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CLINICAL TRIAL PROTOCOL

COMPOUND: Dupilumab/SAR231893

Open-label, interventional, cohort study to evaluate long-term safety of dupilumab in patients with moderate to severe asthma who completed the TRAVERSE-LTS12551 clinical trial

STUDY NUMBER: LPS15023

STUDY NAME: LONG-TERM FOLLOW-UP

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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: Dupixent®	**STUDY No.: LPS15023** **STUDY NAME: LONG-TERM FOLLOW-UP**
TITLE	Open-label, interventional, cohort study to evaluate long-term safety of dupilumab in patients with moderate to severe asthma who completed the TRAVERSE-LTS12551 clinical trial
INVESTIGATOR/TRIAL LOCATION	International
PHASE OF DEVELOPMENT	Phase IIIb
STUDY OBJECTIVE	**Primary objective:** • To describe the long-term safety of dupilumab in the treatment of patients with moderate to severe asthma who completed the previous asthma clinical trial, TRAVERSE-LTS12551.
STUDY DESIGN	Open-label, interventional, outpatient, prospective, multinational, multicenter, noncomparative, single-arm, safety study.
STUDY POPULATION **Main selection criteria**	**Inclusion criteria:** I 01. Patient with asthma who completed the treatment period in the previous dupilumab asthma clinical study TRAVERSE-LTS12551. I 02. Patient is on background dose of medium or high dose inhaled corticosteroid (ICS), as maintained during study TRAVERSE-LTS12551, in combination with a second controller (and/or oral corticosteroid [OCS] for those patients from the original parent study EFC13691). Patients requiring a third controller medication will be allowed (eg, long-acting β-adrenoceptor agonists [LABA], leukotriene receptor antagonist [LTRA], methylxanthines). I 03. Signed written informed consent. **Exclusion criteria:** E 01. Current smoker or cessation of smoking within 6 months prior to enrollment. E 02. Clinically significant comorbidity/lung disease other than asthma. E 03. Alcohol abuse or drug abuse. E 04. Inability to follow drug administration procedures/noncompliance (eg, due to language problems or psychological disorders). E 05. Patient who have received, in the last 3 months, concomitant prohibited treatment: • Anti-immunoglobulin (Ig) E therapy (eg, omalizumab); • Biologic therapy. • Systemic immunosuppressants. • Intravenous Ig therapy. • Nonselective β-adrenergic blockers. • Other investigational drugs. • Live/attenuated vaccines.

	E 06. Patient who develops: a new medical condition or a change in status of an established medical condition; a laboratory abnormality, or requires a new treatment or medication prior to enrollment, which (per Investigator's medical judgment) would adversely affect the participation in this study or would require permanent investigational medicinal product (IMP) discontinuation. E 07. Pregnant or breastfeeding women. E 08. Women of child-bearing potential (WOCBP, following menarche and until becoming post menopausal unless permanently sterile) who: • Do not have a confirmed negative urine test at enrollment. • Who are not protected by one of the following acceptable forms of effective contraception during the study (from Visit 1 to End-of-treatment [EOT]/End-of-study [EOS]): - Established use of oral, injected, implanted, or inserted hormonal contraceptive. - Intrauterine device with copper or intrauterine system with progestogen. - Contraceptive barrier (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 in the study, the vasectomized male partner should be the sole partner of that patient. - True abstinence; periodic abstinence (eg, calendar, ovulation, symptothermal, post ovulation methods) is not an acceptable method of contraception. - Menopausal women (defined as at least 12 consecutive months without menses) are not required to use additional contraception. E 09. Diagnosed active parasitic infection; suspected or high risk of parasitic infection, unless clinical and (if necessary) laboratory assessments have ruled out active infection before the enrollment. E 10. Patients with active autoimmune disease (eg, rheumatoid arthritis, inflammatory bowel disease, primary biliary cirrhosis, systemic lupus erythematosus, multiple sclerosis) or patients who, as per Investigator's medical judgment, are suspected of having high risk for developing autoimmune disease. E 11. Patients who experienced any systemic hypersensitivity reactions to the IMP in the previous dupilumab asthma study TRAVERSE-LTS12551, which, in the opinion of the Investigator, could indicate that continued treatment with dupilumab may present an unreasonable risk for the patient. E 12. Blood eosinophils >1500 cells/mm^3 at the latest available test.

	E 13. History of malignancy within 5 years before enrollment except completely treated in situ carcinoma of the cervix, completely treated and resolved nonmetastatic squamous or basal cell carcinoma of the skin.
Total expected number of patients	750
STUDY TREATMENTS	
Investigational medicinal product	Dupilumab
Formulation	Dupilumab 300 mg prefilled syringes of 150 mg/mL (2.25 mL total volume) to deliver 300 mg in the extractable 2 mL volume.
Route of administration	Subcutaneous (SC).
Dose regimen	300 mg SC every 2 weeks (q2w) with a 600 mg loading dose on Visit 1 (Start-of-treatment Visit) for patients who discontinued treatment for ≥6 weeks after study TRAVERSE-LTS12551.
Noninvestigational medicinal products	**Asthma background controller therapy:** Inhaled corticosteroid, in combination with a second controller. Patients requiring a third controller medication will be allowed (eg, LABA, LTRA, methylxanthines); OCS will be allowed only for those patients from original parent study EFC13691. **Asthma reliever medication:** Patients may receive salbutamol/albuterol hydrofluoroalkane pressurized metered dose inhalers (MDI) or levosalbutamol/levalbuterol hydrofluoroalkane pressurized MDI as reliever medication (as needed) during the study. Nebulizer solutions with either albuterol/salbutamol or levalbuterol/levosalbutamol may be used as an alternative delivery method.
Post trial access to study medication	By continuing to describe long-term safety, this study provides post trial access to study medication for patients from TRAVERSE-LTS12551.
ENDPOINTS	**Primary safety endpoint:** Incidence rates, defined as percentage of patients with treatment-emergent adverse events (TEAEs) and event rates per 100 patient-years. **Secondary endpoints:** • Incidence rates and event rates per 100 patient-years for adverse events of special interest (AESIs) over the study. • Incidence rates for serious adverse events (SAEs)/death over the study. • Incidence rates for adverse events (AEs) leading to study discontinuation over the study.
ASSESSMENT SCHEDULE	**Visit schedule:** On-site visits every 12 weeks throughout the study, for a maximum of 12 post baseline visits. The Start-of-treatment (Visit 1) may be performed on the same day as the TRAVERSE-LTS12551 EOT Visit. **Early termination:** Patients who prematurely and permanently discontinue IMP administration should have the EOT/EOS Visit (Visit 13) performed. Women of child-bearing potential discontinuing treatment will be advised to avoid pregnancy for at least 12 weeks following the last IMP dose.

STATISTICAL CONSIDERATIONS	**Sample size determination:** Qualifying patients completing the treatment period of study TRAVERSE-LTS12551 will be offered to continue in this study. **Primary analysis population:** Safety: All patients receiving at least one dose of study medication during this study. **Primary/key analysis:** All TEAEs, AESIs, SAEs, and AEs leading to treatment discontinuation will be summarized.
DURATION OF STUDY PERIOD (per patient)	Until dupilumab approval for use in asthma and market availability to the patient, or for a maximum of 144 weeks (ie, about 3 years) after the Start-of-treatment (Visit 1), whichever comes first.

1 FLOW CHARTS

1.1 STUDY FLOW CHART

Study periods	Start-of-Treatment	Treatment Period (144 weeks)	End-of-Treatment / End-of-Study
Week (W)	**W0**	**W12-W132 (Visit every 12 weeks)**	**W144**
VISIT	**V1**[a]	**V2–V12**[b]	**V13**[c]
Enrollment			
Informed consent	X		
Patient demography	X		
Eligibility criteria	X		
Treatment			
Contact IRT	X	X	X
IMP dispensation/administration[d]	X	X	
IMP accountability	X	X	X
Injection training/technique observation[e]	X	X	
Dispense home-dosing diary[f]	X	X	
Safety			
Clinical laboratory[g]	X[h]	X	X
Adverse event reporting	X	X	X
Symptom-driven physical examination and vital signs	X	X	X
Concomitant medications	X	X	X

AE = adverse events; eCRF = electronic case report form; EOS = end-of-study; EOT = end-of-treatment; IMP = investigational medicinal product; IRT = interactive response technology; q2w = every 2 weeks; V = (study) visit; W = (study) week; WOCBP = women of child-bearing potential.

a After completing the EOT Visit (V17) in study TRAVERSE-LTS12551, eligible patients should perform Start-of-treatment (V1) in LPS15023. Additional on-site IMP administration visits may be scheduled at the Investigator's discretion for patients who experience hypersensitivity reactions upon retreatment at this visit, or for patients with long off-treatment interval after the completion of study TRAVERSE-LTS12551.

b Visit window is ±7 days with respect to V1, ensuring at least an 11-day interval between 2 consecutive dupilumab administrations.

c Patients who prematurely and/or permanently discontinue treatment will be scheduled for the EOT Visit, and the EOS Visit will be scheduled for 12 weeks later for follow-up on AEs.

d Dispensation of IMP at every visit (except at EOT/EOS). Administration of 300 mg q2w. Loading dose of 600 mg at V1 for patients who discontinued treatment for ≥6 weeks after TRAVERSE-LTS12551. For administrations coinciding with site visits, patients will be monitored at the study site for a minimum of 30 minutes after injections.

e The Investigator or delegate must train the patient (or parent/caregiver[s]) at V1, if starting self-administration, on the preparation and injection of IMP, and review the patient's administration technique at subsequent visits if needed.

f The home-dosing diary should be dispensed at the time of injection training/technique observation.

g Local laboratory tests: Hematology (blood count: erythrocytes, hemoglobin, hematocrit, leukocytes with differential blood count [neutrophils, lymphocytes, monocytes, eosinophils, and basophils], and platelets), and pregnancy test (urine or blood, for WOCBP only). Only clinically significant values will be captured in the eCRF.

h Only for patients who do not roll-over into the study within 4 weeks of EOT or EOS Visit for study TRAVERSE-LTS12551 (see Section 10.1.1).

2 TABLE OF CONTENTS

LIST OF TABLES

3 LIST OF ABBREVIATIONS

AEs:	adverse events
AESIs:	adverse events of special interest
CYP:	cytochrome P450
DRF:	discrepancy resolution form
eCRF:	electronic case report form
EOS:	end-of-study
EOT:	end-of-treatment
GCP:	good clinical practice
HLGT:	high level group term
IB:	investigator's brochure
ICF:	informed consent form
ICH:	International Council for Harmonisation
ICS:	inhaled corticosteroids
IEC:	Independent Ethics Committee
Ig:	immunoglobulin
IL:	interleukin
IL-4Rα:	interleukin-4 receptor alpha
IMP:	investigational medicinal product
IRB:	Institutional Review Board
IRT:	interactive response technology
LABA:	long-acting β-adrenoceptor agonists
LTRA:	leukotriene receptor antagonist
MDI:	metered dose inhalers
NIMP:	noninvestigational medicinal products
OCS:	oral corticosteroids
PT:	preferred term
q2w:	every 2 weeks
SAEs:	serious adverse events
SC:	subcutaneously
SD:	standard deviation
SOC:	system organ class
TB:	tuberculosis
TEAEs:	treatment-emergent adverse events
Th2:	Type 2 T-helper cell
WOCBP:	women of child-bearing potential

4 INTRODUCTION AND RATIONALE

4.1 INTRODUCTION

Asthma is a chronic inflammatory disease of the airways characterized by airway hyper-responsiveness, acute and chronic bronchoconstriction, airway edema, and mucus plugging.

The inflammatory component of asthma involves many cell types, including mast cells, eosinophils, T-lymphocytes, neutrophils, epithelial cells, and their biological products. For most asthma patients, a regimen of controller therapy and reliever therapy provides adequate long-term control. However, it is estimated that 5% to 10% of asthma patients have symptomatic disease despite maximum recommended treatment with combinations of anti-inflammatory and bronchodilator drugs (1).

The poor response of some patients with asthma may reflect the number of cellular and molecular mechanisms operative in asthma. There is increasing interest in distinct phenotypes because targeted therapy is more likely to be successful in patients with similar underlying pathobiologic features (2). Recent therapeutic approaches in asthma have been focused on trying to control the Type 2 T-helper cell (Th2) response. Up-regulation of interleukin(IL)-4 and IL-13 has been implicated as an important inflammatory component of asthma disease progression.

Dupilumab, a fully human monoclonal antibody that binds specifically to the shared interleukin-4 receptor alpha (IL-4Rα) subunit of the IL-4 and IL-13 receptor complexes, is under development as a potential novel treatment for asthma. Dupilumab inhibits IL-4 signaling via the Type I receptor, and both IL-4 and IL-13 signaling through the Type II receptor. Dupilumab belongs to the pharmacological class of immunomodulators, IL inhibitors.

For complete information regarding the preclinical and clinical evaluation of dupilumab to date, including ongoing studies, see the current version of the Investigator's Brochure (IB).

4.2 RATIONALE

From an efficacy perspective, the dosing regimen of 300 mg every 2 weeks (q2w), added to a medium-to-high dose inhaled corticosteroids (ICS) + long-acting β-adrenoceptor agonists (LABA) in adult patients with uncontrolled persistent asthma, showed a clinically meaningful and highly statistically significant reduction versus placebo in the relative risk of severe exacerbations, improvement in lung function ie, forced expiratory volume and asthma symptoms (Asthma Control Questionnaire 5-question Version) (3).

From a safety perspective, dupilumab 300 mg q2w demonstrated an acceptable safety profile and was well tolerated in pivotal trials for asthma and other indications (3, 4), as well as in the long-term safety study TRAVERSE-LTS12551 at the time of the interim analysis at median treatment duration of 51 weeks (data collection cut-off on 31 January 2016).

Overall, approximately 7004 subjects had been enrolled into the dupilumab development program as of 31 May 2017: 222 healthy volunteers, 3392 patients with atopic dermatitis (AD), 3009 patients with asthma, 334 patients with nasal polyposis, and 47 patients with eosinophilic esophagitis. The estimated total number of subjects exposed to dupilumab in clinical studies was 6250 (3286 in AD, 2546 in asthma, 193 in nasal polyposis and 23 in eosinophilic esophagitis, and 202 in healthy volunteer studies).

Study TRAVERSE-LTS12551 (the "parent" study) was designed as an open-label extension study to evaluate the long-term safety and tolerability of dupilumab in patients with asthma who participated in previous dupilumab studies (DRI12544, PDY14192, EFC13579, and EFC13691).

The current LPS15023 study will provide further long-term clinical safety data (adverse events [AEs]/serious adverse events [SAEs] reporting) on dupilumab and extended dupilumab treatment to patients who continue to benefit from treatment. Therefore, a simplified study design is adopted, focusing on long-term clinical safety and late-onset events, while removing the burden of efficacy and patient reported outcome assessments. Safety monitoring will include continued focus on AEs, SAEs, and adverse events of special interest (AESIs, see Section 10.4.1.3).

5 STUDY OBJECTIVES

5.1 PRIMARY

The primary objective of this study is to describe the long-term safety of dupilumab in the treatment of patients with moderate to severe asthma who completed the previous asthma clinical trial, TRAVERSE-LTS12551.

6 STUDY DESIGN

6.1 DESCRIPTION OF THE STUDY

The LPS15023 study is a Phase IIIb, open-label, interventional, outpatient, prospective, multinational, multicenter, noncomparative, single-arm, safety study in patients with moderate to severe asthma who completed the parent study, TRAVERSE-LTS12551, from here on referred to as TRAVERSE.

This study will evaluate the long-term safety of dupilumab 300 mg q2w administered subcutaneously (SC) over a maximum of 144 weeks.

6.2 DURATION OF STUDY PARTICIPATION

6.2.1 Duration of study participation for each patient

The LPS15023 study consists of 3 periods:

- Start-of-treatment (Visit 1).
- Treatment period (Visit 2 to Visit 12).
- End-of-treatment (EOT)/End-of-study (EOS) (Visit 13).

Patients who prematurely and/or permanently discontinue treatment will be scheduled for the EOT Visit, and the EOS Visit will be scheduled for 12 weeks later for follow-up on AEs.

After completing the treatment period in TRAVERSE, eligible patients who have signed the informed consent form (ICF) should perform the assessments of the Start-of-treatment Visit (Visit 1). Patients will receive treatment until dupilumab approval for use in asthma and market availability to patients, or for a maximum of 144 weeks (ie, about 3 years) after the Start-of-treatment (Visit 1), whichever comes first.

6.2.2 Determination of end of clinical trial (all patients)

The end of clinical trial is defined as the “last patient last visit” planned in the protocol, ie, the EOT/EOS Visit (Visit 13). The Sponsor reserves the right to discontinue the study at any time.

6.3 INTERIM ANALYSIS

Interim analyses of data may be conducted to support regulatory submissions or publication activities.

6.4 STUDY COMMITTEES

Not applicable.

7 SELECTION OF PATIENTS

7.1 INCLUSION CRITERIA

I 01. Patient with asthma who completed the treatment period in TRAVERSE.

I 02. Patient is on background dose of medium or high dose ICS, as maintained during TRAVERSE, in combination with a second controller (and/or oral corticosteroids [OCS] for those patients from the original parent study EFC13691). Patients requiring a third controller medication will be allowed (eg, LABA, leukotriene receptor antagonist [LTRA], methylxanthines).

I 03. Signed informed consent.

7.2 EXCLUSION CRITERIA

Patients who have met all inclusion criteria listed in Section 7.1 will be screened for the following exclusion criteria:

E 01. Current smoker or cessation of smoking within 6 months prior to enrollment.

E 02. Clinically significant comorbidity/lung disease other than asthma.

E 03. Alcohol abuse or drug abuse.

E 04. Inability to follow drug administration procedures/noncompliance (eg, due to language problems or psychological disorders).

E 05. Patient who have received, in the last 3 months, concomitant prohibited treatment:

- Anti-immunoglobulin (Ig) E therapy (eg, omalizumab).
- Biologic therapy.
- Systemic immunosuppressants.
- Intravenous Ig therapy.
- Nonselective β-adrenergic blockers.
- Other investigational drugs.
- Live/attenuated vaccines (see Appendix A).

E 06. Patient who develops: a new medical condition or a change in status of an established medical condition; a laboratory abnormality, or requires a new treatment or medication prior to enrollment, which (per Investigator's medical judgment) would adversely affect the participation in this study or would require permanent investigational medicinal product (IMP) discontinuation.

E 07. Pregnant or breastfeeding women.

E 08. Women of child-bearing potential (WOCBP, following menarche and until becoming post menopausal unless permanently sterile) who:

- Do not have a confirmed negative urine test at enrollment.
- Who are not protected by one of the following acceptable forms of effective contraception during the study (from Visit 1 to EOT/EOS):
  - Established use of oral, injected, implanted, or inserted hormonal contraceptive.
  - Intrauterine device with copper or intrauterine system with progestogen.
  - Contraceptive barrier (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 in the study, the vasectomized male partner should be the sole partner of that patient.
  - True abstinence; periodic abstinence (eg, calendar, ovulation, symptothermal, post ovulation methods) is not an acceptable method of contraception.
  - Menopausal women (defined as at least 12 consecutive months without menses) are not required to use additional contraception.

E 09. Diagnosed active parasitic infection; suspected or high risk of parasitic infection, unless clinical and (if necessary) laboratory assessments have ruled out active infection before the enrollment.

E 10. Patients with active autoimmune disease (eg, rheumatoid arthritis, inflammatory bowel disease, primary biliary cirrhosis, systemic lupus erythematosus, multiple sclerosis) or patients who, as per Investigator's medical judgment, are suspected of having high risk for developing autoimmune disease.

E 11. Patients who experienced any systemic hypersensitivity reactions to the IMP in TRAVERSE, which, in the opinion of the Investigator, could indicate that continued treatment with dupilumab may present an unreasonable risk for the patient.

E 12. Blood eosinophils >1500 cells/mm^3 at the latest available test.

E 13. History of malignancy within 5 years before enrollment except completely treated in situ carcinoma of the cervix, completely treated and resolved nonmetastatic squamous or basal cell carcinoma of the skin.

8 STUDY TREATMENTS

8.1 INVESTIGATIONAL MEDICINAL PRODUCT

By continuing to describe long-term safety, this study provides post trial access to study medication for patients from TRAVERSE.

8.1.1 Dupilumab

Dupilumab is supplied as a sterile aqueous solution for SC injection at the concentration of 150 mg/mL in a 2 mL glass prefilled syringe to deliver 300 mg.

8.1.2 Preparation of investigational medicinal product

The IMP will be stored in a refrigerator at 2°C to 8°C (36°F to 46°F) until use. Instructions for IMP administration will be provided in the pharmacy manual and Patient User Instructions for self-administration.

8.1.3 Dose schedule

The IMP will be administered every 14±3 days (q2w). The consecutive doses of the IMP must be separated by ≥11 days to avoid an overdose. If in TRAVERSE the patient was already self-injecting, and/or parent/caregiver(s) was already injecting the patient, the Investigator or delegate will supervise the injection, or the Investigator or delegate will train the patient (and/or parent/caregiver[s]) on how to prepare and inject IMP at Start-of-treatment Visit (Visit 1) and will inject the first injection. For patients who discontinued treatment for ≥6 weeks after TRAVERSE ie, patients requiring a loading dose, the first injection is the first of the 2 injections of IMP (for the 600 mg dose).

Reminder: patients will be monitored for any signs or symptoms of hypersensitivity reactions for a minimum of 30 minutes after IMP injection on-site visit days. For patients who experience hypersensitivity reactions upon retreatment, ie, at the Start-of-treatment Visit (Visit 1), or for patients with long off-treatment interval after the completion of TRAVERSE, additional on-site IMP administration visits may be scheduled at the Investigator's discretion.

Subcutaneous injection sites should be alternated between the 4 quadrants of the abdomen (avoiding navel and waist areas), the upper thighs, or upper arms (lateral side), so that the same site is not injected twice consecutively. Injection in the upper arms could be done only by a trained person (parent/caregiver[s] trained by the Investigator or delegate) or health care professional but not the patient themselves. This instruction pertains to the day of the loading dose as well as for subsequent q2w injections. For each injection, the anatomic site of administration will be recorded in the electronic case report form (eCRF) and in the home-dosing diary.

Detailed instructions for transport, storage, and administration of IMP will be provided to the patient, and Investigators should ensure that these instructions are followed. Patients will complete a home-dosing diary to document compliance with self-injection (or parent/caregiver injection) of IMP.

8.2 NONINVESTIGATIONAL MEDICINAL PRODUCTS

8.2.1 Inhaled corticosteroid and controller therapies

Inhaled corticosteroid and other controller therapies (eg, LABA, LTRA, methylxanthines) and OCS for patients from EFC13691 will be collected in the eCRF.

Patients will continue on background therapy of moderate or high-dose ICS as maintained in TRAVERSE. Background therapy may be modified at any time during the study based on Investigator's judgment. Patients will also be using additional asthma controller therapies initiated during TRAVERSE.

Please see Appendix B for a list of commonly used asthma controller medications.

8.2.2 Albuterol or levalbuterol reliever medication

Patients may receive salbutamol/albuterol hydrofluoroalkane pressurized metered dose inhalers (MDI) or levosalbutamol/levalbuterol hydrofluoroalkane pressurized MDI as reliever medication (as needed) during the study.

Nebulizer solutions with either albuterol/salbutamol or levalbuterol/levosalbutamol may be used as an alternative delivery method.

All other reliever medications other than albuterol/salbutamol or levalbuterol/levosalbutamol should be avoided.

8.3 BLINDING PROCEDURES

Not applicable.

8.3.1 Methods of blinding

Not applicable.

8.4 METHOD OF ASSIGNING PATIENTS TO TREATMENT GROUP

The patient will be considered enrolled in the study once a treatment kit number has been assigned by the Interactive Response Technology (IRT). Therefore, it is important that all inclusion/exclusion criteria are confirmed and all required procedures are completed prior to the enrollment contact to the IRT. Detailed IRT procedure will be provided in the IRT Site Manual.

The study medication will be administered only to patients included in this study following the procedures described in the clinical study protocol. The treatment kit number list will be generated centrally by Sanofi Clinical Supply team. The IMPs are packaged in accordance with this list.

Patients will be enrolled at Visit 1. Patients will be identified by the same identification number used in TRAVERSE. The investigational site will enter the patient tracking information (patient identification number and date of birth) into the IRT during each scheduled protocol visit. The clinical site coordinator will document the patient number and the treatment kit number in the eCRF and in the patient's source documents, and the site patient number on the IMP labels prior to dispensing the IMP to the patient.

8.5 INVESTIGATIONAL MEDICINAL PRODUCT PACKAGING AND LABELING

The IMP dupilumab will be packaged in single-use prefilled syringes. One kit box will contain 2 prefilled syringes. Enough kit boxes will be given to the patients for the treatment period until the next study visit.

Each packaging component will be labeled with the project name and study number, a medication kit number, packaging reference number, Sponsor name, quantity or contents, dispensing instruction, caution statement, "use by" date, and storage conditions.

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

The IMP should be stored at a temperature between 2°C and 8°C in an appropriate and locked room under the responsibility of the Investigator or other authorized persons (eg, pharmacists) in accordance with local regulations, labeling specifications, policies, and procedures.

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

8.7 RESPONSIBILITIES

The Investigator, the hospital pharmacist, patient (or parent/caregiver[s]), or other personnel allowed to store and/or dispense the IMP will be responsible for ensuring that the IMP used in the clinical trial is securely maintained as specified by the Sponsor and in accordance with applicable regulatory requirements.

All IMP 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 issued and returned is maintained.

Any quality issue noticed with the receipt or use of an IMP (deficiency in condition, appearance, pertaining documentation, labeling, expiration date, etc) must be promptly notified to the Sponsor. Some deficiencies may be recorded through a complaint procedure (see Section 10.4.6).

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

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

8.7.1 Treatment accountability and compliance

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

- Proper recording of treatment kit number as required on appropriate screen(s) of eCRF for accounting purposes:
  - All medication treatment kits (whether empty or unused) are returned by the patient at each visit that treatment dispensing is planned.
  - The completed patient injection sheet (returned to the site at each visit), returned treatment kit boxes, and any unused prefilled syringes will be used for drug accountability purposes.
  - The Investigator or designee tracks treatment accountability/compliance, either by the injection sheet or by counting the number of used treatment kits, and fills in the appropriate page of the patient treatment log.
  - The monitor in charge of the study then checks the data entered on the IMP administration page by comparing them with the IMP that has been retrieved and the patient treatment log form.

8.7.2 Return and/or destruction of treatments

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

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 the study:

- Anti-IgE therapy (eg, omalizumab).
- Biologic therapy.

- Systemic immunosuppressants.
- Intravenous Ig therapy.
- Nonselective β-adrenergic blockers.
- Other investigational drugs.
- Live/attenuated vaccines (see Appendix A).

8.8.2 Permitted concomitant medication

The following asthma-related and other relevant concomitant treatments are permitted:

- Leukotriene antagonists/modifiers.
- Long-acting β-adrenoceptor agonists.
- Allergen immunotherapy stable dose.
- Antihistamines.
- Systemic (oral or injectable) corticosteroids:
  - Oral corticosteroids are allowed as background controller medication for the patients from the original parent study EFC13691 only.
  - Oral corticosteroids are allowed as treatment for asthma exacerbations and/or AEs as per Investigator's decision, for any patient.
- Ocular, intranasal, or topical corticosteroids.
- Methylxanthines (eg, theophylline, aminophyllines).
- Lipoxygenase inhibitors (eg, zileuton).
- Cromones for asthma (eg, cromolyn sodium solution for nebulization, nedocromil dry-powder inhaler).
- Cromones for other reasons (eg, ophthalmic formulations for allergic conjunctivitis, nasal formulations for allergic rhinitis).
- Short- and long-acting anti-cholinergic drugs (ipratropium bromide and tiotropium).

8.8.3 Cytochrome P450 precaution

The risk of indirect effects of dupilumab, via modulation of IL-4 and IL-13 activities, on the pharmacokinetics of selected cytochrome P450 (CYP) substrates (midazolam, omeprazole, warfarin, caffeine, and metoprolol) has been studied in 14 adult patients with moderate to severe AD.

The results of this study showed no evidence for a clinically meaningful effect of dupilumab on the activity of CYP3A, CYP2C19, CYP2C9, CYP1A2, or CYP2D6. Some examples of CYP450 substrates with narrow therapeutic index are provided in Appendix C.

9 ASSESSMENT OF INVESTIGATIONAL MEDICINAL PRODUCT

9.1 PRIMARY ENDPOINT

9.1.1 Primary safety endpoint

Incidence rates, defined as the percentage of patients reporting any treatment-emergent adverse events (TEAEs), and event rates per 100 patient-years.

9.2 SECONDARY ENDPOINTS

- Incidence rates and event rates per 100 patient-years for AESIs over the study.
- Incidence rates for SAEs/death over the study.
- Incidence rates for AEs leading to study discontinuation over the study.

Note: AEs, SAEs, AESIs, AEs leading to IMP discontinuation, and death will be collected from the time of informed consent signature and then at each visit until the EOT/EOS (Visit 13). The safety analysis will be based on the reported AEs and clinical laboratory data. The study specific and general safety criteria are detailed in Section 10.4.1.

Adverse events, AESIs, SAEs, AEs leading to IMP discontinuation and deaths will be reported as described in Section 10.4.2 and analyzed as in Section 11.4.3.1.

9.2.1 Adverse events

Refer to Section 10.4 to Section 10.7 for further details.

9.2.2 Laboratory safety variables

Clinical laboratory data will be limited to hematology (blood count: erythrocytes, hemoglobin, hematocrit, leukocytes with differential blood count [neutrophils, lymphocytes, monocytes, eosinophils, and basophils] and platelets), and pregnancy testing.

Only clinically significant laboratory test results will be recorded as AEs in the eCRF.

9.3 FUTURE USE OF SAMPLES

Not applicable.

9.4 APPROPRIATENESS OF MEASUREMENTS

This is an open-label extension study with no comparator or control group.

The study aims to collect long-term clinical safety data and extended dupilumab treatment to patients who may continue to benefit from treatment. Local laboratories will be used to support identification and follow-up of clinically significant findings captured as AEs in the eCRF. Likewise, symptom-driven physical examination findings, and vital signs at each visit that are deemed clinically significant will be captured as AEs in the eCRF. Further clinical procedures required to identify and follow-up AE, may be performed at the discretion of the Investigator.

10 STUDY PROCEDURES

10.1 VISIT SCHEDULE

The LPS15023 study consists of 3 periods:

- Start-of-treatment Visit (Visit 1): After completing the EOT Visit (Visit 17) in TRAVERSE, eligible patients should rollover into LPS15023.
- Treatment period (Visit 2 to Visit 12): Open-label treatment for up to 144 weeks (Visit 13, approximately 3 years).
- End-of-treatment/End-of-study (Visit 13).

Patients who prematurely and/or permanently discontinue treatment will be scheduled for the EOT Visit, and the EOS Visit will be scheduled for 12 weeks later for follow-up on AEs.

It is preferred that all study visits take place in the morning.

Safety blood tests will be performed at a local laboratory; depending on the site's local laboratory and facilities, either blood or urine may be assessed for pregnancy testing for WOCBP.

10.1.1 Visit 1 (Start-of-treatment, Week 0)

There is no time limit between the TRAVERSE EOT Visit and the evaluation for eligibility to participate in this study.

Ideally, patients should be evaluated for eligibility to participate in this study as soon as they complete the TRAVERSE EOT Visit. The Start-of-treatment (Visit 1) for this study may be performed on the same day as the TRAVERSE EOT Visit. If this is not possible or if the patient completed participation in TRAVERSE prior to the opening of enrollment in this study, **and** more than 4 weeks have elapsed between TRAVERSE EOT Visit date and the LPS15023 Start-of-treatment (Visit 1) date, the following additional assessments will be required:

- Collect blood samples for hematology: Blood count (erythrocytes, hemoglobin, hematocrit, and leukocytes), differential blood count (neutrophils, lymphocytes, monocytes, eosinophils, and basophils), and platelets.
- For **WOCBP only**, blood or urine pregnancy test.

Following a discussion of participation in the clinical trial, the written informed consent (and assent in case of adolescents) form must be signed and dated before the following activities are performed:

- Review inclusion and exclusion criteria to assess eligibility.
- If the patient meets all inclusion and does not meet any exclusion criteria, contact IRT to register the visit, confirm the patient's number and receive the first treatment kits' numbers assignment.

- Confirm and update (if required) previously collected patient's demographic information, asthma history (including allergy history and smoking habits), and other medical and surgical history (including significant prior and concurrent illnesses).
- Symptom-driven physical examination and vital signs should be performed in patients presenting with signs or symptoms.
- Commence AE reporting from the time of the signature of the informed consent for participation in LPS15023.
- Record study IMP/noninvestigational medicinal products (NIMP) and all other concomitant medication use with start date/dose in the eCRF.
- Instruct the patient to continue the background ICS/LABA or ICS and controller therapy stabilized during TRAVERSE.
- Dispense and administer IMP (see Section 8.1.3):
  - For patients starting to perform self-injection, the Investigator or delegate should train the patient (or parent/caregiver[s]) regarding injection of IMP. The patient (or parent/caregiver[s]) may perform the injection under the supervision of the Investigator or delegate, if the patient (or parent/caregiver[s]) was already (self) injecting in TRAVERSE.
  - Patients should be monitored for at least 30 minutes after each administration of IMP for any signs or symptoms of a hypersensitivity reaction.
- Schedule appointment for next visit.
- Reminder: Sexually active WOCBP are required to practice an acceptable contraception (as defined in E 08) during the entire study duration, while taking dupilumab and for 12 weeks after the last IMP dose. Study investigators should counsel all study patients, with special attention towards adolescent patients, regarding the importance of practicing responsible and effective contraception during the entire study duration.
- Dispense home-dosing diary and instruct the patient to take the study IMP/NIMP medication regularly, fill in the diary, and call the site in case of any signs and symptoms of AEs and/or any problems with the injection/IMP.

10.1.2 Additional on-site visits

Additional on-site IMP administration visits may be scheduled at the Investigator's discretion for patients who experience hypersensitivity reactions upon retreatment, ie, at the Start-of-treatment Visit (Visit 1), or for patients with long off-treatment interval after the completion of TRAVERSE.

10.1.3 Visits 2 to 12 (Treatment period, Weeks 12 to 132)

These will be the treatment period visits. Patients should attend an onsite visit every 12 weeks.

The following procedures will be performed during these visits:

- Contact IRT to register the visit and obtain treatment kits' numbers.
- Inquire for any AEs. In case of any such occurrences, AEs should be recorded and reported.

- Symptom-driven physical examination and vital signs should be performed in patients presenting with signs or symptoms.
- Collect the home-dosing diary and check for regular administration of study IMP/NIMP medication.
- Collect all used and unused IMP (applicable to all interim visits).
- Record study IMP/NIMP and all other concomitant medication use with start date/dose in the eCRF.
- Collect blood samples for hematology: Blood count (erythrocytes, hemoglobin, hematocrit, and leukocytes), differential blood count (neutrophils, lymphocytes, monocytes, eosinophils, and basophils), and platelets.
- For **WOCBP only**, blood or urine pregnancy test.
- Capture as AEs all clinically significant laboratory values in the eCRF.
- Dispense and administer IMP:
  - Review the patient's administration technique.
  - Patients will be monitored at the study site for a minimum of 30 minutes after the injection.
- Remind the patient to continue the background ICS/LABA or ICS and controller therapy stabilized during TRAVERSE.
- Schedule appointment for next visit.
- Dispense home dosing dairy and instruct the patient to take the study IMP/NIMP medication regularly, fill in the home-dosing diary, and call the site in case of any signs and symptoms of AEs and/or any problems with the injection/IMP.
- Patients who discontinue study medication prematurely and permanently should be scheduled for the EOT/EOS Visit.

10.1.4 Visit 13 (End-of-treatment/End-of-study, Week 144)

This will be the end of treatment and the last study visit (except for patients who prematurely and/or permanently discontinue treatment, see Section 10.1.5).

The following procedures will be performed during this visit:

- Contact IRT to register the EOT/EOS Visit.
- Inquire for any AEs. In case of any such occurrences, AEs should be recorded and reported.
- Symptom-driven physical examination and vital signs should be performed in patients presenting with signs or symptoms.
- Collect the home-dosing diary and check for regular administration of study IMP/NIMP medication.
- Collect all used and unused IMP.
- Record study IMP/NIMP and all other concomitant medication use with start date/dose in the eCRF.

- Collect blood samples for hematology: Blood count (erythrocytes, hemoglobin, hematocrit, and leukocytes), differential blood count (neutrophils, lymphocytes, monocytes, eosinophils, and basophils), and platelets.
- For **WOCBP only**, blood or urine pregnancy test; WOCBP discontinuing treatment must be advised to avoid pregnancy for at least 12 weeks following the last IMP dose.
- Capture as AEs all clinically significant laboratory values in the eCRF.

10.1.5 End-of-study Visit

Patients who prematurely and/or permanently discontinue treatment will be scheduled for the EOT Visit, and the EOS Visit will be scheduled for 12 weeks later for follow-up on AEs.

The following procedure will be performed during this visit:

- Inquire for any AEs. In case of any such occurrences, AEs should be recorded and reported.

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 data collected in the eCRF should be transcribed directly from source documents. Data recorded on the patient home-dosing diary will be transcribed to the eCRF.

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

The IMP should be continued whenever possible. In case the IMP is stopped, it should be determined whether the stop can be made temporarily; permanent IMP discontinuation should be a last resort. Any IMP discontinuation must be fully documented in the eCRF.

- Pregnancy will lead to definitive treatment discontinuation in all cases.
- Stopping rules described in Appendix D should be applied.

10.3.1 Temporary treatment discontinuation with investigational medicinal product

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 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, number of missed injections and duration must be recorded by the Investigator in the appropriate screen(s) of the eCRF.

The following definition can be considered:

Eg, temporary treatment discontinuation decided by the Investigator corresponds to more than 1 dose not administered to the patient.

10.3.2 Permanent treatment discontinuation with investigational medicinal product

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

10.3.3 List of criteria for permanent treatment discontinuation

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 reason(s) for treatment discontinuation and this should be documented in the eCRF.

Any abnormal laboratory value will be rechecked for confirmation before making a decision of permanent discontinuation of the IMP for the concerned patient.

The following criteria will lead to permanent treatment discontinuation:

- 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 (see Section 10.6).
- At the specific request of the Sponsor.
- In the event of a protocol deviation, at the discretion of the Investigator or the Sponsor.
- Pregnancy (Note: dupilumab should be stopped but patient should be followed up until delivery).
- Anaphylactic reactions or systemic allergic reactions that are related to IMP and require treatment.
- Diagnosis of a malignancy during study, excluding carcinoma in situ of the cervix, or squamous or basal cell carcinoma of the skin.
- Any opportunistic infection, such as tuberculosis (TB) or other infections whose nature or course may suggest an immunocompromised status (see Appendix E).

10.3.4 Handling of patients after permanent treatment discontinuation

If possible, and after the permanent discontinuation of treatment, patients will be assessed using the procedure normally planned for the last dosing day with the IMP (Visit 13). In case of an ongoing AE at the EOT/EOS Visit, patients may be followed up to recovery or stabilization of the AE.

All cases of permanent treatment discontinuation must be recorded by the Investigator in the appropriate screen(s) of the eCRF when considered as confirmed.

10.3.5 Procedure and consequence for patient withdrawal from study

Patients may withdraw from the study before study completion if they decide to do so or if they no longer wish to take the IMP, at any time and irrespective of the reason without any effect on their care.

The Investigators should discuss with them about attending the EOT/EOS Visit. The value of their study data collected at the the EOT/EOS Visit will be emphasized as important to the public health value of the study.

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

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

In addition, a patient may withdraw his/her consent to stop participating in the study, ie, patient will not attend the EOT/EOS Visit. Withdrawal of consent for treatment should be distinguished from withdrawal of consent for the EOT/EOS Visit and from withdrawal of consent for non-patient contact follow-up, eg, medical record checks. The site should document any case of withdrawal of consent.

For patients who fail to return to the site, unless the patient withdraws consent, the Investigator must make the best effort to recontact the patient (eg, contact patient's family or private physician, review 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).

Patients who have withdrawn from the study cannot be reallocated (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 **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

An **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 medical or surgical 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 a medically important event. The list is not intended to be exhaustive.

- Intensive treatment in an emergency room or at home for:
  - Allergic bronchospasm.
  - Blood dyscrasias (ie, agranulocytosis, aplastic anemia, bone marrow aplasia, myelodysplasia, pancytopenia, etc.).
  - Convulsions (seizures, epilepsy, epileptic fit, absence, etc.).
- Development of drug dependence or drug abuse.
- 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 (only if judged unusual/significant by the Investigators).

10.4.1.3 Adverse event of special interest

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

The following is a list of AESIs for this study. For these AESIs, the Sponsor will be informed immediately (ie, within 24 hours), per SAE notification described in Section 10.4.1.2, even if not fulfilling a seriousness criterion, using the corresponding screens of the eCRF:

- Anaphylactic reactions or acute allergic reactions that require immediate treatment (see Appendix F).
- Injection site reactions that are severe and last longer than 24 hours.
- Any serious infection, any bacterial infection requiring treatment with parenteral antibiotics for longer than 2 weeks, any parasitic infection, any systemic opportunistic infection (see Appendix E), any viral infection requiring antiviral treatment, or any uncommon, atypical, or unusually frequent or persistent infection and TB that requires anti-TB medication. For details, refer to Section 10.6.3.

Note: Candidiasis – all cases should be collected as AEs (or SAEs if requirements met), however, only cases which are NOT cutaneous (systemic or mucous membranes involved) unless involvement is extensive, will be considered as AESI.

- Pregnancy (female patient or female partner):
  - Pregnancy occurring in a female patient entered in the clinical trial or in a female partner of a male patient entered in the clinical trial. It will be qualified as an SAE only if it fulfills one of the seriousness criteria (see Section 10.4.1.2).
  - In the event of pregnancy in a female participant, IMP should be permanently discontinued.
  - Follow-up of the pregnancy in a female participant or in a female partner of a male participant is mandatory until the outcome has been determined.
- Symptomatic overdose (serious or nonserious) with the IMP/NIMP.
  - An overdose (accidental or intentional) with the IMP/NIMP is an event suspected by the Investigator or spontaneously notified by the patient and defined as at least twice the planned dose during an interval of less than 11 days. The circumstances (ie, accidental or intentional) should be clearly specified in the verbatim and symptoms, if any, entered on separate AE forms.

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

10.4.2 General guidelines for reporting adverse events

- All AEs, regardless of seriousness or relationship to IMP/NIMP, spanning from the signature of the ICF until the end of the study as defined by the protocol for that patient, are to be recorded on the corresponding screen(s) of the eCRF.
- 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 or by the study procedure(s).
- 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 pre specified study end-date (EOT/EOS Visit), should be followed until resolution, stabilization, or death and related data will be collected.
- When treatment is prematurely and permanently discontinued, the patient's observations will continue until the end of the study as defined by the protocol for that patient.
- The following laboratory abnormalities are considered clinically significant and will be recorded as AEs:
  - Symptomatic and/or
  - Requiring either corrective treatment or consultation, and/or
  - Leading to IMP discontinuation or modification of dosing, and/or
  - Fulfilling a seriousness criterion, and/or
  - Defined as an AESI.

Instructions for AE reporting are summarized in Table 1 in Section 10.4.5.

10.4.3 Instructions for reporting serious adverse events

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

- ENTER (within 24 hours) the information related to the SAE in the appropriate screens of the eCRF; the system will automatically send a notification to the monitoring team after approval of the Investigator within the eCRF 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 eCRF 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 of the SAE. 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 eCRF 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 reporting adverse events of special interest

For AESIs, the Sponsor must be informed immediately (ie, within 24 hours), as per SAE notification guidelines described in Section 10.4.3, even if not fulfilling a seriousness criterion, using the corresponding screen(s) of the eCRF.

Instructions for AE reporting are summarized in Table 1 in Section 10.4.5.

10.4.5 Guidelines for management of specific laboratory abnormalities

Decision trees for the management of neutropenia and thrombocytopenia by Sanofi are provided in Appendix D. These abnormalities should be monitored, documented, and managed according to the related flow chart in Appendix D.

In addition, eosinophil counts >3000 cells/µL (3.0 giga/L) at any time during the study are to be reported as AEs.

Table 1 - Summary of adverse event reporting instructions

Event category	Reporting timeframe	Specific events in this category	Case report form completion		
			AE form	Safety complementary form	Other specific forms
Adverse Event (non-SAE, non-AESI)	Routine	Any AE that is not SAE or AESI	Yes	No	No
Serious Adverse Event (non-AESI or AESI)	Expedited (within 24 hours)	Any AE meeting seriousness criterion per Section 10.4.1.2	Yes	Yes	No
Adverse Event of Special Interest	Expedited (within 24 hours)	Acute hypersensitivity/anaphylaxis	Yes	Yes	No
		Injection site reactions	Yes	Yes	No

Event category	Reporting timeframe	Specific events in this category	Case report form completion		
			AE form	Safety complementary form	Other specific forms
		Infections (see Section 10.4.1.3 for details)	Yes	Yes	No
		Pregnancy	Yes	Yes	Yes
		Symptomatic overdose	Yes	Yes	No

Abbreviations: AE = adverse event; AESI = adverse event of special interest; SAE = serious adverse event

10.4.6 Guidelines for reporting investigational medicinal product complaints

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

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

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 IMP (suspected unexpected serious adverse reaction), to the regulatory authorities, Independent Ethics Committee (IECs)/Institutional Review Boards (IRBs) as appropriate and to the Investigators.
- All SAEs that are expected and at least reasonably related to the IMPs to the regulatory authorities, according to local regulations.

Exacerbations of asthma, as pre-existing condition, will be considered expected for purposes of regulatory reporting, unless the event is life-threatening or with fatal outcome (refer to the current IB).

Any other AE not listed as an expected event in the IB or in this protocol will be considered unexpected.

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

10.6 SAFETY INSTRUCTIONS

During the study, all patients will be monitored for safety signals and will be instructed to call the site in case of any signs and symptoms of AEs and/or any problems with the injection/IMP.

In addition, any problems related to dupilumab injection administration should be documented in the specific screen(s) of the eCRF for local injection reactions recording.

10.6.1 Hypersensitivity

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

Allergic reactions may be defined as an immunologically mediated response to a pharmaceutical and/or formulation agent in a sensitized person. Signs and symptoms are often experienced during or shortly after therapeutic administration. Anaphylaxis may represent the most severe form of allergic reactions; see Appendix F, which describes the clinical criteria for the diagnosis of anaphylaxis.

Patients should be monitored for at least 30 minutes after each study-site IMP administration for any signs or symptoms of a hypersensitivity reaction. Furthermore, the patients will be advised, when the IMP is administered at home, to self-monitor for 30 minutes after administration for potential signs and symptoms that may suggest a hypersensitive reaction.

10.6.2 Severe injection site reactions

Based on the SC mode of administration of high doses of protein and on a higher incidence of local injection site reactions observed at the highest dose level (300 mg weekly), 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.

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

10.6.3 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.

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, IL-13, and IL-5, subsequently generating IgG1 and IgE-secreting cells, and eliciting eosinophilia. 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. Since dupilumab binds to IL-4Rα, preventing IL-4 and IL-13 binding and activation of their respective receptors, it inhibits Th2 cytokine production. Therefore, patients treated with 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 enrollment. 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, particularly when conditions are conducive to infection (eg, extended stay, rural or heavily populated informal settlements, lack of running water, consumption of uncooked, undercooked, or otherwise potentially contaminated food, close contact with carriers and vectors). Subsequent medical assessments (eg, stool exam, blood tests) 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.

Infections defined in Section 10.4.1.3 should be reported as AESIs within 24 hours.

A complete diagnostic work-up should be performed (ie, cultures, 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:

- Infections or infestations that do not respond to medical treatment should have study IMP discontinued until the infection is resolved.
- For any opportunistic infection, such as TB or other infections whose nature or course may suggest an immunocompromised status (see Appendix E), patients must be permanently discontinued from IMP.

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 objective of the study is to continue to evaluate the long-term safety and tolerability of dupilumab in patients with asthma who participated in the previous long-term study TRAVERSE. Therefore, all qualifying patients completing the treatment period in TRAVERSE will be offered to enroll in this study.

It is expected that approximately 750 patients will enroll in this study.

11.2 DISPOSITION OF PATIENTS

Enrolled patients consist of all the patients who signed informed consent and had a treatment kit number allocated and recorded in IRT database, and regardless of whether the treatment kit was used or not.

The safety population consists of the patients who actually received at least one dose or part of a dose of dupilumab in the current study.

11.3 ANALYSIS POPULATIONS

11.3.1 Efficacy populations

Not applicable.

11.3.2 Safety population

The primary analysis population is the safety population, which is defined as all patients who have actually received at least one dose or part of a dose of dupilumab during this study.

The treatment-emergent period is defined as the time from the first dose of dupilumab during this study up to the EOT/EOS (Visit 13).

11.4 STATISTICAL METHODS

11.4.1 Extent of study treatment exposure and compliance

The extent of study treatment exposure and compliance will be summarized using the safety population.

11.4.1.1 Extent of investigational medicinal product exposure

Duration of exposure to IMP is defined as: last dose date – first dose date of dupilumab + dose interval, regardless of unplanned intermittent discontinuations. Duration of exposure will be summarized using descriptive statistics such as mean, standard deviation (SD), median, minimum, and maximum.

11.4.1.2 Compliance

A given administration of IMP will be considered "noncompliant" if the patient did not take the planned dose of treatment as required by the protocol.

Percentage of compliance for a patient will be defined as 100 x (the number of administrations the patient was compliant divided by the total number of administrations the patient was to take during the treatment period).

Treatment compliance will be summarized by categories (eg, >80% compliant, >60-80% compliant, >40-60% compliant, <40% compliant). The percentage of patients with compliance <80% will be summarized. In addition, the number and percentage of patients with at least 1 above-planned dosing administration will be given, as well as the number and percentage of patients with 0, (0, 20%, and >20%) under-planned dosing administrations. In addition, overall compliance will be summarized descriptively (N, mean, SD, median, minimum, and maximum).

11.4.2 Analyses of efficacy endpoints

Not applicable.

11.4.3 Analyses of safety data

All safety analysis will be performed on the safety population.

11.4.3.1 Adverse events

Adverse events reported in this study will be coded using the version of the Medical Dictionary for Regulatory Activities in effect at Sanofi at the time of database lock. Adverse events occurred during the treatment-emergent period will be considered as TEAE.

11.4.3.1.1 Treatment-emergent adverse events

Incidence of TEAE and the number of TEAEs per 100 patient-years (total number of events adjusted for the total duration of exposure) will be presented by system organ class (SOC), high level group term (HLGT), and preferred term (PT) sorted in alphabetical order, the number and percentage (%) of patients experiencing a TEAE.

In the derivation of incidence of AEs, multiple occurrences of the same event in the same patient will be counted only once in the tables. The denominator will be based on the total number of patients in the safety population.

The proportion of patients with at least one TEAE, serious TEAE, and TEAE leading to discontinuation of the study will be tabulated. In addition TEAEs will be described according to maximum intensity and relationship to the study drug.

11.4.3.1.2 Adverse events

An overview summary will be presented of the number (%) of patients with:

- Any TEAE.
- Any SAE and AEs leading to death (regardless of treatment-emergent status).
- Any treatment-emergent SAEs.
- Any AE leading to permanent study discontinuation.

11.4.3.1.3 Adverse events of special interest

The incidence of each AESI and the number of AESIs per 100 patient-years will be presented; AESI definitions can be found in Section 10.4.1.3.

11.4.3.1.4 Death

The following summaries for deaths will be presented:

- Number (%) of patients who died by study period (TEAE, on-study) and reasons for death.
- TEAE leading to death (death as an outcome on the AE eCRF screen as reported by the Investigator) by primary SOC, HLGT, and PT showing number (%) of patients.

11.4.3.1.5 Clinical laboratory evaluations, vital signs, and physical examination findings

Clinically significant test results will be recorded as AEs; overall AE summaries will include all AEs.

11.4.4 Concomitant medications

All concomitant medications will be summarized according to the World Health Organization Drug Dictionary, by anatomic class and therapeutic category using the number (%) of patients taking the medication. Asthma controller and reliever medication use will be summarized separately, in addition to all concomitant medications used.

11.5 INTERIM ANALYSIS

Interim analyses of data may be conducted to support regulatory submissions or publication activities.

12 ETHICAL AND REGULATORY CONSIDERATIONS

12.1 ETHICAL AND REGULATORY STANDARDS

This clinical trial will be conducted by the Sponsor, the Investigator, and delegated Investigator staff and Subinvestigator, in accordance with consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki, and the International Council for Harmonisation (ICH) guidelines for Good Clinical Practice (GCP), all applicable laws, rules and regulations.

This clinical trial will be recorded in a free, publicly accessible, internet-based registry, no later than 21 days after the first patient enrollment, in compliance with applicable regulatory requirements and with Sanofi public disclosure commitments.

12.2 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 (and the parent[s] or guardian[s], if applicable) 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 ICF should be signed, name filled in and personally dated by the patient, by the patient's parent(s) 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 ICF will be provided to the patient (for adult patients) or patient's parent(s) or patient's legally accepted representative for pediatric patients. Local law must be observed in deciding whether 1 or both parents/guardians consent is required. If only 1 parent or guardian signs the consent form, the Investigator must document the reason for only 1 parent or guardian's signature.

In addition, participants will assent as detailed below or will follow the ethics committee (IRB/IEC) approved standard practice for pediatric participants at each participating center (age of assent to be determined by the IRB's/IEC's or be consistent with the local requirements):

- Participants who can read the assent form will do so before writing their name and dating or signing and dating the form.
- Participants who can write but cannot read will have the assent form read to them before writing their name on the form.
- Participants who can understand but who can neither write nor read will have the assent form read to them in presence of an impartial witness, who will sign and date the assent form to confirm that assent was given.

The ICF and the assent 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.

In relation with the population of patients exposed in the trial ie, pediatric/minor patients, the IRB/IEC should ensure proper advice from specialist with pediatrics expertise (competent in the area of clinical, ethical, and psychosocial problems in the field of pediatrics) according to national regulations. This should be documented.

12.3 HEALTH AUTHORITIES AND INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE

As required by local regulation, the Investigator or the Sponsor must submit this clinical trial protocol to the health authorities (competent regulatory authority) and the appropriate 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 IRB/IEC composition.

The clinical trial (study number, clinical trial protocol title and version number), the documents reviewed (clinical trial protocol, ICF, Investigator's curriculum vitae, etc) and the date of the review should be clearly stated on the written (IRB/IEC) approval/favorable opinion.

The 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 health authorities (competent regulatory authority), as required by local regulation, in addition to the IRB/IEC before implementation, unless the change is necessary to eliminate an immediate hazard to the patients, in which case the health authorities (competent regulatory authority) and the IRB/IEC should be informed as soon as possible. They 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 IB will be sent to the IRB/IEC and to health authorities (competent regulatory authority), as required by local regulation.

A progress report is sent to the 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 INVESTIGATORS

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 eCRF, 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 regulatory authorities for taking all reasonable steps to ensure the proper conduct of the clinical trial as regards ethics, clinical trial protocol compliance, and integrity and validity of the data recorded on the eCRFs. 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 GCP, the monitoring team must check the eCRF entries against the source documents, except for the pre identified source data directly recorded in the eCRF. The ICF 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 eCRFs (eg, patient's medical file, appointment books, original laboratory records). 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 AND ADDITIONAL REQUEST

It is the responsibility of the Investigator to maintain adequate and accurate eCRFs (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 eCRFs 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 eCRF 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 eCRF.

The computerized handling of the data by the Sponsor 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 eCRF.

13.5 USE OF COMPUTERIZED SYSTEMS

The complete list of computerized systems used for the study is provided in a separate document which is maintained in the Sponsor trial master file.

14 ADDITIONAL REQUIREMENTS

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, personal data in relation to the patients, the CRFs, the IB, 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.

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.

The Investigator shall not and shall cause the delegated Investigator staff /Subinvestigator not to mention any information or the Product in any application for a patent or for any other intellectual property rights.

All the results, data, documents and inventions, which arise directly or indirectly from the clinical trial in any form, shall be the immediate and exclusive property of the Sponsor.

The Sponsor may use or exploit all the results at its own discretion, without any limitation to its property right (territory, field, continuance). The Sponsor shall be under no obligation to patent, develop, market or otherwise use the results of the clinical trial.

As the case may be, the Investigator and/or the Subinvestigators shall provide all assistance required by the Sponsor, at the Sponsor's expense, for obtaining and defending any patent, including signature of legal documents.

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.
- 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.

14.6 INSURANCE COMPENSATION

The Sponsor certifies that it has taken out a liability insurance policy covering all clinical trials under its sponsorship. This insurance policy is in accordance with local laws and requirements. The insurance of the Sponsor does not relieve the Investigator and the collaborators from any obligation to maintain their own liability insurance policy. An insurance certificate will be provided to the IECs/IRBs or regulatory authorities in countries requiring this document.

14.7 SPONSOR AUDITS AND INSPECTIONS BY REGULATORY AGENCIES

For the purpose of ensuring compliance with the clinical trial protocol, GCP, 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 By the Sponsor

The Sponsor has the right to terminate the participation of either an individual site or the study at any time, for any reason, including but not limited to the following:

- The information on the product leads to doubt as to the benefit/risk ratio.
- Patient enrollment is unsatisfactory.
- 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.
- Noncompliance of the Investigator or Subinvestigator, delegated staff with any provision of the clinical trial protocol, and breach of the applicable laws and regulations or breach of the ICH GCP.
- 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 By the Investigator

The Investigator may terminate his/her participation upon 30 days' prior written notice if the study site or the Investigator for any reason becomes unable to perform or complete the clinical trial.

In the event of premature discontinuation of the study or premature close-out of a site, for any reason whatsoever, the appropriate IRB/IEC and regulatory 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.

14.10 PUBLICATIONS AND COMMUNICATIONS

The Investigator undertakes not to make any publication or release pertaining to the study and/or results of the study prior to the Sponsor's written consent, being understood that the Sponsor will not unreasonably withhold its approval.

As the study is being conducted at multiple sites, the Sponsor agrees that, consistent with scientific standards, a primary presentation or publication of the study results based on global study outcomes shall be sought. However, if no multicenter publication is submitted, underway, or planned within 12 months of the completion of this study at all sites, the Investigator shall have the right to publish or present independently the results of this study in agreement with other Investigators and stakeholders. The Investigator shall provide the Sponsor with a copy of any such presentation or publication for review and comment at least 30 days in advance of any presentation or submission for publication. In addition, if requested by the Sponsor, any presentation or submission for publication shall be delayed for a limited time, not to exceed 90 days, to allow for filing of a patent application or such other justified measures as the Sponsor deems appropriate to establish and preserve its proprietary rights.

The Investigator shall not use the name(s) of the Sponsor and/or its employees in advertising or promotional material or publication without the prior written consent of the Sponsor. The Sponsor shall not use the name(s) of the Investigator and/or the collaborators in advertising or promotional material or publication without having received his/her and/or their prior written consent(s).

The Sponsor has the right at any time to publish the results of the study.

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 to the clinical trial protocol without agreement by the Sponsor and prior review and documented approval/favorable opinion from the IRB/IEC and/or notification/approval of health authorities (competent regulatory authority) of an amendment, as required by local regulation, 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 IRB/IEC prior to its implementation, unless there are overriding safety reasons.

In case of substantial amendment to the clinical trial protocol, approval from the health authorities (competent regulatory authority) will be sought before implementation.

In some instances, an amendment may require a change to the ICF. The Investigator must receive an IRB/IEC approval/favorable opinion concerning the revised ICF prior to implementation of the change and patient signature should be recollected if necessary.

16 BIBLIOGRAPHIC REFERENCES

1. Godard P, Chanez P, Siraudin L, Nicoloyannis N, Duru G. Costs of asthma are correlated with severity: A 1-yr prospective study. Eur Respir J. 2002;19(1):61-7.

2. Levine SJ and Wenzel SE. Narrative review: the role of Th2 immune pathway modulation in the treatment of severe asthma and its phenotypes. Ann Intern Med. 2010;152(4):232–7.

3. Wenzel S, Castro M, Corren J, Maspero J, Wang L, Zhang B, et al. Dupilumab efficacy and safety in adults with uncontrolled persistent asthma despite use of medium-to-high-dose inhaled corticosteroids plus a long-acting β 2 agonist: a randomised double-blind placebo controlled pivotal Phase 2b dose-ranging trial. Lancet. 2016;388(10039):31-44.

4. Simpson EL, Bieber T, Guttman-Yassky E, Beck LA, Blauvelt A, Cork MJ, et al; SOLO 1 and SOLO 2 Investigators. Two Phase 3 Trials of Dupilumab versus Placebo in Atopic Dermatitis. N Engl J Med. 2016;375(24):2335-48.

17 APPENDICES

Appendix A. List of prohibited live, attenuated vaccines

- Bacillus Calmette-Guérin anti-TB vaccine.
- Chickenpox (Varicella).
- Intranasal influenza (FluMist-Influenza); inactive influenza vaccine delivered by injection is permitted.
- Measles (Rubella).
- Measles-mumps-rubella combination.
- Measles-mumps-rubella-varicella combination.
- Mumps.
- Oral polio (Sabin).
- Oral typhoid.
- Rotavirus.
- Rubella.
- Smallpox (Vaccinia).
- Varicella Zoster (shingles).
- Yellow fever.

This list is indicative and not exhaustive.

Appendix B. Examples of commonly used asthma controller therapies

Controller groups	Medications
CS	Beclomethasone dipropionate CFC
CS	Beclomethasone dipropionate HFA
CS	Budesonide
CS	Ciclesonide
CS	Fluticasone propionate
CS	Mometasone furoate
CS	Triamcinolone acetonide
CS	Fluticasone furoate
CS/LABA	Fluticasone propionate/salmeterol
CS/LABA	Fluticasone propionate/formoterol
CS/LABA	Fluticasone puroate /ilanterol
CS/LABA	Budesonide /formoterol
CS/LABA	Mometasone furoate/formoterol
CS/LABA	Beclomethasone dipropionate/formoterol
LABA	Salmeterol
LABA	Formoterol
LABA	Bambuterol
LABA	Clenbuterol
LABA	Tulobuterol
LABA	Vilanterol
LABA	Olodaterol
LABA	ndacaterol
LAMA	Tiotropium
LAMA	Glucopyrronium bromide
LAMA	Aclidinium bromide
LAMA	Umeclidinium
Anti-Leukotrienes	Montelukast
Anti-Leukotrienes	Pranlukast
Anti-Leukotrienes	Zafirlukast
Anti-Leukotrienes	Zileuton
Methylxanthines	Aminophylline
Methylxanthines	Theophylline
Methylxanthines	Dyphylline
Methylxanthines	Oxtriphylline
Methylxanthines	Diprophylline

Controller groups	Medications
Methylxanthines	Acebrophylline
Methylxanthines	Bamifylline
Methylxanthines	Doxofylline

This list is indicative and not exhaustive.

Appendix C. Examples of CYP substrates with narrow therapeutic range

CYP[a] enzymes	Substrates with narrow therapeutic range[b]
CYP1A2	Theophylline, tizanidine
CYP2C8	Paclitaxel
CYP2C9	Warfarin, phenytoin
CYP2C19	S-mephenytoin
CYP3A[c]	Alfentanil, astemizole[d], cisapride[d], cyclosporine[e], dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus[e], terfenadine[d]
CYP2D6	Thioridazine

CYP = cytochrome

a 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

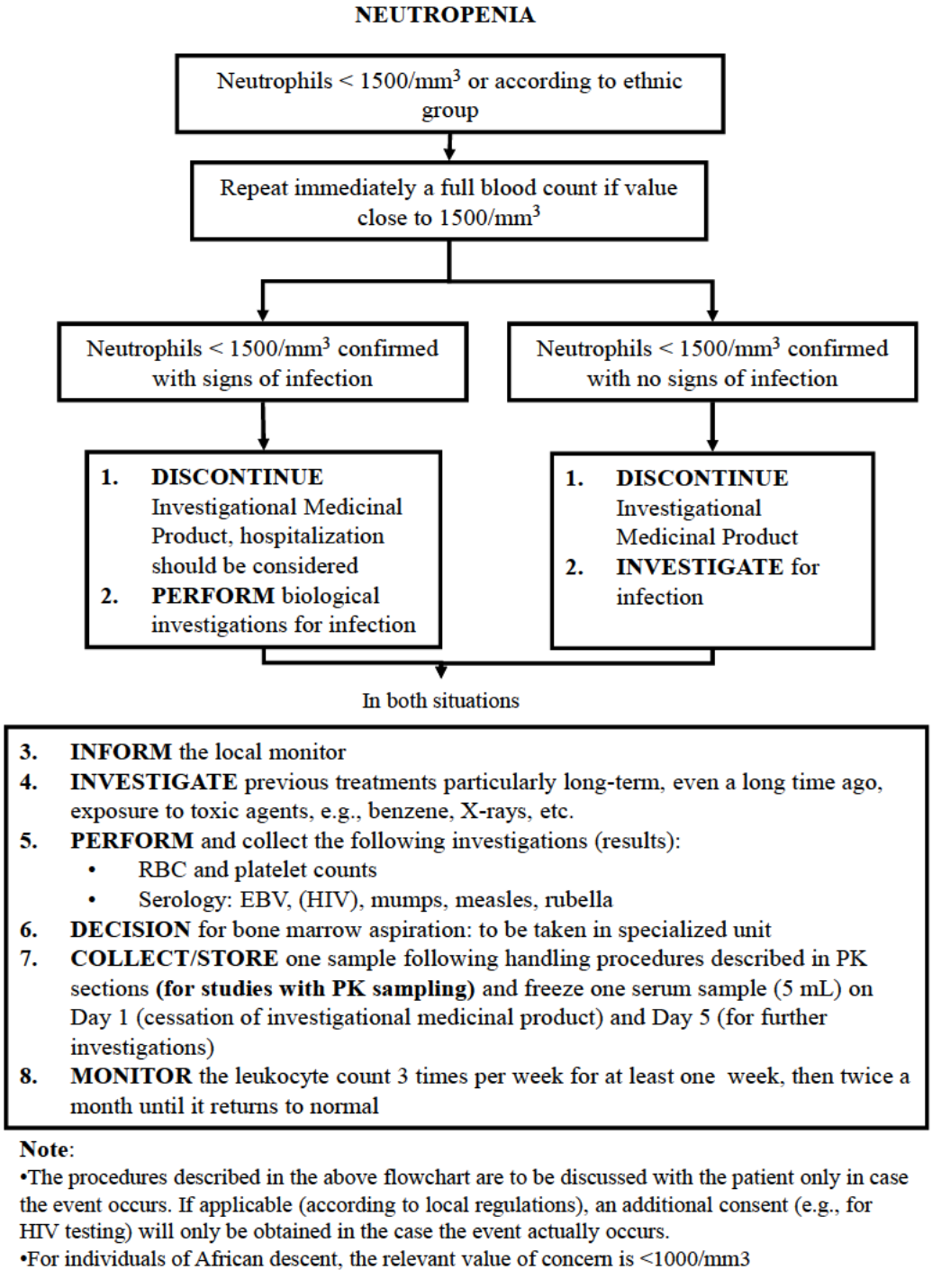
b CYP substrates with narrow therapeutic range refers to drugs whose exposure-response relationship indicates that small changes in their exposure levels by the concomitant use of CYP inhibitors or inducers may lead to either serious safety concerns (eg, Torsades de Pointes) or loss of therapeutic effect

c Because a number of CYP3A substrates (eg, darunavir, maraviroc) are also substrates of P-glycoprotein, the observed increase in exposure could be due to inhibition of both CYP3A and P-glycoprotein

d Withdrawn from the United States market because of safety reasons

e Prohibited medication during the study

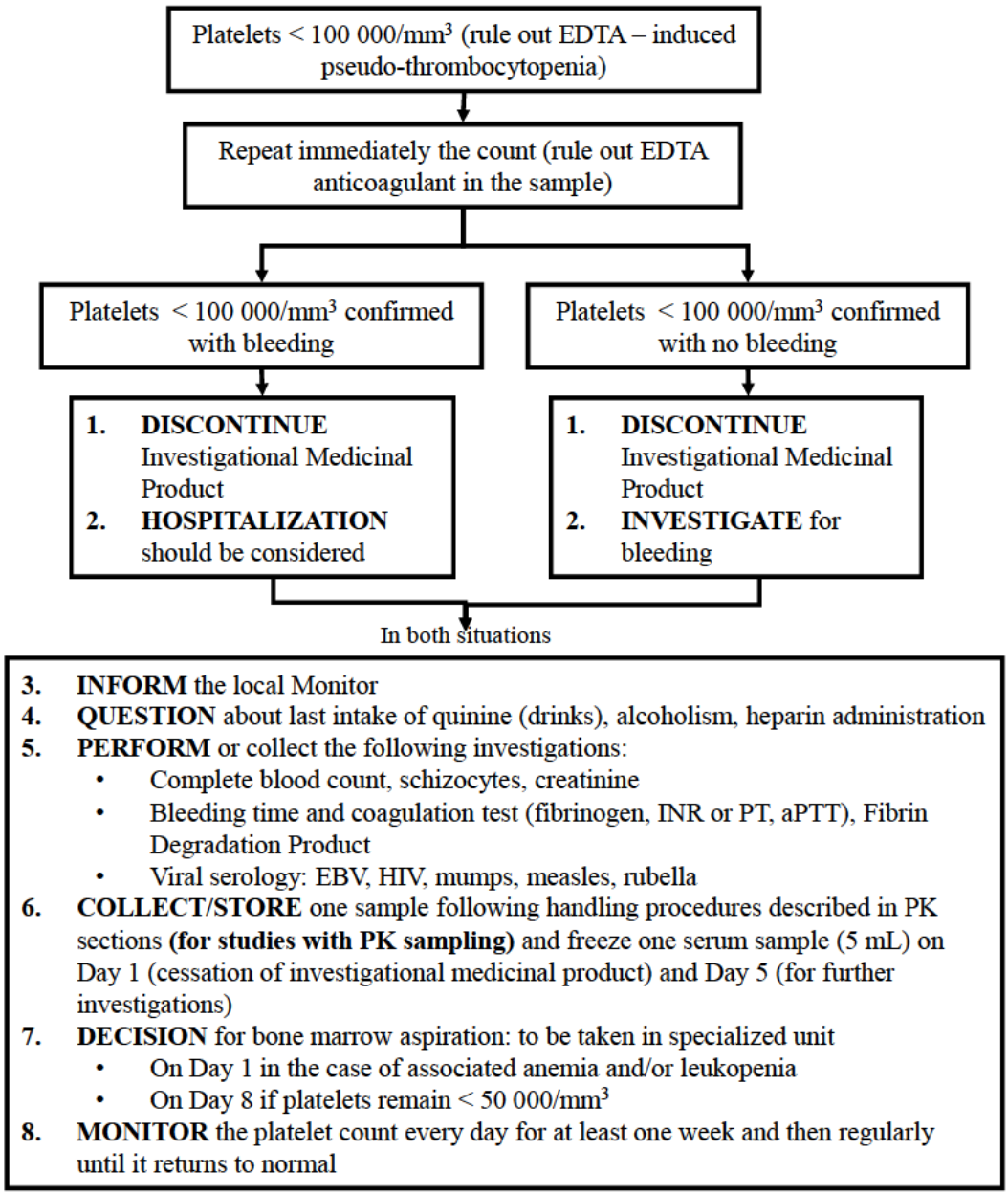
Appendix D. General guidance for the follow-up of laboratory abnormalities by Sanofi



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 is to be recorded as an AE only if at least 1 of the criteria listed in the general guidelines for reporting AEs in Section 10.4.2 is met.

THROMBOCYTOPENIA



Note:
The procedures above flowchart are to be discussed with the patient only in case described in the 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 is to be recorded as an AE only if at least 1 of the criteria listed in the general guidelines for reporting AEs in Section 10.4.2 is met.

Appendix E. List of opportunistic infections

This list is indicative and not exhaustive.

- Aspergillosis.
- Blastomyces dermatitidis (endemic in the south-eastern and south-central states US, along Mississippi and Ohio Rivers).
- Candidiasis – only systemic or extensive mucosal or cutaneous candidiasis.
- Coccidioides immitis (endemic south-western US and Central and South America).
- Cryptococcus.
- Cytomegalovirus.
- Herpes Simplex (disseminated).
- Herpes Zoster (disseminated; ophthalmic; involvement of ≥2 dermatomes).
- Histoplasmosis (pulmonary or disseminated; most common tropical areas Tennessee-Ohio-Mississippi river basins).
- Listeriosis.
- Mycobacterium avium.
- Nontuberculosis mycobacteria.
- Pneumocystis pneumonia.

Appendix F. Definition of anaphylaxis

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

(Adapted from *Sampson HA, Munoz-Furlong A, Campbell RL, Adkinson NF, Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: Summary report—Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol 2006; 117(2): 391-7)*

Clinical criteria for diagnosing anaphylaxis:

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

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

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

LPS15023 16.1.1 Protocol

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm)
[redacted]	Regulatory Approval	[redacted]
	Clinical Approval	
	Clinical Approval	