:</td>
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<tr>
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<td></td>
<td>1. who have required systemic corticosteroids (for example oral, intravenous, intramuscular corticosteroids) within the 2 months before screening or are scheduled to receive systemic corticosteroids during the study period for another condition</td>
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<tr>
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<td>1. who have required intranasal corticosteroid drops within 1 month prior to screening</td>
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<td>- <strong>E 06.</strong> Patients who have undergone any nasal surgery within 6 months before screening or have had more than 2 surgeries for nasal polyps in the past was replaced with:</td>
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<tr>
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<td>Patients who have undergone any nasal surgery (including polypectomy) within 6 months before screening or have had more than</td>
</tr>
</tbody>
</table>

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5 sinonasal surgeries in the past of which maximal 2 were surgeries changing the lateral wall structure of the nose

- **Change in the prohibited concomitant medication section**
  - The following text was added: Initiation of a new allergen immunotherapy (only continuation of allergen immunotherapy in place for ≥ 3 months prior to Visit 1 is permitted)

- **Change in permitted concomitant medication**
  - Initiation of allergen immunotherapy (allergen immunotherapy in place for ≥ 3 months prior to Visit 1 is permitted), was replaced with:
    - Allergen immunotherapy in place for ≥ 3 months prior to Visit 1 is permitted

- **Hypersensitivity**
  - The wording ‘As no IMP administration at home was allowed in the study’ was removed from protocol. Furthermore, the patients will be advised, when the IMP is administered at home, to self-monitor for potential signs and symptoms that may suggest a hypersensitive reaction for 1 hour after administration

- **Change in the FEV threshold at screening visit**
  - FEV ≥ 60% (of predicted normal) was replaced with:
    - FEV > 60% (of predicted normal)

- **Bibliographic references**
    - was replaced with: