NCT02134028

AMENDED CLINICAL TRIAL PROTOCOL 02

COMPOUND: SAR231893

Open-label extension study to evaluate the long-term safety and tolerability of dupilumab in patients with asthma who participated in a previous dupilumab asthma clinical study

STUDY NUMBER: LTS12551

STUDY NAME: LIBERTY ASTHMA TRAVERSE

VERSION DATE/STATUS: 31-Oct-2016 /Approved

CLINICAL STUDY DIRECTOR: [redacted]

Protocol Amendment 04	Version number 1: (electronic 1.0)	Date: 31-Oct-2016
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Amended Clinical Trial Protocol 02 (Germany)	Version number: 1 (electronic 1.0)	Date: 22 -Dec-2015
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NAMES AND ADDRESSES OF

COORDINATING INVESTIGATOR	Name: Address: Tel: Fax: E-mail:	
MONITORING TEAM'S REPRESENTATIVE	Name: Address: Tel: Fax: E-mail:	
SPONSOR	Company: Address:	
OTHER EMERGENCY TELEPHONE NUMBERS		

CLINICAL TRIAL SUMMARY

COMPOUND: Dupilumab (SAR231893) **STUDY No: LTS12551**	
TITLE	Open-label extension study to evaluate the long-term safety and tolerability of dupilumab in patients with asthma who participated in a previous dupilumab asthma clinical study
INVESTIGATOR/TRIAL LOCATION	Worldwide
PHASE OF DEVELOPMENT	Phase 2b/Phase 3.
STUDY OBJECTIVES	**Primary objective** • To evaluate the long-term safety and tolerability of dupilumab in patients with asthma who participated in a previous dupilumab asthma clinical study (DRI12544, PDY14192, EFC13579, EFC13691). **Secondary objectives** • To evaluate the long-term efficacy of dupilumab in patients with asthma who participated in a previous dupilumab asthma clinical study. • To evaluate dupilumab in patients with asthma who participated in previous dupilumab asthma clinical study, with regard to: - systemic exposure; - anti-drug antibodies (ADA); - biomarkers.
STUDY DESIGN	Multinational, multicenter, open-label, extension study evaluating dupilumab 300 mg subcutaneously (SC) every 2 weeks (q2w) for 1-year (48 weeks) or 2-year (96 weeks) treatment duration. Patients enrolled prior to Amendment 04 approval will continue to participate in the 2-year treatment duration; patients enrolled after Amendment 04 approval will participate in the 1-year treatment duration. At enrollment, patients will be on medium or high dose of inhaled corticosteroid (ICS) and at least one other asthma controller medication, as maintained during the parent study in which they participated (including asthma background controller therapy with oral corticosteroids [OCS] only for patients from Study EFC13691). The clinical trial consists of 3 periods: • Enrollment period: Combined V1/V2 Visit: Eligible patients from PDY14192, EFC13579, and EFC13691 studies should rollover into LTS12551 the same day as the *end-of-treatment visit of the parent* study. - Note**:** A screening period of 0 to 3 weeks was proposed only for patients rolling over from DRI12544. Enrollment from Study DRI12544 is complete, thus the screening period does not apply anymore. • Treatment period: 48 or 96 weeks open-label treatment.

	- Patients enrolled prior to Amendment 04 approval will continue to participate in the 2-year treatment duration; patients enrolled after Amendment 04 approval will participate in the 1-year treatment duration. During the open-label treatment period, patients will continue taking their background controller therapy, as maintained during the parent study or as modified based on Investigator's judgment. • Post-treatment period: 12 weeks. - Upon completion of the open-label treatment period (or following early discontinuation of investigational medicinal product [IMP]) patients will continue into the post-treatment period. During this period, patients will receive their background controller regimen, as maintained during the open-label treatment period or as modified based on Investigator's judgment (eg, taking into account the reduction of dupilumab levels over time upon completion of the treatment period).
STUDY POPULATION **Main selection criteria**	**Main inclusion criteria** Eligible patients who have completed the treatment period in a previous dupilumab asthma study (PDY14192, EFC13579, EFC13691) or patients with asthma who completed the treatment and follow-up periods in previous dupilumab asthma Study DRI12544 may be enrolled in the LTS12551 study. **Main exclusion criteria** Patients who experienced any hypersensitivity reactions to IMP in the previous dupilumab asthma study, which, in the opinion of the Investigator, could indicate that continued treatment with dupilumab may present an unreasonable risk for the patient. For the complete list of inclusion/exclusion criteria, please refer to the relevant sections of the full protocol.
Total expected number of patients	The total number of patients to participate is approximately 2206 (including a number of adolescent patients [aged 12 years to less than 18 years] that will not exceed the sum of adolescent patients enrolled in the parent studies).
STUDY TREATMENT(s)	
Investigational medicinal product(s) (IMP) **Formulation**	Dupilumab. Note: At the time of Amendment 04, all patients have been transitioned to prefilled syringes. Prefilled syringes: Sterile dupilumab will be provided at the concentration of 150 mg/mL in glass prefilled syringes (2.25 mL total volume) to deliver 300 mg in the extractable 2 mL volume.
Route of administration	SC.

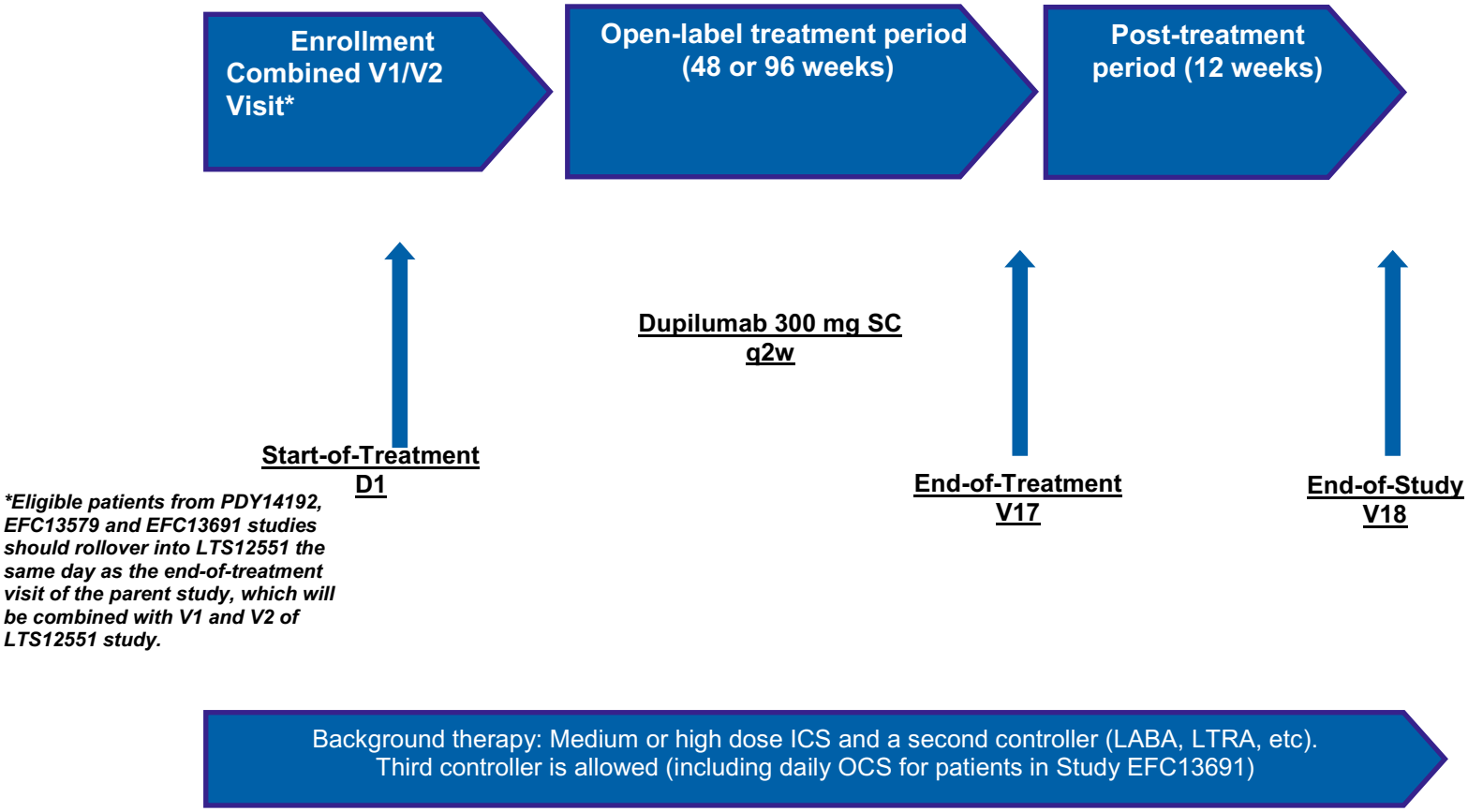
Dose regimen	Eligible patients will receive dupilumab 300 mg (SC) q2w, of open-label treatment for 48 weeks (1 year) for patients enrolled after approval of Amendment 04 or 96 weeks (2 years) for patients enrolled prior to Amendment 04 approval. Note: Enrollment from Study DRI12544 is complete; all patients were given a 600 mg loading dose on Day 1.
Noninvestigational medicinal product(s) (if applicable) **Formulation**	**Asthma background controller therapy:** Inhaled corticosteroid, in combination with a second controller. Patients requiring a third controller medication are allowed (eg, long-acting beta-agonist [LABA], leukotriene receptor antagonist [LTRA], methylxanthines, etc); OCS only for those patients from 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 levalabuterol/levosalbutamol may be used as an alternative delivery method.
Route(s) of administration	Oral inhalation, nebulizers: ICS, ICS combination, albuterol/salbutamol or levalbuterol/levosalbutamol; for other background controllers according to the label.
Dose regimen	Inhaled corticosteroid (medium or high dose); albuterol/salbutamol or levalbuterol/levosalbutamol (as needed); other background controllers according to the label.
ENDPOINT(S)	**Primary endpoint** • The number (n) and percentage (%) of patients experiencing any treatment-emergent adverse events (TEAEs). **Secondary endpoints** • Safety and tolerability - Vital signs. - Physical examination. - Electrocardiogram (ECG). - Clinical laboratory tests. • Efficacy - Forced expiratory volume in 1 second (FEV_1). - Asthma Control Questionnaire–5 question version (ACQ-5). - Severe asthma exacerbation events, during the treatment period. - Asthma Quality of Life Questionnaire - Standardized [AQLQ(S)]. - EuroQol 5 dimensions questionnaire, 3-level version (EQ-5D-3L). - Health care resource utilization questionnaire. - Morning and evening peak expiratory flow (PEF). - Asthma symptom scores. - Number of inhalations/day of salbutamol/albuterol or levosalbutamol/levalbuterol for symptom relief.

	- Nocturnal awakenings due to asthma requiring use of reliever medication. - Prescribed OCS dose for patients from the EFC13691 study. • Dupilumab systemic exposure and anti-drug antibodies - Serum dupilumab concentrations. - Anti-drug antibodies. • Biomarkers - Blood: Eosinophil count. - Serum: Immunoglobulins (Ig), total IgE.
ASSESSMENT SCHEDULE	• Enrollment period: Combined V1/V2 Visit: Eligible patients from PDY14192, EFC13579, and EFC13691 studies should rollover into LTS12551 on the same day as the *end-of-treatment visit of the parent* study. • Treatment period: Open-label treatment for 48 weeks (1 year) for patients enrolled after approval of Amendment 04 or 96 weeks (2 years) for patients enrolled prior to Amendment 04 approval. • Post-treatment period: 12 weeks. Study visits are performed q2w (ie, twice a month / approximately q2w) during the first 3 months of study (up to Visit 8), every month during the next 3 months (up to Visit 11), and every 3 months up to the End-of-Treatment (EOT) Visit. In addition, monthly telephone contacts will be performed after Week 24/Month 6 (Visit 11).
STATISTICAL CONSIDERATIONS	**Sample size determination** The study size is predicated on the overall size of the parent studies; hence, the maximum number of patients to participate will correspond to the sum of the total number of patients enrolled in the DRI12544, PDY14192, EFC13579, and EFC13691 studies. **Analysis population** Safety population is defined as the patients exposed to dupilumab during LTS12551, regardless of the amount of treatment administered. The treatment-emergent period is defined as the time from the first dose of dupilumab in LTS12551 up to the last dose of dupilumab plus 2 weeks (one dose interval) plus 12 weeks (follow-up period duration). **Primary analysis** The primary analysis of this study is the number (n) and percentage (%) of patients experiencing any TEAE, which will be summarized using descriptive statistics. Each adverse event (AE)/TEAE will be coded according to the version of the Medical Dictionary for Regulatory Activities (MedDRA) in effect at sanofi as of the time of database lock. **Analysis of secondary endpoints** All analyses will be done descriptively on the safety population.

	Graphical time course profiles will be provided when appropriate for documentation of outcomes.
DURATION OF STUDY PERIOD (per patient)	**Enrollment period**: • For patients coming from PDY14192, EFC13579, and EFC13691, enrollment should be done at the Combined V1/V2 Visit (ie, on the same day as *the end-of-treatment visit of the parent study* combined with Visit 1 and Visit 2 of LTS12551 study). - Note: A screening period of 0 to 3 weeks was proposed only for patients rolling over from DRI12544. Enrollment from Study DRI12544 is complete, thus the screening period does not apply anymore. **The (open-label) treatment period** is: • 48 weeks (1 year) for patients enrolled after Amendment 04 approval or • 96 weeks (2 years) for patients enrolled prior to Amendment 04 approval. **The post-treatment period** is 12-weeks. The total study duration, per patients, is a maximum of 108 weeks (or 111 weeks considering a maximum screening period of 3 weeks for Study DRI12544) for the patients enrolled prior to Amendment 04 approval and a maximum of 60 weeks for the patients enrolled after Amendment 04 approval.

1 FLOW CHARTS

1.1 GRAPHICAL STUDY DESIGN



D = Study Day; LABA = long-acting beta agonists; LTRA = leukotriene receptor antagonists OCS = oral corticosteroids; q2w = every 2 weeks; V = Study Visit

1.2 STUDY FLOW CHART FOR PATIENTS ENROLLED PRIOR TO AMENDMENT 04

	SOT[a] (D1)																EOT[b]	EOS
Study periods	**Enrollment: Combined V1/V2***		**Open-label treatment period (96 weeks)**														**Post-treatment period (12 weeks)**	
Week (W)	**W0**		**W2**	**W4**	**W6**	**W8**	**W10**	**W12**	**W16**	**W20**	**W24**	**W36**	**W48**	**W60**	**W72**	**W84**	**W96**	**W108**
Month (M)				**M1**		**M2**		**M3**	**M4**	**M5**	**M6**	**M9**	**M12**	**M15**	**M18**	**M21**	**M24**	**M27**
VISIT	1[c]	2[c]	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Enrollment																		
Informed consent	X																	
Patient demography	X																	
Medical & surgical history	X																	
Chest imaging (MRI was already implemented for Germany[d]	X																	
Entry criteria	X																	
Treatment																		
Call IVRS	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
IMP dispense/administration[e]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Injection training/technique observation[f]	X																	
Dispense and download electronic diary/PEF meter (no longer used following amendment 04)[g]																		

	SOT[a] (D1)																EOT[b]	EOS
Study periods	**Enrollment: Combined V1/V2***		**Open-label treatment period (96 weeks)**														**Post-treatment period (12 weeks)**	
Week (W)	**W0**		**W2**	**W4**	**W6**	**W8**	**W10**	**W12**	**W16**	**W20**	**W24**	**W36**	**W48**	**W60**	**W72**	**W84**	**W96**	**W108**
Month (M)				**M1**		**M2**		**M3**	**M4**	**M5**	**M6**	**M9**	**M12**	**M15**	**M18**	**M21**	**M24**	**M27**
VISIT	**1**[c]	**2**[c]	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**
Prior & concomitant medication	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Efficacy																		
Spirometry[h]	X**		X	X		X		X			X		X		X	X	X	X
ACQ-5[i]	X**										X		X					
AQLQ(S)[i]	X**										X		X					
EQ-5D-3L (no longer performed following Amendment 04)																		
Resource utilization[j]	X**							X			X		X		X	X	X	X
Safety																		
Vital signs[k]	X**		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination	X**							X			X		X		X	X	X	X
ECG	X**										X		X				X	X
Adverse event reporting	<- ---------- X ----------→																	
Laboratory testing																		
Clinical laboratories[l]	X**			X				X			X		X		X		X	X
Pregnancy test: Urine[m]	X**			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis[n]	X**							X			X		X		X	X	X	X
PK sampling[o]	X**			X				X			X		X		X		X	X

	SOT[a] (D1)																EOT[b]	EOS
Study periods	**Enrollment: Combined V1/V2***		**Open-label treatment period (96 weeks)**														**Post-treatment period (12 weeks)**	
Week (W)	**W0**		**W2**	**W4**	**W6**	**W8**	**W10**	**W12**	**W16**	**W20**	**W24**	**W36**	**W48**	**W60**	**W72**	**W84**	**W96**	**W108**
Month (M)				**M1**		**M2**		**M3**	**M4**	**M5**	**M6**	**M9**	**M12**	**M15**	**M18**	**M21**	**M24**	**M27**
VISIT	**1**[c]	**2**[c]	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**
ADA[o]	X**							X			X		X		X		X	X
Serum immunoglobulins (no longer performed following Amendment 04)[o]																		
Serum total IgE (no longer performed following Amendment 04)[o]																		
[redacted]																		
Hepatitis B viral load[q]	X**							X			X		X		X		X	
Reminder																		
ICS and controller therapy reminder[r]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Medication withhold reminder[r]	X		X		X		X			X		X		X	X	X	X	
Next visit fasting reminder[r]			X				X			X		X		X		X	X	
Safety follow-up: Monthly phone contact after Week-24[s]												<---------- X ---------->						

Abbreviations: ACQ-5 = Asthma Control Questionnaire-5-question version; ADA = anti-drug antibodies; ALT = alanine aminotransferase; ALP = alkaline phosphatase; ANA = anti-nuclear antibody; AST = aspartate aminotransferase; AQLQ(S)= Asthma Quality of Life Questionnaire (standardized); BUN = blood urea nitrogen; CPK = creatine phosphokinase; ECG = electrocardiogram; e-CRF = electronic case report form; EOS = End-of-Study; EOT = End-of-Treatment; EQ-5D-3L = EuroQol 5 dimensions questionnaire 3-level version; IgE = immunoglobulin E; IMP = Investigational Medicinal Product; IVRS = Interactive Voice Response System; HBcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HCV Ab = hepatitis C virus antibodies; HIV = Human Immunodeficiency Virus; HRCT = High resolution computed tomography; ICS = inhaled corticosteroid; IRB = Institutional Review Board;; LABA = long-acting beta-agonist; LAMA = long-acting muscarinic antagonist; M = (Study) Month; MRI = Magnetic Resonance Imaging; PEF = peak expiratory flow; PK = pharmacokinetic; q2w = every 2 weeks; SOT = Start-of-Treatment; V = (Study) Visit; W = (Study) Week.

* Eligible patients from PDY14192, EFC13579, and EFC13691 studies should rollover into LTS12551 the same day as the *end-of-treatment visit of the parent study* (which will be combined with V1 and V2 of LTS12551 study).

** Data for the baseline procedures at D1 will be obtained from the *end-of-treatment visit of the PDY14192, EFC13579, and EFC13691 parent studies* (see Section 10).

a Start-of-Treatment/Enrollment (Combined V1/V2) Visit for patients from PDY14192, EFC13579, and EFC13691 studies, after having performed the assessments of *end-of-treatment visit in the parent study*. Visit windows for subsequent visits are ±3 days in the first 12 weeks and ±1 week for the remainder of the study.

b Patients who discontinue treatment early are scheduled, as soon as possible, for the EOT Visit, followed by the EOS Visit. If LTS12551 is terminated, then the next visit for all involved patients will be the EOT Visit, followed by the EOS Visit.

c Eligible patients in PDY14192, EFC13579, and EFC13691 studies should rollover into LTS12551 the same day as the *end-of-treatment visit of the parent study*. Visit 1 and Visit 2 of LTS12551 study should be combined with the *end-of-treatment visit of the PDY14192, EFC13579 or EFC13691 parent studies*.

d Chest imaging: Chest X-ray, MRI or HRCT will be performed only if no chest imaging results obtained within the previous 12 months are available. At the Investigator's discretion (and based on local regulations) chest imaging may be performed during the study (eg, 1 year after the last chest imaging assessment or after a year's treatment).

e Every 2 weeks (q2w) the IMP administrations must be separated by at least 11 days. The treatment period visits occur q2w up to Visit 8 (Month 3), every month up to Visit 11 (Month 6), and every 3 months for the remaining duration of the study. For IMP administrations coinciding with treatment period visits, patients will be monitored at the study site for a minimum of 30 minutes after injections. If the patient or the Investigator decides not to administer IMP at home, the injections can be performed at the study site by way of unscheduled visits.

f The injection training is for patients who are willing to perform self-injection. The Investigator or delegate should review the patient's self-administration technique at the Combined V1/V2 Visit.

g Electronic diary / PEF meter will no longer be used in this study due to Amendment 04 (see Section 10.6).

h Spirometry should be done at the study site approximately the same time of the day (preferably in the morning, but it could be done at a different time of the day). Spirometry will be performed after a washout period of bronchodilators according to their action duration (for example, withholding the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours and withholding the last dose of LABA for at least 12 hours [ultra-LABA like vilanterol should be withheld for at least 24 hours] and withholding the last dose of LAMA for at least 24 hours). Also spirometry should be performed prior to IMP administration, as applicable.

i ACQ-5 and AQLQ(S) paper forms are completed during clinic visits. Data will be collected into the e-CRF. Note: For patients from PDY14192 study, AQLQ(S) paper form must be completed at the Combined V1/V2 Visit as part of the LTS12551 assessments.

j A questionnaire of health care resource utilization (reliever medication, specialist visit, hospitalization, emergency or urgent medical care facility visit, outcome, sick leaves, etc). Data will be collected into the e-CRF.

k Vital signs: blood pressure (mmHg), heart rate (beats per minute), respiratory rate (breaths per minute), body temperature (degrees Celsius), and body weight (kg) will be measured at each visit. Height (cm) will only be measured at the Enrollment (Combined V1/V2) Visit. Vital signs will be measured in the sitting position using the same arm at each visit and will be measured prior to IMP administration at the clinic visits.

l Clinical laboratories: Hematology: blood count (erythrocytes, hemoglobin, hematocrit, leukocytes), differential blood count (neutrophils, lymphocytes, monocytes, eosinophils, basophils), and platelets. Serum chemistry: total bilirubin (in case of values above the normal range, differentiation in conjugated and non-conjugated bilirubin), ALT, AST, ALP, total protein, albumin, total cholesterol, CPK, glucose, creatinine, BUN, uric acid, bicarbonate and electrolytes (sodium, potassium, chloride). At enrollment, clinical laboratory testing results are collected from the parent study for HBsAg, HBsAb, HBcAb, total HBcAb, HCVAb, HIV screen (Anti-HIV-1 and HIV-2 antibodies) and ANA (ie, since these tests were scheduled at the visit prior to the *end-of-treatment visit of the PDY14192, EFC13579 or EFC13691 parent study*). In addition, results from hepatitis B virus DNA (HBV DNA) testing and HCV virus RNA (HCV RNA) testing should be collected for those patients who were HBsAg negative and HBcAb positive, and/or HCVAb positive; also anti--double-strand DNA antibody results for patients with ANA positive (≥1:160 titer). Note: Japanese patients who have rolled over from DRI12544 study should be retested for hepatitis B (HBsAg, HBsAb, and HBcAb), after Visit 1, at any time during the LTS12551 study, via the earliest scheduled study visit, after IRB approval for Local Amendment 03 (Japan).

m A negative serum pregnancy test was obtained at Visit 1, prior to Start-of-Treatment, for patients coming from DRI12544. Qualifying pregnancy test for patients coming from PDY14192, EFC13579, and EFC13691 studies will be the urine pregnancy test.

n Urinalysis: pH, glucose, ketones, leukocyte esterase blood, protein, nitrate, urobilinogen, and bilirubin (by dipstick).

o Samples will be collected prior to IMP administration, during the treatment period. Note: Serum immunoglobulins (including IgE) will no longer be assayed in LTS12551 study due to Amendment 04.

[redacted]

q This is only applicable for patients in Japan (or other countries/regions if there is a local regulatory requirement) who are HBsAg negative and HBsAb positive at screening during the parent study or at the additional test due to Local Amendment 03 (Japan).

r Remind patient to continue the background therapy of ICS and controller therapies; remind patient to withhold bronchodilators according to their action duration, for example, withholding the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours and withholding the last dose of LABA for at least 12 hours (ultra-LABA like vilanterol should be withheld for at least 24 hours) and withholding the last dose of LAMA for at least 24 hours prior to next visit; remind patient for the next visit in the fasting state.

s Monthly telephone contact with patient after Week-24 to collect safety information.

1.3 STUDY FLOW CHART FOR PATIENTS ENROLLED AFTER AMENDMENT 04

	SOT[a] (D1)												EOT[b]	EOS
Study periods	**Enrollment: Combined V1/V2***		**Open-label treatment period (48 weeks)**										**Post-treatment period (12 weeks)**	
Week (W)	**W0**		**W2**	**W4**	**W6**	**W8**	**W10**	**W12**	**W16**	**W20**	**W24**	**W36**	**W48**	**W60**
Month (M)				**M1**		**M2**		**M3**	**M4**	**M5**	**M6**	**M9**	**M12**	**M15**
VISIT	**1**[c]	**2**[c]	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**17**	**18**
Enrollment														
Informed consent	X													
Patient demography	X													
Medical & surgical history	X													
Chest imaging (MRI was already implemented for Germany)[d]	X													
Entry criteria	X													
Treatment														
Call IVRS	X		X	X	X	X	X	X	X	X	X	X	X	X
IMP dispense/administration[e]	X		X	X	X	X	X	X	X	X	X	X		
Injection training / technique observation[f]	X													
Dispense and download electronic diary/PEF meter (no longer used following Amendment t04)[g]														
Prior & concomitant medication	X		X	X	X	X	X	X	X	X	X	X	X	X
Efficacy														
Spirometry[h]	X**		X	X		X		X			X		X	X

	SOT[a] (D1)												EOT[b]	EOS
Study periods	**Enrollment: Combined V1/V2***		**Open-label treatment period (48 weeks)**										**Post-treatment period (12 weeks)**	
Week (W)	**W0**		**W2**	**W4**	**W6**	**W8**	**W10**	**W12**	**W16**	**W20**	**W24**	**W36**	**W48**	**W60**
Month (M)				**M1**		**M2**		**M3**	**M4**	**M5**	**M6**	**M9**	**M12**	**M15**
VISIT	**1**[c]	**2**[c]	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**17**	**18**
ACQ-5[i]	X**										X		X	
AQLQ(S)[i]	X**										X		X	
EQ-5D-3L (no longer performed following Amendment 04)														
Resource utilization[j]	X**							X			X		X	X
Safety														
Vital signs[k]	X**		X	X	X	X	X	X	X	X	X	X	X	X
Physical examination	X**							X			X		X	X
ECG	X**										X		X	X
Adverse event reporting	<- ---------- X ----------→													
Laboratory testing														
Clinical laboratories[l]	X**			X				X			X		X	X
Pregnancy test: Urine[m]	X**			X	X	X	X	X	X	X	X	X	X	X
Urinalysis[n]	X**							X			X		X	X
PK sampling[o]	X**			X				X			X		X	X
ADA[o]	X**							X			X		X	X
Serum immunoglobulins (no longer performed following Amendment 04)[o]														
Serum total IgE (no longer performed following Amendment 04)[o]														

	SOT[a] (D1)												EOT[b]	EOS
Study periods	**Enrollment: Combined V1/V2***		**Open-label treatment period (48 weeks)**										**Post-treatment period (12 weeks)**	
Week (W)	**W0**		**W2**	**W4**	**W6**	**W8**	**W10**	**W12**	**W16**	**W20**	**W24**	**W36**	**W48**	**W60**
Month (M)				**M1**		**M2**		**M3**	**M4**	**M5**	**M6**	**M9**	**M12**	**M15**
VISIT	**1**[c]	**2**[c]	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**17**	**18**
Hepatitis B viral load[q]	X**							X			X		X	
Reminder														
ICS and controller therapy reminder[r]	X		X	X	X	X	X	X	X	X	X	X	X	
Medication withhold reminder[r]	X		X		X		X			X	X	X	X	
Next visit fasting reminder[r]			X				X			X		X	X	
Safety follow-up: Monthly phone contact after Week-24[s]												←---------- X ----------→		

Abbreviations: ACQ-5 = Asthma Control Questionnaire 5-question version; ADA = Anti-drug antibodies; ALT = alanine aminotransferase; ALP = alkaline phosphatase; ANA = anti-nuclear antibody; AST = aspartate aminotransferase; AQLQ(S)= Asthma Quality of Life Questionnaire (standardized); BUN = blood urea nitrogen; CPK = creatine phosphokinase; ECG = Electrocardiogram; e-CRF = electronic case report form; EOS = End-of-Study; EOT = End-of-Treatment; EQ-5D-3L = EuroQol 5 dimensions questionnaire, 3-level version; IgE = immunoglobulin E; IMP = Investigational Medicinal Product; IVRS = Interactive Voice Response System; HBcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HCV Ab = hepatitis C virus antibodies; HIV = Human Immunodeficiency Virus; HRCT = high resolution computed tomography; ICS = inhaled corticosteroid; IRB = Institutional Review Board; LABA = long-acting beta-agonist; LAMA = long-acting muscarinic antagonist; M = (Study) Month; MRI = Magnetic Resonance Imaging; PEF = peak expiratory flow; PK = pharmacokinetic; q2w = every 2 weeks; SOT = Start-of-Treatment; V = (Study) Visit; W = (Study) Week.

* Eligible patients from PDY14192, EFC13579, and EFC13691 studies should rollover into LTS12551 the same day as the *end-of-treatment visit of the parent study* (which will be combined with V1 and V2 of LTS12551 study).

** Data for the baseline procedures at D1 will be obtained from the *end-of-treatment visit of the PDY14192, EFC13579 or EFC13691 parent studies* (see Section 10).

a Start-of-Treatment/Enrollment (Combined V1/V2) Visit for patients from PDY14192, EFC13579, and EFC13691 studies, after having performed the assessments of *end-of-treatment visit in the parent study*. Visit windows for subsequent visits are ±3 days in the first 12 weeks and ±1 week for the remainder of the study.

b Patients who discontinue treatment early are scheduled, as soon as possible, for the EOT Visit, followed by the EOS Visit. If LTS12551 is terminated, then the next visit for all involved patients will be the EOT Visit, followed by the EOS Visit.

c Eligible patients in PDY14192, EFC13579, and EFC13691 studies should rollover into LTS12551 the same day as the *end-of-treatment visit of the parent study*. Visit 1 and Visit 2 of LTS12551 study should be combined with the *end-of-treatment visit of the PDY14192, EFC13579 or EFC13691 parent* studies.

d Chest imaging: Chest X-ray, MRI or HRCT will be performed only if no chest imaging results obtained within the previous 12 months are available. At the Investigator's discretion (and based on local regulations) chest imaging may be performed during the study (eg, 1 year after the last chest imaging assessment or after a year's treatment).

e Every 2 weeks (q2w) the IMP administrations must be separated by at least 11 days. The treatment period visits occur q2w up to Visit 8 (Month 3), every month up to Visit 11 (Month 6), and every 3 months for the remaining duration of the study. For IMP administrations coinciding with treatment period visits, patients will be monitored at the study site for a minimum of 30 minutes after injections. If the patient or the Investigator decides not to administer IMP at home, the injections can be performed at the study site by way of unscheduled visits.

f The injection training is for patients who are willing to perform self-injection. The Investigator or delegate should review the patient's self-administration technique at the Combined V1/V2 Visit.

g Electronic diary/PEF meter will no longer be used in this study due to Amendment 04 (see Section 10.6).

h Spirometry should be done at the study site approximately the same time of the day (preferably in the morning, but it could be done at a different time of the day). Spirometry will be performed after a washout period of bronchodilators according to their action duration (for example, withholding the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours and withholding the last dose of LABA for at least 12 hours [ultra-LABA like vilanterol should be withheld for at least 24 hours] and withholding the last dose of LAMA for at least 24 hours). Also spirometry should be performed prior to IMP administration, as applicable.

i ACQ-5 and AQLQ(S) paper forms are completed during clinic visits. Data will be collected into the e-CRF. Note: For patients from PDY14192 study, AQLQ(S) paper form will be completed at the Combined V1/V2 Visit.

j A questionnaire of health care resource utilization (reliever medication, specialist visit, hospitalization, emergency or urgent medical care facility visit, outcome, sick leaves, etc). Data will be collected into the e-CRF.

k Vital signs: blood pressure (mmHg), heart rate (beats per minute), respiratory rate (breaths per minute), body temperature (degrees Celsius), and body weight (kg) will be measured at each visit. Height (cm) will only be measured at the Enrollment (Combined V1/V2) Visit. Vital signs will be measured in the sitting position using the same arm at each visit and will be measured prior to IMP administration at the clinic visits.

l Clinical laboratories: Hematology: blood count (erythrocytes, hemoglobin, hematocrit, leukocytes), differential blood count (neutrophils, lymphocytes, monocytes, eosinophils, basophils), and platelets. Serum chemistry: total bilirubin (in case of values above the normal range, differentiation in conjugated and non-conjugated bilirubin), ALT, AST, ALP, total protein, albumin, total cholesterol, CPK, glucose, creatinine, BUN, uric acid, bicarbonate and electrolytes (sodium, potassium, chloride). At enrollment, clinical laboratory testing results study are collected from the parent study for HBsAg, HBsAb, HBcAb, total HBcAb, HCVAb, HIV screen (Anti-HIV-1 and HIV-2 antibodies) and ANA (ie, since these tests were scheduled at the visit prior to the *end-of-treatment visit of the PDY14192, EFC13579 or EFC13691 parent studies*). In addition, results from hepatitis B virus DNA (HBV DNA) testing and HCV virus RNA (HCV RNA) testing should be collected for those patients who were HBsAg negative and HBcAb positive, and/or HCVAb positive; also anti-double-strand DNA antibody results for patients with ANA positive (≥1:160 titer). Note: Japanese patients who have rolled over from DRI12544 study should be retested for hepatitis B (HBsAg, HBsAb, and HBcAb), after Visit 1, at any time during the LTS12551 study, via the earliest scheduled study visit, after IRB approval for Local Amendment 03 (Japan).

m A negative serum pregnancy test was obtained at Visit 1, prior to Start-of-Treatment, for patients coming from DRI12544. Qualifying pregnancy test for patients coming from PDY14192, EFC13579, and EFC13691 studies will be the urine pregnancy test.

n Urinalysis: pH, glucose, ketones, leukocyte esterase blood, protein, nitrate, urobilinogen, and bilirubin (by dipstick).

o Samples will be collected prior to IMP administration, during the treatment period. Note: Serum immunoglobulin (including IgE) will no longer be assayed in LTS12551 study due to Amendment 04.

[redacted]

q This is only applicable for patients in Japan (or other countries/regions if there is a local regulatory requirement) who are HBsAg negative and HBsAb positive at screening during the parent study or at the additional test due to Local Amendment 03 (Japan).

r Remind patient to continue the background therapy of ICS and controller therapies; remind patient to withhold bronchodilators according to their action duration, for example, withholding the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours, and withholding the last dose of LABA for at least 12 hours (ultra-LABA like vilanterol should be withheld for at least 24 hours) and withholding the last dose of LAMA for at least 24 hours prior to next visit; remind patient for the next visit in the fasting state.

s Monthly telephone contact with patient after Week-24 to collect safety information.

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3 LIST OF ABBREVIATIONS

ACQ5:	Asthma Control Questionnaire-5-question version
ADA:	anti-drug antibody
AE:	adverse event
AESI:	adverse events of special interest
ALP:	alkaline phosphatase
ALT:	alanine aminotransferase
ANA:	anti-nuclear antibody
AQLQ(S):	Asthma Quality of Life Questionnaire-Standardized
AST:	aspartate aminotransferase
ATS:	American Thoracic Society
BUN:	blood urea nitrogen
CPK:	creatine phosphokinase
CSR:	clinical study report
CYP:	cytochrome
DMC:	Data Monitoring Committee
DRF:	discrepancy resolution form
ECG:	electrocardiogram
e-CRF:	electronic case report form
EOS:	End-of-Study
EOT:	End-of-Treatment
EQ-5D-3L:	EuroQol 5 dimensions questionnaire 3-level version
FEV_1:	forced expiratory volume in 1 second
GCP:	Good Clinical Practice, good clinical practice
HBcAb:	hepatitis B core antibody
HBsAg:	hepatitis B surface antigen
HBV DNA:	hepatitis B virus deoxyribonucleic acid
HCV Ab:	hepatitis C virus antibodies
HCV RNA:	hepatitis C virus ribonucleic acid
HIV:	human immunodeficiency virus
HLGT:	high level group term
HLT:	high level term
HRCT:	high resolution computed tomography
ICF:	Informed Consent Form
ICH:	International Council on Harmonisation
ICS:	inhaled corticosteroids
IgE:	immunoglobulin E
IgM:	immunoglobulin M
IL-13:	interleukin-13
IL-4:	interleukin-4
IL-4Rα:	interleukin-4 receptor alpha subunit
IMP:	Investigational Medicinal Product

IRB/IEC:	Institutional Review Board / Institutional Ethics Committee
IVRS/IWRS:	Interactive Voice Response System/Interactive Web Response System
LABA:	Long acting beta adrenoceptor agonists
LAMA:	long-acting muscarinic antagonist
LFT:	liver function test
LTRA:	leukotriene receptor antagonists
MCID:	Minimal Clinically Important Difference
MDI:	metered dose inhalers
MRI:	Magnetic Resonance Imaging
OCS:	oral cortiocosteroids
PCSA:	potentially clinically significant abnormality
PD:	pharmacodynamics
PEF:	peak expiratory flow
PT:	preferred term
SAE:	serious adverse events
SAP:	statistical analysis plan
SC:	subcutaneous
SD:	standard deviation
SEM:	standard error of the mean
SOC:	system organ class
TB:	tuberculosis
TEAE:	treatment-emergent adverse events
Th2:	type 2 helper T-cell
ULN:	upper limit of normal
VAS:	Visual Analogue Scale

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. These patients account for many hospital admissions, use of emergency services, and unscheduled physician visits (1).

Additionally, the long-term adverse effects of systemic and inhaled corticosteroids (ICS) on bone metabolism, adrenal function, and growth in children lead to attempts to minimize the amount of corticosteroid usage. Lastly, the consequences of unresponsiveness to therapy or lack of compliance with therapy is loss of asthma control and ultimately, asthma exacerbation and medical sequelae of such events.

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 T-helper cell-2 response. Up-regulation of interleukin-4 (IL-4) and interleukin-13 (IL-13) has been implicated as an important inflammatory component of asthma disease progression. Dupilumab, a fully human monoclonal antibody (mAb) 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, interleukin 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.

4.2 RATIONALE

An initial demonstration of the efficacy and safety of dupilumab was provided in the randomized, double-blind, placebo-controlled, parallel-group Phase 2a study (ACT11457). This study investigated the effects of dupilumab administered subcutaneously (SC) once weekly for 12 weeks as compared to placebo on the incidence of asthma exacerbations in patients with persistent moderate to severe eosinophilic asthma.

The primary endpoint was the occurrence of an asthma exacerbation; the secondary endpoints included a range of measures of asthma control. Effects on various type 2 helper T-cell (Th2) associated biomarkers and safety and tolerability are also evaluated (3).The ACT11457 study showed an 87% reduction in asthma exacerbations after 12-week of treatment with dupilumab (5.8%) versus placebo (44.2%). A rapid improvement of lung function, as measured by forced expiratory volume in 1 second (FEV_1) and reduction of Th2-associated biomarkers levels were also observed (3).

The DRI12544 study (phase 2b), a randomized, double-blind, placebo-controlled, dose-ranging study, evaluated several dose regimens of dupilumab in patients with moderate to severe uncontrolled asthma (300 mg every 2 weeks [q2w] with a 600 mg loading dose, 200 mg q2w with a 400 mg loading dose, 300 mg every 4 weeks [q4w] with a 600 mg loading dose, 200 mg q4w with a 400 mg loading dose), administered over 24 weeks. The primary efficacy endpoint was the change from baseline in FEV_1 at Week 12, in patients with baseline blood eosinophil counts of at least 300 eosinophils per µL (HEos). Several secondary efficacy endpoints were evaluated including: the annualized severe asthma exacerbation rate, percentage change from baseline in FEV_1, time to severe exacerbation, etc. For the primary endpoint, all dupilumab dose regimens (except for the 200 mg q4w) showed a clinically meaningful and statistically significant improvement in FEV_1 at Week 12 in comparison with placebo in the high blood eosinophil count (HEos) population. For the secondary endpoints assessed in the overall population and the subgroup with eosinophil counts of fewer than 300 eosinophils per µL, dupilumab q2w (both the 200 mg and 300 mg) resulted in significant increases in FEV_1 (L) compared with placebo at Week 12 that were sustained through to week 24. Both doses of dupilumab q2w also resulted in significant increases in percentage change in FEV_1 compared with placebo through to Week 24 in the overall population and in the two subgroups. In addition, both the 200 mg q2w and 300 mg q2w dose regimens of dupilumab demonstrated as compared to placebo, a significant reduction in the annualized rate of severe asthma exacerbations and a delayed time to first severe asthma exacerbation event, during the treatment period.(4)

LTS12551 is 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 study. The dose of 300 mg q2w, which is the highest dose administered in Study DRI12544 and the phase 3 pivotal Study EFC13579, has been selected as the dose to be evaluated in Study LTS12551. This dosing regimen is within the range of SC doses administered to healthy volunteers in R668-AS-0907 study and a higher dosing regimen of 300 mg qw was tested in the ACT11457. Additionally, 300 mg q2w (for 24 weeks) SC is the highest dose-regimen that was tested in DRI12544, a randomized, double-blind, placebo controlled dose-ranging efficacy study (phase 2b). Treatment with dupilumab was generally well tolerated in these previous studies. The dosing regimen of 300 mg SC q2w is also the higher of the two doses selected for Study EFC13579 (QUEST), it is anticipated to saturate the targeted receptors and to allow for the attainment of an optimally efficacious concentration. Furthermore, in Study DRI12544, treatment effects on lung function and biomarkers of inflammation were similar at 200 mg q2w and 300 mg q2w, suggesting a plateauing of the dose-response below exposures achieved at 300 mg qw.

From a safety perspective, the mean exposure following a dose of 300 mg of dupilumab q2w at steady state is 2 to 3 times below the exposure range of SC doses of 300 mg administered every

week in the Proof of Concept studies in asthma (ACT11457) and atopic dermatitis (R668-AD1117).

From an efficacy perspective the dosing regimen of 300 mg q2w, added to a medium-to-high dose ICS + Long-acting β adrenoceptor agonists (LABA) in adult patients with uncontrolled persistent asthma, showed a clinically meaningful and highly statistically significant reduction in the relative risk of severe exacerbations, improvement in lung function (FEV_1) and asthma symptoms (Asthma Control Questionnaire 5-question Version [ACQ5]) (4).

A loading dose of 600 mg dupilumab was administered on Day 1 for patients enrolling into LTS12551 from the DRI12544 study after a 3-month dupilumab-free follow-up period, which allow systemic concentrations to reach steady state faster, and potentially reduce the time to clinical effect. Loading dose will not apply to patients from other parent studies, as they will rollover into LTS12551 the same day as the end-of-treatment (EOT) visit in the parent study and thus there will be no interruption in treatment.

The dose regimens used in the 3 ongoing parent studies were 300 mg q2w and 200 mg q2w versus placebo (52 week treatment) in study EFC13579; 300 mg q2w versus placebo (24 week treatment) in study EFC13691); and 300 mg q2w versus placebo (12 weeks treatment) in study PDY14192 (Phase 2).

The LTS12551 study is intended to provide a long-term safety database to better identify potential late onset adverse events (AEs) associated with the use of dupilumab given on top of ICS/LABA or ICS and other controller background therapies (LABA, leukotriene receptor antagonists (LTRA), long-acting muscarinic antagonist (LAMA), theophylline, etc) including oral corticosteroids (OCS). Efficacy, dupilumab concentration and anti-dupilumab antibody and associated biomarkers will also be analyzed in the study to deepen the scientific understanding of anti-drug antibody (ADA) development and the change of serum biomarkers over the course of the study.

5 STUDY OBJECTIVES

5.1 PRIMARY

To evaluate the long-term safety and tolerability of dupilumab in patients with asthma who participated in a previous dupilumab asthma clinical study (DRI12544, PDY14192, EFC13579, EFC13691).

5.2 SECONDARY

- To assess the long-term efficacy of dupilumab in patients with asthma who participated in a previous dupilumab asthma clinical study.
- To evaluate dupilumab in patients with asthma who participated in a previous dupilumab asthma clinical study, with regard to:
  - Systemic exposure;
  - Anti-drug antibodies;
  - Biomarkers.

6 STUDY DESIGN

6.1 DESCRIPTION OF THE PROTOCOL

Multinational, multicenter, open-label, extension study evaluating dupilumab 300 mg (SC) q2w for 1-year (48 weeks) or 2-year (96 weeks) treatment duration. Patients enrolled prior to Amendment 04 approval will continue to participate in the 2-year treatment duration; patients enrolled after Amendment 04 approval will participate in the 1-year treatment duration.

At enrollment, patients will be on medium or high dose of ICS and at least one other asthma controller medication, as maintained during the parent study in which they participated (including asthma background controller therapy with OCS only for patients from Study EFC13691).

For a schematic study design please see Section 1.1.

6.2 DURATION OF STUDY PARTICIPATION

6.2.1 Duration of study participation for each patient

LTS12551 study consists of 3 periods (See Section 10):

Enrollment period: Combined V1/V2 Visit: Eligible patients from PDY14192, EFC13579, and EFC13691 studies should rollover into LTS12551 the same day as *the end-of-treatment visit of the parent study*.

Note: A screening period of 0 to 3 weeks was proposed only for patients rolling over from DRI12544. Enrollment from Study DRI12544 is complete, thus the screening period does not apply anymore.

Treatment period: 48 or 96 weeks open-label treatment.

Patients enrolled prior to Amendment 04 approval, will continue to participate in the 2-year treatment duration; patients enrolled after Amendment 04 approval will participate in the 1-year treatment duration. During the open-label treatment period, patients will continue taking their background controller therapy, as maintained during the parent study or as modified based on Investigator's judgment.

Post-treatment period: 12 weeks.

Upon completion of the open-label treatment period (or following early discontinuation of Investigational Medicinal Product [IMP]) patients will continue into the post-treatment period. During this period, patients will continue their background controller therapy, as maintained during the open-label treatment period or as modified based on Investigator's judgment (eg, taking into account the reduction of dupilumab levels over time upon completion of the treatment period).

6.2.2 Determination of end of clinical trial (all patients)

The end of the clinical trial in all participating study sites is reached when the last patient last visit is completed as protocol defined.

6.3 INTERIM ANALYSIS

Interim study reports may be prepared to support regulatory submissions of an indication in the dupilumab project or other purposes. No alpha adjustment is needed for the final clinical study report (CSR).

6.4 STUDY COMMITTEES

6.4.1 Data monitoring committee

A data monitoring committee (DMC) with members' who are independent from the Sponsor and Investigators is commissioned for the dupilumab clinical development program. This committee is comprised of externally-based individuals with expertise in the diseases under study, biostatistics, or clinical research. The DMC will monitor the safety data of patients at regular intervals and is responsible for providing recommendations for protecting the safety and ensuring the welfare of these patients and provide sanofi with appropriate recommendations in a timely manner to ensure the welfare and safety of the study patients.

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

7 SELECTION OF PATIENTS

7.1 INCLUSION CRITERIA

I 01. Patients with asthma who completed the treatment period in a previous dupilumab asthma clinical study (ie, PDY14192, EFC13579 or EFC13691) or patients with asthma who completed the treatment and follow-up periods in pervious dupilumab asthma Study DRI12544.

I 02. Patient is on background dose of moderate or high dose ICS, as maintained during the parent study in which they participated, in combination with a second controller (and/or OCS for those patients from EFC13691). Patients requiring a third controller medication are allowed (eg, LABA, LTRA, methylxanthines, etc).

I 03. Signed written informed consent.

7.2 EXCLUSION CRITERIA

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

7.2.1 Exclusion criteria related to study methodology

E 01. Deleted.

E 02. Chronic obstructive pulmonary disease or other lung diseases (eg, emphysema, idiopathic pulmonary fibrosis, Churg-Strauss syndrome, allergic bronchopulmonary aspergillosis) which impair pulmonary function tests.

E 03. Current smoker or cessation of smoking within 6 months prior to enrollment.

E 04. Clinically significant comorbidity / lung disease other than asthma.

E 05. Alcohol abuse or drug abuse.

E 06. Inability to follow the procedures of the study / noncompliance (eg, due to language problems or psychological disorders).

E 07. Deleted.

E 08. Deleted.

E 09. Deleted.

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

E 11. Deleted.

E 12. Patient is Investigator or any Subinvestigator, research assistant, pharmacist, study coordinator, other staff or relative thereof directly involved in the conduct of the protocol.

E 13. Deleted.

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

E 14. Deleted.

E 15. Deleted.

7.2.3 Exclusion criteria related to the current knowledge of sanofi compound

E 16. 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 of the patient in this study or would require permanent IMP discontinuation.

E 17. Pregnant or breastfeeding women.

E 18. Women of childbearing potential (premenopausal female biologically capable of becoming pregnant) 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, including the 12-week follow-up period:
  - Established use of oral, injected, implanted or inserted hormonal contraceptive.
  - Intrauterine device (IUD) with copper or intrauterine system (IUS) 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 the study, the vasectomized male partner should be the sole partner for that patient.
  - True abstinence; periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) is not an acceptable method of contraception.
  - Menopausal women (defined as at least 12 consecutive months without menses) are not required to use additional contraception.

E 19. Diagnosed active parasitic infection; suspected or high risk of parasitic infection, unless clinical and (if necessary) laboratory assessments have ruled out active infection before enrolment.

E 20. History of human immunodeficiency virus (HIV) infection or positive HIV screen (Anti-HIV-1 and HIV-2 antibodies).

E 21. Deleted.

E 22. Deleted.

E 23. Live, attenuated vaccinations within 12 weeks prior to enrollment or planned live, attenuated vaccinations during the study (see Appendix A).

E 24. Patients with active autoimmune disease or patients using immunosuppressive therapy for autoimmune disease (eg, rheumatoid arthritis, inflammatory bowel disease, primary biliary cirrhosis, systemic lupus erythematosus, multiple sclerosis, etc) or patients who are suspected of having high risk for developing autoimmune disease.

E 25. Patients with any of the following result at enrolment:

- Positive (or indeterminate) hepatitis B surface antigen (HBsAg); or
- Positive Immunoglobulin M (IgM) hepatitis B core antibody (HBcAb); or
- Positive total HBcAb confirmed by positive hepatitis B virus deoxyribonucleic acid (HBV DNA); or
- Positive hepatitis C virus antibodies (HCV Ab) confirmed by positive hepatitis C virus ribonucleic acid (HCV RNA)

E 26. Patients who experienced any hypersensitivity reactions to IMP in the previous dupilumab asthma study, which, in the opinion of the Investigator, could indicate that continued treatment with dupilumab may present an unreasonable risk for the patient.

E 27. Deleted.

E 28. Deleted.

E 29. Deleted.

E 30. Deleted.

E 31. Blood eosinophils >1500 cells/mm^3.

E 32. History of malignancy within 5 years before the screening visit, 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

8.1.1 Dupilumab

Note: At the time of Amendment 04, all patients have been transitioned to prefilled syringes.

Dupilumab is supplied as a sterile aqueous solution for SC injection at the concentration of 150 mg/mL in glass prefilled syringes (2.25 mL total volume) to deliver 300 mg in the extractable 2 mL volume.

8.1.2 Preparation of investigational product

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

8.1.3 Dose schedule

The IMP is administered every 14±3 days (q2w). The consecutive doses of the IMP must be separated by ≥11 days to avoid an overdose. Reminder: Patients will be monitored for any signs or symptoms of hypersensitivity reactions for a minimum of 30 minutes after IMP injection.

At the Enrollment (Combined V1/V2) Visit, the Investigator or delegate will train the patient (and/or caregiver[s]) how to prepare and inject IMP for the first injection or if the patient is already self-injecting (in the parent study), the Investigator or delegate will supervise the self-injection.

For subsequent doses, which are not given at the study site, specific pages will be provided to the patients to record information related to the injections. The pages will be kept as source data in the patient's study file.

If the patient (or caregiver) is unable or unwilling to administer IMP, arrangements must be made for qualified site personnel and/or healthcare professionals (eg, visiting nurse service) to administer IMP for the doses that are not scheduled to be given at the study site.

If the study visit is not performed at the study site as scheduled, the dose will be administered by the patient and/or their caregiver/healthcare professional, or arrangements must be made for a visit to the site to administer the IMP.

When IMP is administered at home, the patients must be advised by the site staff, to self-monitor for at least 30 minutes after administration for potential signs and symptoms that may suggest a hypersensitivity reaction.

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 trained by Investigator or delegate) or health care professional but not the patient themselves. For each injection, the anatomic site of administration will be recorded in the electronic case report form (e-CRF) and, as applicable, the home dosing diary.

Detailed instructions for transport, storage, preparation, and administration of IMP are provided to the patient.

Patients will complete a home dosing diary to document compliance with self-injection (or parent or caregiver injection) of IMP.

8.2 NONINVESTIGATIONAL MEDICINAL PRODUCT(S)

8.2.1 Inhaled corticosteroid and controller therapies

Inhaled corticosteroid and other controller therapies (ie, LABA, LTRA, LAMA, theophylline, etc) and OCS for patients from EFC13691 will be collected in the e-CRF.

8.2.1.1 Enrollment V1/V2 visit (combined with the end-of-treatment visit of parent study)

Patients will be on background asthma therapy of moderate or high-dose ICS as maintained in the parent study. Patients will also be using additional asthma controller therapies initiated during the parent study.

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

8.2.1.2 Open-label treatment period

During the open-label treatment period, patients will continue the background therapy dose regimen as maintained in the parent study or as modified based on Investigator's judgment.

See Appendix B for the most commonly used asthma controller therapies.

8.2.1.3 Post-treatment period

Upon completion of the open-label treatment period (or following early discontinuation of IMP) patients will continue into the post-treatment period, with their background controller therapy dose regimen as maintained over the open-label treatment period or as modified based on Investigator's judgment (eg, taking into account the reduction of dupilumab levels over time upon completion of the treatment period).

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 levalabuterol/levosalbutamol may be used as an alternative delivery method.

Study personnel should convert salbutamol/albuterol nebulizer and levosalbutamol/levalbuterol nebulizer use as shown on Table 1 and Table 2:

Table 1 - Conversion from Salbutamol/Albuterol Nebulizer Solution to Puffs

Salbutamol/Albuterol Nebulizer Solution – Total Daily Dose (mg)	Number of Puffs*
1.26	2
2.5	4
5	8
7.5	12
10	16

*Conversion factor: salbutamol/albuterol nebulizer solution (2.5 mg) corresponds to 4 puffs.

Example: Patient received 3 salbutamol/albuterol nebulizer treatments (2.5 mg/treatment) between 7 and 11 AM. Total daily = 7.5 mg (12 puffs).

Table 2 - Conversion from Levosalbutamol/Levalbuterol Nebulizer Solution to Puffs

Levosalbutamol/Levalbuterol Nebulizer Solution – Total Daily Dose (mg)	Number of Puffs
1.25	4
2.5	8
3.75	12
5	16

Example of levosalbutamol/levalbuterol Nebulizer-to-Puff Conversion: Patient received 3 levosalbutamol/levalbuterol nebulizer treatments (1.25 mg/treatment) between 7 and 11 AM. Total daily = 3.75 mg (12 puffs).

All other reliever medications rather 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 study medication will be administered only to patients included in this study following the procedures described in the clinical study protocol. The 7-digits serialized treatment kit number will be generated centrally by sanofi clinical supply team. The IMPs are packaged in accordance with this list.

The patients will be identified by the same identification number used in the parent study. The investigational site will enter the patient tracking information for patient identification number, into the Interactive Voice Response System/Interactive Web Response System (IVRS/IWRS) during each scheduled protocol visit. The treatment allocation will be performed centrally by IVRS/IWRS. The clinical site coordinator will document the patient number and the treatment kit number in the e-CRF and in the patient's source documents, and the patient number on the IMP label prior to dispensing to the patient.

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

8.5 PACKAGING AND LABELING

Note: At the time of Amendment 04, all patients have been transitioned to prefilled syringes.

The IMP dupilumab will be packaged in single-use prefilled syringes. One kit box will contain one prefilled syringe. When dupilumab administration occurs at home, enough kit boxes will be given to the patients for the period of the treatment until the next study visit.

Each packaging component will be labeled with the project 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. 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 (36°F to 46°F) 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 should be managed according to the rules provided by the Sponsor.

8.7 RESPONSIBILITIES

The Investigator, the hospital pharmacist, or other personnel allowed to store and dispense the IMP 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) should be promptly notified to the Sponsor. Some deficiencies may be recorded through a complaint procedure.

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 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 e-CRF page 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

All partially used or unused treatment kits will be retrieved by the Sponsor or destroyed at the study site. All used prefilled syringes should be kept in a sharp-container by the patients and be returned to sites for destroy. The Investigator will not destroy any unused IMP unless the Sponsor provides written authorization.

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.

8.8 CONCOMITANT MEDICATION

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

8.8.1 Prohibited concomitant medication

The following concomitant treatments are not permitted during the study:

- Anti-immunoglobulin E (IgE) therapy (eg, omalizumab);
- Biologic therapy;
- Systemic immunosuppressants;
- Intravenous immunoglobulin (IVIG) therapy;
- Non-selective beta-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;
- Allergen immunotherapy stable dose;
- Antihistamines;
- Systemic (oral or injectable) corticosteroids:
  - Oral corticosteroids are allowed as background controller medication for the patients from 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 DPI);
- 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 (CYP) precaution

The impact of dupilumab on cytochrome P450 (CYP) enzyme activity has not been studied and the effect of dupilumab on levels of IL-4 and IL-13 has not been fully characterized.

However, IL-4 was reported to up-regulate CYP2E1, 2B6, 3A4 mRNA expression or down-regulate CYP1A2 mRNA (12, 13). Human peripheral blood mononuclear cells (PBMC) incubated with various Th2 cytokines showed that IL-4 and IL-13 increased mRNA expression of CYP2B6 and CYP3A4 (14). Since the clinical significance of the limited in vitro findings for IL-4 and IL-13 involvement in CYP regulation and the impact of dupilumab on CYP enzymes is not fully understood, during the study treatment and at least up to the end of follow-up, caution should be used for drugs which are metabolized via these CYP isoforms and which have a narrow therapeutic index. Close clinical observation and/or laboratory monitoring as applicable are required when the investigational product is started or stopped in order to enable early detection of toxic manifestations or lack of activity/efficacy of these drugs, followed by dose adjustment or their withdrawal if needed. Some examples of CYP450 substrates with narrow therapeutic index are provided in Appendix C.

9 ASSESSMENT OF INVESTIGATIONAL MEDICINAL PRODUCT

9.1 PRIMARY ENDPOINT

The primary endpoint of this study is the number (n) and percentage (%) of patients experiencing any treatment-emergent adverse events (TEAE).

Adverse events, serious adverse events (SAEs), adverse events of special interest (AESI), AEs leading to IMP discontinuation and death will be collected from the date of the signed informed consent form (ICF) for participation in LTS12551 (planned at the Combined V1/V2 Visit). The study specific and general safety criteria are detailed in Section 10.4.1. To assure the continuing safety of patients in this study, an Independent DMC will be responsible for reviewing the safety data on a periodic basis throughout the course of the study as outlined in Section 6.2.

Adverse events, AESIs, SAEs, AEs leading to IMP discontinuation and deaths will be reported as described in Section 10.4.1 and analyzed as in Section 11.4.3.

Safety Observations

- The Investigator should take all appropriate measures to ensure the safety of the patients. Notably, he/she should follow-up the outcome of SAEs/AESIs until clinical recovery is complete and laboratory results have returned to normal, or until progression has been stabilized, or death. In all cases, this may imply that observations will continue beyond the last planned visit per protocol, and that additional investigations may be requested by the Sponsor.
- When treatment is prematurely discontinued, the patient's observations will continue until the end of the study as defined by the protocol for that patient.
- In the case of any SAE/AESI requiring immediate notification, being brought to the attention of the Investigator at any time after the end of the study for the patient, and considered by him/her to be caused by the investigational product with a reasonable possibility, this should be reported to the Sponsor.

9.2 SECONDARY ENDPOINTS

9.2.1 Safety and tolerability

The following parameters will be analyzed (see also Section 11.4.3.1.4 for analysis):

- Vital signs.
- Physical examination.
- Electrocardiogram (ECG) variables.
- Clinical laboratory tests.

9.2.1.1 Vital signs

Vital signs, including blood pressure (mmHg), heart rate (beats per minute), respiratory rate (breaths per minute), body temperature (degrees Celsius), and body weight (kg) will be measured at every scheduled treatment visit (see flow charts Section 1.2 and Section 1.3). Height (cm) will only be measured at enrollment. Vital signs will be measured in the sitting position using the same arm at each visit, and will be measured prior to receiving investigational product at the study visits.

9.2.1.2 Physical examination

Physical examinations will include an assessment of general appearance, skin, eyes, ear/nose/throat, heart, chest, abdomen, reflexes, lymph nodes, spine, and extremities. All deviations from normal will be recorded, including those attributable to the patient's disease. Physical examinations will be performed as per the schedule of assessments (see flow charts Section 1.2 and Section 1.3).

9.2.1.3 Electrocardiogram (ECG) variables

A 12-lead ECG will be performed as per the schedule of assessments (see flow charts Section 1.2 and Section 1.3). A minimum of 3 complexes in an appropriate lead (lead II) will be averaged to determine the PR-interval, QT/QTc-interval, and QRS-complex (and heart rate will also be measured) for each ECG.

The Investigator should review the ECG and document his interpretation, signed and dated on the ECG print out. The original trace is kept as source data. Electrocardiogram tracings are also read manually by independent, certified and "centralized" cardiologists, who determine ECG parameters and who in addition alert the Investigator and the Sponsor of any clinically significant findings or changes. These manually read tracings are the ECG tracing of record for this clinical trial. A specific written manual regarding the procedures related to the centralized ECG reading are provided to each Investigator. Refer to the ECG manual for further details.

Notes: Any abnormal ECG parameter should be immediately rechecked for confirmation before making a decision of permanent discontinuation of treatment with dupilumab for the concerned patient.

9.2.1.4 Clinical laboratory tests

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

The following laboratory tests will be performed (as per the schedule of assessments, see flow charts in Section 1.2 and Section 1.3). Patients will be informed of fasting requirements for hematology and serum chemistry assessments.

- Hematology: Blood count (erythrocytes, hemoglobin, hematocrit, leukocytes), differential blood count (neutrophils, lymphocytes, monocytes, eosinophils, and basophils) and platelets.
- Serum chemistry: Total bilirubin (in case of values above the normal range, differentiation in conjugated and non-conjugated bilirubin), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), total protein, albumin, total cholesterol, creatine phosphokinase (CPK), glucose, creatinine, blood urea nitrogen (BUN), uric acid, bicarbonate, and electrolytes (sodium, potassium, and chloride).
- Urine analysis: pH, glucose, ketones, leukocyte esterase blood, protein, nitrate, urobilinogen, and bilirubin (by dipstick). If any parameter on the dipstick is abnormal, a urine sample should be sent to the central laboratory for testing. If positive for proteins, microscopic analysis is performed by central laboratory.
- Serum immunoglobulin, including IgE, are no longer to be assayed due to Amendment 04.
- Clinical laboratory testing: hepatitis screen (HBsAg, HBcAb-IgM), HCVAb, HIV screen (anti-HIV-1 and HIV-2 antibodies), and anti-nuclear antibody (ANA). Anti-ds DNA antibody will be tested if ANA is positive (≥1:160 titer). Japanese patients who have rolled over from DRI12544 study should be retested for hepatitis B (HBsAg, HBsAb, and HBcAb), after Visit 1, at any time during the LTS12551 study, via the earliest scheduled study visit, after IRB approval for Local Amendment 03 (Japan).
- Hepatitis B viral load testing: For patients in Japan (or other countries/regions if there is local regulatory requirement) who were HBsAg negative and HBsAb positive at screening during the parent study, or at the additional test due to Local Amendment 03 (Japan).

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

9.2.1.4.1 Pregnancy test

Qualifying pregnancy test for patients coming from PDY14192, EFC13579, and EFC13691 studies will be the urine pregnancy test. See the schedule of assessments for details of the timing of tests (see flow charts in Section 1.2 and Section 1.3).

9.2.2 Efficacy

The following efficacy **parameters** will be analyzed (see Section 11.4.2 for analysis):

- Forced expiratory volume in 1 second (FEV_1) (see Section 9.2.2.1).
- Asthma Control Questionnaire – 5 question version (ACQ-5) (see Section 9.2.2.2).
- Severe asthma exacerbation events during the treatment period (see Section 9.2.2.3).

- Asthma Quality of Life Questionnaire - standardized [AQLQ(S)] (see Appendix E).
- EuroQol 5 dimensions questionnaire 3-level version (EQ-5D-3L) (see Section 9.2.2.5).
- Health care resource utilization questionnaire (see Section 9.2.2.6).
- Morning and evening peak expiratory flow (PEF) (see Section 9.2.2.7.1).
- Morning and evening asthma symptom scores (see Section 9.2.2.7.2).
- Number of inhalations/day of salbutamol/albuterol or levosalbutamol/levalbuterol for symptom relief (see Section 9.2.2.7.3).
- Nocturnal awakenings due to asthma requiring the use of reliever medication (see Section 9.2.2.7).
- Prescribed OCS dose for patients from the EFC13691 study (see Section 9.2.2.8).

9.2.2.1 Forced expiratory volume in 1 second (FEV_1)

The FEV_1 is part of the spirometry assessment and will be performed as per the schedule of assessments (see flow charts in Section 1.2 and Section 1.3).

A spirometer that meets the 2005 American Thoracic Society (ATS) / European Respiratory Society (ERS) recommendations will be used. The ATS/ERS Standardization of Spirometry should be used as a guideline (5). Spirometry should be done at approximately the same time of the day at each visit throughout the study. Pulmonary function tests should be performed in the morning if possible, but could be done at a different time of the day. Spirometry will be performed after a washout period of bronchodilators according to their action duration, eg, withholding the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours and withholding the last dose of LABA for at least 12 hours (ultra-LABA like vilanterol should be withheld for at least 24 hours) and withholding the last dose of LAMA for at least 24 hours. This should be verified before performing the measurements.

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

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

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

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

important, corresponding to the Minimal Clinically Important Difference (MCID) defined by the developer.

Measurement properties such as reliability, ability to detect change have been documented in the literature (6).

ACQ-5 will be performed as per the schedule of assessments (see flow charts in Section 1.2 and Section 1.3). ACQ-5 paper forms are completed and data will be entered into the e-CRF. The ACQ-5 will be done in those countries where a validated translation is available.

9.2.2.3 Severe asthma exacerbation events

Severe asthma exacerbation events are defined as a deterioration of asthma requiring:

- Use of systemic corticosteroids for ≥3 days:
  - For patients from the EFC13691 study who entered the LTS12551 study taking systemic corticosteroids: the use of systemic corticosteroids at least double the dose currently used for ≥3 days.

OR

- Hospitalization or emergency room visit because of asthma, requiring systemic corticosteroids.

See Section 10.4.1.1 for asthma exacerbation reporting.

9.2.2.4 Asthma Quality of Life Questionnaire with standardized activities (AQLQ[S])

The AQLQ(S) was designed to measure the functional impairments that are most troublesome to patient as a result of their asthma (see Appendix E). The instrument is comprised of 32 items, each rated on a 7-point Likert scales from 1 to 7. The AQLQ(S) has 4 domains. The domains and the number of items in each domain are as follows:

- Symptoms (12 items);
- Activity limitation (11 items);
- Emotional function (5 items);
- Environmental stimuli (4 items).

A global score is calculated ranging from 0 to 7 and a score by domain. Higher scores indicate better quality of life. The instrument has been used in many clinical trials, and it has been shown to be reliable, valid (patient interviews), and sensitive to change. It will be done in those countries where a validated translation is available. A MCID is available (7).

AQLQ(S) will be measured as per the schedule of assessments (see flow charts in Section 1.2 and Section 1.3). A paper questionnaire will be used during LTS12551 study and data will be entered into the e-CRF.

9.2.2.5 EuroQol 5 dimensions questionnaire, 3-level version (EQ-5D-3L)

The EuroQol 5 dimensions questionnaire, 3-level version (EQ-5D-3L, see Appendix G) is validated and reliable self-report health status questionnaire which consists of 6 questions used to calculate a health utility score for use in health economic analysis. The EQ-5D-3L essentially consists of 2 pages; the EQ-5D-3L descriptive system and the EQ Visual Analogue Scale (VAS). The EQ-5D-3L descriptive system comprises 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 3 levels: no problem, some problems, and severe problems. The EQ-VAS records the respondent's self-rated health on a vertical visual analogue scale. The EQ-VAS "thermometer" has endpoints of 100 (best imaginable health state) at the top and 0 (worst imaginable health state) at the bottom.

Upon approval of Amendment 04, this questionnaire will no longer be performed for any patients.

9.2.2.6 Health care resource utilization

A questionnaire of health care resource utilization (reliever medication, specialist visit, hospitalization, emergency or urgent medical care facility visit, outcome, sick leaves, etc) will be administered as per the schedule of assessments (see flow charts in Section 1.2 and Section 1.3).

9.2.2.7 Disease-specific, daily efficacy assessments

All the data detailed in this section will no longer be collected for all patients upon approval of Amendment 04.

Prior to Amendment 04, on a daily basis throughout the study, the patient used an electronic diary / PEF meter to:

- Measure morning and evening PEF;
- Respond to the morning and evening asthma symptom scale questions;
- Indicate the number of inhalations/day of salbutamol/albuterol or levosalbutamol/levalbuterol for symptom relief;
- Record the number of inhalations/day of background ICS and controller therapies used.

9.2.2.7.1 Record the number of nocturnal awakenings and Peak expiratory flow

Prior to Amendment 04, at Visit 1, patients were issued an electronic PEF meter for recording morning (AM) and evening (PM) PEF, daily salbutamol/albuterol or levosalbutamol/levalbuterol, morning and evening asthma symptom scores, number of nocturnal awakenings due to asthma symptoms and number of night time awakenings due to asthma symptoms that required reliever medications. Patients were instructed on the use of the device, and written instructions on the use of the electronic PEF meter were provided to the patients. In addition, the Investigator instructed the patients on how to record the following variables in the electronic PEF meter:

- AM PEF performed within 15 minutes after arising (between 5:30 AM and 10:00 AM) prior to taking any albuterol or levalbuterol.

- PM PEF performed in the evening (between 5:30 PM and 10:00 PM) prior to taking any albuterol or levalbuterol.
- Patients should try to withhold albuterol or levalbuterol for at least 6 hours prior to measuring their PEF.
- Three PEF efforts will be performed by the patient; all 3 values were recorded by the electronic PEF meter, and the highest value will be used for evaluation.

Baseline AM PEF will be the mean AM measurement recorded for the 7 days prior to the first dose of IMP, and baseline PM PEF will be the mean PM measurement recorded for the 7 days prior to the first dose of investigational product or at least 4 days' measurement for setting up the stability limit, prior to dosing in the LTS12551 study.

9.2.2.7.2 Asthma Symptom Score

Prior to Amendment 04, patients recorded overall symptom scores twice a day prior to measuring PEF. The patient's overall asthma symptoms experienced during the waking hours were recorded in the evening (PM symptom score). Symptoms experienced during the night were recorded upon arising (AM symptom score). Baseline symptom scores will be the mean AM and mean PM scores recorded for the 7 days prior to the first dose of investigational product. Patients were instructed to record the severity of symptoms as follows:

AM symptom score:

- 0 = No asthma symptoms, slept through the night;
- 1 = Slept well, but some complaints in the morning. No nighttime awakenings;
- 2 = Woke up once because of asthma (including early awakening);
- 3 = Woke up several times because of asthma (including early awakening);
- 4 = Bad night, awake most of the night because of asthma.

PM symptom score:

- 0 = Very well, no asthma symptoms;
- 1 = One episode of wheezing, cough, or breathlessness;
- 2 = More than one episode of wheezing, cough, or breathlessness without interference of normal activities;
- 3 = Wheezing, cough, or breathlessness most of the day, which interfered to some extent with normal activities;
- 4 = Asthma very bad. Unable to carry out daily activities as usual.

9.2.2.7.3 Reliever use

Prior to Amendment 04, the number of salbutamol/albuterol or levosalbutamol/levalbuterol inhalations were recorded daily by the patients in the electronic diary / PEF meter. The baseline

number of salbutamol/albuterol or levosalbutamol/levalbuterol inhalations/day will be based on the mean of the 7 days prior to the first dose of investigational product.

9.2.2.8 Prescribed oral corticosteroids (OCS) dose for patients from the EFC13691 study

For patients from EFC13691 the prescribed background therapy with OCS will be recorded in the e-CRF.

For the patients from the EFC13691 study only, the following 3 efficacy endpoints will be derived using the prescribed dose of the background OCS medications. The baseline OCS dose is the original baseline value from the EFC13691 study.

- Percentage change from baseline in OCS dose;
- Proportion of patients achieving a reduction of 50% or greater in their OCS dose compared with the original baseline in the parent study;
- Percentage of patients that were able to be tapered off completely of OCS.

9.3 OTHER ENDPOINTS

9.3.1 Pharmacokinetics and anti-dupilumab antibodies

9.3.1.1 Sampling time

Blood samples collected before the IMP administration are used for the determination of functional dupilumab and anti-dupilumab antibodies (also known as ADAs). Samples will be collected as per the schedule of assessments (see flow charts in Section 1.2 and Section 1.3). The date of collection should be recorded in the patient e-CRF. The date and time will also be collected on the central laboratory requisition form and entered into the database through data transfers from the central laboratory.

In the event of any SAE or any AESI of anaphylactic reactions or systemic allergic reactions that are related to IMP and require treatment, or severe injection site reaction lasting longer than 24 hours, samples will be collected near the onset and resolution of the event for any additional analysis if required or for archival purposes. An unscheduled systemic drug concentration page ("PK page") in the e-CRF must be completed as well.

Pre-existing ADAs are defined as:

- An ADA positive response in the assay at baseline with all post-treatment ADA results negative, OR
- An ADA positive response at baseline with all post-treatment ADA responses less than 4-fold over baseline titer levels.

Treatment-emergent ADAs are defined as:

- An ADA positive response in the assay post first dose, when baseline results are negative or missing.

Treatment-boosted ADAs are defined as:

- An ADA positive response in the assay post first dose that is greater-than or equal to 4-fold over baseline titer levels, when baseline results are positive.

Treatment-emergent ADA responses are further classified as Transient, Persistent or Indeterminate:

a) Persistent Response: defined as a treatment-emergent response with two or more consecutive ADA positive sampling time points, separated by more than 12-week period (with no ADA negative samples in between).

b) Indeterminate Response: defined as a treatment-emergent response with only the last collected sample positive in the ADA assay.

c) Transient Response: defined as a treatment-emergent response that is not considered persistent OR indeterminate.

Unused samples collected for drug concentration or ADA analyses may be used for research purpose.

9.3.1.2 Pharmacokinetics handling procedure

It is extremely important to collect all blood samples as close to the protocol-specified time as possible. The reasons for any missed or lost blood samples should be documented. Special procedures for collection, storage, and shipping of serum are described in separate operational manuals. An overview of handling procedure for samples used in the determination of drug concentration and ADA is provided in Table 3.

9.3.1.3 Bioanalytical method

Serum samples will be assayed using validated methods as described in Table 4.

Table 4 - Summary of bioanalytical methods for dupilumab and anti-dupilumab antibody

Analyte	Functional dupilumab	Anti-dupilumab antibody
Matrix	Serum	Serum
Analytical technique	ELISA	Electrochemiluminescence
Lower limit of quantification	0.078 mg/L	Not applicable
Site of bioanalysis	Regeneron	Regeneron

Abbreviation: ELISA = Enzyme-linked immunosorbent assay.

9.3.1.4 Pharmacokinetics parameters

Predose serum samples will be used for functional dupilumab and anti-dupilumab antibodies determination as per the schedule of assessments (see flow charts in Section 1.2 and Section 1.3). Titer values will be reported for all ADA positive responses.

Patients will be scheduled for follow-up based on the overall assessment of antibody titers and clinical presentation.

9.3.2 Pharmacogenetic assessment

No pharmacogenetics samples will be taken during this study.

9.3.3 Pharmacodynamic variables

Several biomarkers related to asthmatic inflammation, Th2 polarization and possible IL-4/IL13 activity will be assessed for their value in predicting therapeutic response and/or in documenting the time course of drug response. Sampling will be conducted as per the schedule of assessments (see flow charts in Section 1.2 and Section 1.3). More detailed information on the collection, handling, transport and preservation of samples (eg, minimum volumes required for blood collection and for aliquots for each biomarker assay) will be provided in a separate laboratory manual.

9.3.3.1 Whole blood biomarkers

Eosinophilia is recognized as a marker for diagnosing and predicting risk of exacerbations in asthma. Eosinophils and Th2 cytokines play a central role in the pathophysiology of severe asthma. Eosinophil count has been used to guide treatment decisions in severe asthma. In LTS12551 study, blood eosinophil count will be measured as part of the standard 5-part white

blood cell (WBC) differential cell count on a hematology auto analyzer (as per the schedule of assessments for hematology in the flow charts Section 1.2 and Section 1.3).

9.3.3.2 Serum biomarkers [redacted]

Serum total IgE: It has been widely recognized and reported that IgE levels correlate with asthma severity and bronchial hyper-responsiveness (8). Interleukin-4 regulates IgE synthesis in human lung (9). Interleukin-4, in combination with IL-13, induces the class switch–recombination to IgE by B-cells (10), (11). Anti-IgE therapy has been reported to decrease asthma exacerbation and the requirement for inhaled steroid therapy. In the ACT11457 and DRI12544 studies, IgE steadily declined throughout the treatment periods without reaching a steady state. In DRI12544, total IgE and several antigen-specific IgEs declined >50% from baseline during 24 weeks of treatment. This suggested that dupilumab may have the function of gradually desensitizing mast cells by decreasing surface coating with IgE. The IgE measurement in the LTS12551 study will help us better understand how the IgE level changes during the long-term dupilumab treatment.

Serum total IgE will be measured with a quantitative method (eg, ImmunoCAP) approved for diagnostic testing and will no longer be performed in the LTS12551 study, due to Amendment 04.

Serum immunoglobin assay: IgA, IgG, and IgG1-4, IgM level will no longer be collected in the LTS12551 study, due to Amendment 04.

[redacted]

9.3.4 Quality of life / health economic variables / other endpoints (optional)

Please see Section 9.2.2 for details of the quality of life and health economic variables that are collected as part of this study.

10 STUDY PROCEDURES

10.1 VISIT SCHEDULE

The LTS12551 study consists of 3 periods:

- **Enrollment period:** Combined V1/V2 Visit: Eligible patients from PDY14192, EFC13579 and EFC13691 studies should rollover into LTS12551 the same day as *the end-of-treatment visit of the parent study*.
  - **Note:** A screening period of 0 to 3 weeks was proposed only for patients rolling over from DRI12544. Enrollment from study DRI12544 is complete, thus the screening period does not apply anymore.
- **Treatment period**: Open-label treatment for 48 weeks (1 year) for patients enrolled after approval of Amendment 04 or 96 weeks (2 years) for patients enrolled prior to Amendment 04 approval.

  During the open-label treatment period, patients will continue their background therapy dose regimen, as maintained in the parent study or as modified based on Investigator's judgment.
- **Post-treatment period**: 12 weeks.

The study visits should be performed on the planned dates (relative to the first injection) and be adhered to within the ±3 day visit window with the first 12 weeks and ±1 week for the remaining study period. Monthly telephone contact should be done with patient after Week 24 to collect safety information.

It is preferred that all study visits take place in the morning. The results of the evaluation will be recorded on the appropriate e-CRF pages. Prior to all screening assessments, after discussion of participation in the study, the written consent form must be signed and dated.

If a patient is prematurely discontinued from treatment, EOT should be scheduled and all assessments planned at the EOT Visit should be performed.

10.1.1 For patients enrolled prior to Amendment 04

The visit schedule for patients enrolled prior to Amendment 04 are shown in the study flowchart in Section 1.2.

10.1.1.1 Enrollment: Combined V1/V2 Visit (Start-of-Treatment, Week 0, D1)

Eligible patients from parent studies are considered to be candidates for the LTS12551 study. Following a discussion of participation in the clinical trial, the informed consent (and assent in case of adolescents) must be obtained before any protocol related investigations.

This study is using a central laboratory for blood tests assessments.

For patients coming from PDY14192, EFC13579, and EFC13691 studies:

- Visit 1 and Visit 2 should be combined with *the end-of-treatment visit of the PDY14192, EFC13579 or EFC13691 parent studies*. The majority of the V1/V2 assessments and laboratory procedures for this study correspond to the *end-of-treatment visit of the PDY14192, EFC13579, and EFC13691 parent studies*.

The following activities are performed at the Enrollment (Combined V1/V2) Visit:

- Obtain signature of informed consent for participation in LTS12551.
- Review inclusion and exclusion criteria to assess eligibility.
- If the patient meets all inclusion and does not meet any exclusion criteria, contact IVRS/IWRS to register the visit, confirm the patient's number and receive the first treatment kit number assignment.
- Collect patient's demographic information, asthma history (including allergy history and smoking habits), eligibility module, other medical and surgical history (including significant prior and concurrent illnesses), prior and concomitant medications, ICF, chest imaging, and IMP administration (via e-CRF pages).
- Commence AE reporting from the time of the signature of the informed consent for participation in LTS12551 (anticipated to be at the Combined V1/V2 Visit).
- Record all medication use with start dose in the e-CRF.
- Inquire about background asthma therapy tolerability.
- Instruct the patient to continue the background ICS/LABA or ICS and controller therapy stabilized during the parent study.
- Perform chest imaging (X-ray, Magnetic resonance imaging (MRI) or high resolution computed tomography (HRCT) scan) if no chest imaging within the previous 12 months is available[1].

Dispense and administer IMP (see Section 8.1.3)

- For those patients willing to perform self-injection, the Investigator or delegate will train the patient (or parent or caregiver) regarding preparation and injection of IMP and may inject the study medication or the patient (or parent or caregiver) may perform the injection under the supervision of the Investigator or delegate, if the patient is already self-injecting from the parent study.
- Document the training/supervision for IMP self-injection in the patient's study file.

[1] Chest X-ray, MRI or HRCT will be performed only if no chest imaging results within the previous 12 months are available. At the Investigator's discretion (and based on local regulations) chest imaging may be performed during the study (eg, 1 year after the last chest imaging assessment or after a year's treatment).

- 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 and remind patient to withhold bronchodilators according to their action duration, eg, withholding the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours and withholding the last dose of LABA for at least 12 hours (ultra-LABA like vilanterol should be withheld for at least 24 hours) and withholding the last dose of LAMA for at least 24 hours prior to the next visit.
- Reminder: Sexually active female patients of reproductive potential are required to practice an acceptable contraception (as defined in E18 or local protocol amendment in case of specific local requirement) during the entire study duration, while taking dupilumab and for 12 weeks after the last IMP dose. Study sites should counsel all study patients, with special attention towards adolescent patients, regarding the importance of practicing responsible and effective contraception during the study and 12 weeks after the last dose.

The following will be obtained from the parent study PDY14192, EFC13579 and EFC13691 studies and do not have to be repeated in LTS12551:

- Measure vital signs (blood pressure, heart rate, respiration rate, body temperature, weight [kg], height [cm]).
- Perform physical examination including major body systems examination.
- Administer paper ACQ-5, AQLQ(S), and health care resource utilization questionnaire. Note: For patients coming from Study PDY14192, AQLQ(S) is not obtained from the parent study, so those patients will have to complete the paper questionnaire at the Combined V1/V2 Visit in LTS12551 study.
- Spirometry:
  - Spirometry will be performed after withholding the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours, the last dose of LABA for at least 12 hours (ultra-LABA like vilanterol should be withheld for at least 24 hours) and the last dose of LAMA for at least 24 hours, and prior to the administration of IMP. This will be verified before performing the measurements.
- Perform 12-lead ECG.
- Collect blood samples for the following (fasting - overnight fast or minimum of 8 hours fast):
  - Hematology: Blood count (erythrocytes, hemoglobin, hematocrit, leukocytes), differential blood count (neutrophils, lymphocytes, monocytes, eosinophils, basophils), and platelets.
  - Serum chemistry: Total bilirubin (in case of values above the normal range, differentiation in conjugated and non-conjugated bilirubin), ALT, AST, ALP, total protein, albumin, total cholesterol, CPK, glucose, creatinine, BUN, uric acid, bicarbonate, and electrolytes (sodium, potassium, chloride).

- Serology: HBsAg, hepatitis B surface antibody (HBsAb), HBcAb, total HBcAb, HCV Ab, HIV screen (Anti-HIV-1 and HIV-2 antibodies) and ANA; (these tests were scheduled at the visit prior to the *end-of-treatment visit of the PDY14192, EFC13579 or EFC13691 parent studies*). In addition, results from HBV DNA testing and HCV virus RNA (HCV RNA) testing should be collected for those patients who were HBsAg negative and HBcAb positive, and/or HCV Ab positive; also anti-double-strand DNA antibody results for patients with ANA positive (≥1:160 titer).

- Serum sample for PK and ADA (before dose of IMP).
- Eosinophil count (derived from clinical laboratory test).
- [redacted]
- Urine for urinalysis (dipstick) (see Section 9.2.1.4).
- Urine pregnancy test (for women of childbearing potential).

10.1.1.2 Visit 3 (Week 2)

- Record all medication use with start dose in e-CRF including starting dose.
- Inquire about AEs/SAEs and background asthma therapy tolerability.
- Measure vital signs (blood pressure, heart rate, respiration rate, body temperature, weight).
- Perform spirometry
  - Spirometry will be performed after withholding the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours and withholding the last dose of LABA for at least 12 hours (ultra-LABA like vilanterol should be withheld for at least 24 hours) and withholding the last dose of LAMA for at least 24 hours. This will be verified before performing the measurements.
- Call IVRS/IWRS to register visit and obtain next treatment kit number (up to Visit 7, 1 kit to be dispensed at each visit).
- Dispense and administer IMP:
  - 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 the parent study.
- Schedule appointment for next visit and remind patient to withhold the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours and withholding the last dose of LABA for at least 12 hours (ultra-LABA like vilanterol should be withheld for at least 24 hours) and withholding the last dose of LAMA for at least 24 hours prior to the next visit.
- Remind patient to come for the next visit in fasting state.

10.1.1.3 Visit 4 (Month 1, Week 4)

- Record all medication use with start dose in e-CRF including starting dose.
- Inquire about AEs/SAEs and background asthma therapy tolerability.
- Measure vital signs (blood pressure, heart rate, respiration rate, body temperature, weight).
- Perform spirometry:
  - Spirometry will be performed after the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours and withholding the last dose of LABA for at least 12 hours (ultra-LABA like vilanterol should be withheld for at least 24 hours) and withholding the last dose of LAMA for at least 24 hours prior to administration of investigational product. This will be verified before performing the measurements.
- Perform blood sampling for:
  - Clinical laboratories.
  - Serum sample (predose) for PK.
- Perform urine pregnancy test (for women of childbearing potential).
- Call IVRS/IWRS to register visit and obtain treatment kit number.
- Dispense and administer IMP:
  - Patients will be monitored at the study site for a minimum of 30 minutes after the injection.
- Remind patient to continue the background therapy and schedule appointment for next visit.

10.1.1.4 Visit 5 (Week 6)

- Record all medication use with start dose in e-CRF including starting dose.
- Inquire about AEs/SAEs and background asthma therapy tolerability.
- Measure vital signs (blood pressure, heart rate, respiration rate, body temperature, weight).
- Perform urine pregnancy test (for women of childbearing potential).
- Call IVRS/IWRS to register visit and obtain treatment kit number.
- Dispense and administer IMP:
  - Patients will be monitored at the study site for a minimum of 30 minutes after the injection.
- Remind patient to continue the background therapy.
- Schedule appointment for next visit and remind patient to withhold the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours and withholding the last dose of LABA for at least 12 hours (ultra-LABA like vilanterol should be withheld

for at least 24 hours) and withholding the last dose of LAMA for at least 24 hours prior to the next visit.

10.1.1.5 Visit 6 (Month 2, Week 8)

- Record all medication use with start dose in e-CRF including starting dose.
- Inquire about AEs/SAEs and background asthma therapy tolerability.
- Measure vital signs (blood pressure, heart rate, respiration rate, body temperature, weight).
- Perform spirometry:
  - Spirometry will be performed after withholding the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours and withholding the last dose of LABA for at least 12 hours (ultra-LABA like vilanterol should be withheld for at least 24 hours) and withholding the last dose of LAMA for at least 24 hours prior to administration of investigational product. This will be verified before performing the measurements.
- Perform urine pregnancy test (for women of childbearing potential).
- Call IVRS/IWRS to register visit and obtain treatment kit number.
- Dispense and administer IMP:
  - Patients will be monitored at the study site for a minimum of 30 minutes after the injection.
- Remind patient to continue the background therapy and schedule appointment for next visit.

10.1.1.6 Visit 7 (Week 10)

- Record all medication use with start dose in e-CRF including starting dose.
- Inquire about AEs/SAEs and background asthma therapy tolerability.
- Measure vital signs (blood pressure, heart rate, respiration rate, body temperature, weight).
- Perform urine pregnancy test (for women of childbearing potential).
- Call IVRS/IWRS to register visit and obtain treatment kit number.
- Dispense and administer IMP:
  - Patients will be monitored at the study site for a minimum of 30 minutes after the injection.
- Remind patient to continue the background therapy.
- Schedule appointment for next visit and remind patient to withhold the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours and withholding the last dose of LABA for at least 12 hours (ultra-LABA like vilanterol should be withheld for at least 24 hours) and withholding the last dose of LAMA for at least 24 hours prior to the next visit.

- Remind patients for the next visit in fasting state.

10.1.1.7 Visit 8 (Month 3, Week 12)

- Record all medication use with start dose in e-CRF including starting dose.
- Inquire about AEs/SAEs and background asthma therapy tolerability.
- Measure vital signs (blood pressure, heart rate, respiration rate, body temperature, weight).
- Perform physical examination.
- Administer health care resource utilization questionnaire.
- Perform spirometry:
  - Spirometry will be performed after withholding the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours and withholding the last dose of LABA for at least 12 hours (ultra- LABA like vilanterol should be withheld for at least 24 hours) and withholding the last dose of LAMA for at least 24 hours prior to administration of investigational product. This will be verified before performing the measurements.
- Perform blood sampling for:
  - Clinical laboratories.
  - Serum sample (predose) for PK and anti-dupilumab antibody analysis.
  - Hepatitis B viral load testing: For patients in Japan (or other countries/regions if there is local regulatory requirement) who were HBsAg negative and HBsAb positive at screening during the parent study, or at the additional test due to Local Amendment 03 (Japan).
- Perform urine pregnancy test (for women of childbearing potential).
- Obtain urine for urinalysis (dipstick).
- Call IVRS/IWRS to register visit and obtain treatment kits' numbers.
- Dispense and administer IMP:
  - Patients will be monitored at the study site for a minimum of 30 minutes after the injection.
  - After Week 12, for patients (or parents caregivers) unable or unwilling to self-administer IMP, arrangements must be made for the patient to receive IMP injections at the study site as unscheduled visits, or for qualified site personnel and/or a professional caregiver to administer IMP at home at q2w intervals.
- Remind patient to continue the background therapy and schedule appointment for next visit.

10.1.1.8 Visit 9 (Month 4, Week 16)

- Record all medication use with start dose in e-CRF including starting dose.

- Inquire about AEs/SAEs and background asthma therapy tolerability.
- Measure vital signs (blood pressure, heart rate, respiration rate, body temperature, weight).
- Perform urine pregnancy test (for women of childbearing potential).
- Call IVRS/IWRS to register visit and obtain treatment kits' numbers.
- Dispense and administer IMP:
  - Patients will be monitored at the study site for a minimum of 30 minutes after the injection.
  - After Week 12, for patients (or parents caregivers) unable or unwilling to self-administer IMP, arrangements must be made for the patient to receive IMP injections at the study site as unscheduled visits, or for qualified site personnel and/or a professional caregiver to administer IMP at home at q2w intervals.
- Remind patient to continue the background therapy and schedule appointment for next visit.

10.1.1.9 Visit 10 (Month 5, Week 20);

- Record all medication use with start dose in e-CRF including starting dose.
- Inquire about AEs/SAEs and background asthma therapy tolerability.
- Measure vital signs (blood pressure, heart rate, respiration rate, body temperature, weight).
- Perform urine pregnancy test (for women of childbearing potential).
- Call IVRS/IWRS to register visit and obtain treatment kits' numbers.
- Dispense and administer IMP:
  - Patients will be monitored at the study site for a minimum of 30 minutes after the injection.
  - After Week 12, for patients (or parents caregivers) unable or unwilling to self-administer IMP, arrangements must be made for the patient to receive IMP injections at the study site as unscheduled visits, or for qualified site personnel and/or a professional caregiver to administer IMP at home at q2w intervals.
- Remind patient to continue the background therapy.
- Schedule appointment for next visit and remind patient to withhold the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours and withholding the last dose of LABA for at least 12 hours (ultra-LABA like vilanterol should be withheld for at least 24 hours) and withholding the last dose of LAMA for at least 24 hours prior to the next visit.
- Remind patients for the next visit in fasting state.

10.1.1.10 Visit 11 (Month 6, Week 24)

- Record all medication use with start dose in e-CRF including starting dose.

- Inquire about AEs/SAEs and background asthma therapy tolerability.
- Measure vital signs (blood pressure, heart rate, respiration rate, body temperature, weight).
- Perform physical examination.
- Administer paper ACQ-5, AQLQ(S), and health care resource utilization questionnaire.
- Perform spirometry:
  - Spirometry will be performed after withholding the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours and withholding the last dose of LABA for at least 12 hours (ultra-LABA like vilanterol should be withheld for at least 24 hours) and withholding the last dose of LAMA for at least 24 hours prior to administration of investigational product. This will be verified before performing the measurements.
- Perform 12-lead ECG.
- Perform blood sampling for:
  - Clinical laboratories.
  - Serum sample (predose) for PK and anti-dupilumab antibody analysis.
  - Hepatitis B viral load testing: For patients in Japan (or other countries/regions if there is local regulatory requirement) who were HBsAg negative and HBsAb positive at screening during the parent study, or at the additional test due to Local Amendment 03 (Japan).
- Perform urine pregnancy test (for women of childbearing potential).
- Obtain urine for urinalysis (dipstick).
- Call IVRS/IWRS to register visit and obtain treatment kits' numbers.
- Dispense and administer IMP:
  - Patients will be monitored at the study site for a minimum of 30 minutes after the injection.
  - After Week 12, for patients (or parents caregivers) unable or unwilling to self-administer IMP, arrangements must be made for the patient to receive IMP injections at the study site as unscheduled visits, or for qualified site personnel and/or a professional caregiver to administer IMP at home at q2w intervals.
- Remind patient to continue the background therapy and schedule appointment for next visit.
- Perform monthly telephone contact with patient after Week 24 (Visit 11) to collect safety information.

10.1.1.11 Visit 12 (Month 9, Week 36)

- Record all medication use with start dose in e-CRF including starting dose.
- Inquire about AEs/SAEs and background asthma therapy tolerability.

- Measure vital signs (blood pressure, heart rate, respiration rate, body temperature, weight).
- Perform urine pregnancy test (for women of childbearing potential).
- Call IVRS/IWRS to register visit and obtain treatment kits' numbers.
- Dispense and administer IMP:
  - Patients will be monitored at the study site for a minimum of 30 minutes after the injection.
  - After Week 12, for patients (or parents caregivers) unable or unwilling to self-administer IMP, arrangements must be made for the patient to receive IMP injections at the study site as unscheduled visits, or for qualified site personnel and/or a professional caregiver to administer IMP at home at q2w intervals.
- Remind patient to continue the background therapy.
- Schedule appointment for next visit and remind patient to withhold the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours and withholding the last dose of LABA for at least 12 hours (ultra-LABA like vilanterol should be withheld for at least 24 hours) and withholding the last dose of LAMA for at least 24 hours prior to the next visit.
- Remind patients for the next visit in fasting state.
- Perform monthly telephone contact with patient after Week 24 (Visit 11) to collect safety information.

10.1.1.12 Visit 13 (Month 12, Week 48)

- Record all medication use with start dose in e-CRF including starting dose.
- Inquire about AEs/SAEs and background asthma therapy tolerability.
- Measure vital signs (blood pressure, heart rate, respiration rate, body temperature, weight).
- Perform physical examination.
- Administer paper ACQ-5, AQLQ(S), and health care resource utilization questionnaire.
- Perform spirometry:
  - Spirometry will be performed after withholding the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours and withholding the last dose of LABA for at least 12 hours (ultra-LABA like vilanterol should be withheld for at least 24 hours) and withholding the last dose of LAMA for at least 24 hours prior to administration of investigational product. This will be verified before performing the measurements.
- Perform 12-lead ECG.
- Perform blood sampling for:
  - Clinical laboratories.
  - Serum sample (predose) for PK and anti-dupilumab antibody analysis.

- Hepatitis B viral load testing: For patients in Japan (or other countries/regions if there is local regulatory requirement) who were HBsAg negative and HBsAb positive at screening during the parent study, or at the additional test due to Local Amendment 03 (Japan).

- Perform urine pregnancy test (for women of childbearing potential).
- Obtain urine for urinalysis (dipstick).
- Call IVRS/IWRS to register visit and obtain treatment kit numbers.
- Dispense and administer IMP:
  - Patients will be monitored at the study site for a minimum of 30 minutes after the injection.
  - After Week 12, for patients (or parents caregivers) unable or unwilling to self-administer IMP, arrangements must be made for the patient to receive IMP injections at the study site as unscheduled visits, or for qualified site personnel and/or a professional caregiver to administer IMP at home at q2w intervals.
- Remind patient to continue the background therapy and schedule appointment for next visit.
- Perform monthly telephone contact with patient after Week 24 (Visit 11) to collect safety information.

10.1.1.13 Visit 14 (Month 15, Week 60);

- Record all medication use with start dose in e-CRF including starting dose.
- Inquire about AEs/SAEs and background asthma therapy tolerability.
- Measure vital signs (blood pressure, heart rate, respiration rate, body temperature, weight).
- Perform urine pregnancy test (for women of childbearing potential).
- Call IVRS/IWRS to register visit and obtain treatment kits' numbers.
- Dispense and administer IMP:
  - Patients will be monitored at the study site for a minimum of 30 minutes after the injection.
  - After Week 12, for patients (or parents caregivers) unable or unwilling to self-administer IMP, arrangements must be made for the patient to receive IMP injections at the study site as unscheduled visits, or for qualified site personnel and/or a professional caregiver to administer IMP at home at q2w intervals.
- Remind patient to continue the background therapy.
- Schedule appointment for next visit and remind patient to withhold the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours and withholding the last dose of LABA for at least 12 hours (ultra-LABA like vilanterol should be withheld for at least 24 hours) and withholding the last dose of LAMA for at least 24 hours prior to the next visit.

- Remind patients for the next visit in fasting state.
- Perform monthly telephone contact with patient after Week 24 (Visit 11) to collect safety information.

10.1.1.14 Visit 15 (Month 18, Week 72)

- Record all medication use with start dose in e-CRF including starting dose.
- Inquire about AEs/SAEs and background asthma therapy tolerability.
- Measure vital signs (blood pressure, heart rate, respiration rate, body temperature, weight).
- Perform physical examination, including major body systems examination.
- Administer health care resource utilization questionnaire.
- Perform spirometry:
  - Spirometry will be performed after withholding the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours and withholding the last dose of LABA for at least 12 hours (ultra-LABA like vilanterol should be withheld for at least 24 hours) and withholding the last dose of LAMA for at least 24 hours prior to administration of investigational product. This will be verified before performing the measurements.
- Perform blood sampling for:
  - Clinical laboratories.
  - Serum sample (predose) for PK and anti-dupilumab antibody analysis.
  - Hepatitis B viral load testing: For patients in Japan (or other countries/regions if there is local regulatory requirement) who were HBsAg negative and HBsAb positive at screening during the parent study, or at the additional test due to Local Amendment 03 (Japan).
- Perform urine pregnancy test (for women of childbearing potential).
- Obtain urine for urinalysis (dipstick).
- Call IVRS/IWRS to register visit and obtain treatment kits' numbers.
- Dispense and administer IMP:
  - Patients will be monitored at the study site for a minimum of 30 minutes after the injection.
  - After Week 12, for patients (or parents caregivers) unable or unwilling to self-administer IMP, arrangements must be made for the patient to receive IMP injections at the study site as unscheduled visits, or for qualified site personnel and/or a professional caregiver to administer IMP at home at q2w intervals.
- Remind patient to continue the background therapy.
- Schedule appointment for next visit and remind patient to withhold withholding the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours and

withholding the last dose of LABA for at least 12 hours (ultra-LABA like vilanterol should be withheld for at least 24 hours) and withholding the last dose of LAMA for at least 24 hours prior to the next visit.

- Perform monthly telephone contact with patient after Week 24 (Visit 11) to collect safety information.

10.1.1.15 Visit 16 (Month 21, Week 84)

- Record all medication use with start dose in e-CRF including starting dose.
- Inquire about AEs/SAEs and background asthma therapy tolerability.
- Measure vital signs (blood pressure, heart rate, respiration rate, body temperature, weight).
- Perform physical examination.
- Administer health care resource utilization questionnaire.
- Perform spirometry:
  - Spirometry will be performed after withholding the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours and withholding the last dose of LABA for at least 12 hours (ultra-LABA like vilanterol should be withheld for at least 24 hours) and withholding the last dose of LAMA for at least 24 hours prior to administration of investigational product. This will be verified before performing the measurements.
- Call IVRS/IWRS to register visit and obtain treatment kits' numbers.
- Dispense and administer IMP:
  - Patients will be monitored at the study site for a minimum of 30 minutes after the injection.
  - After Week 12, for patients (or parents caregivers) unable or unwilling to self-administer IMP, arrangements must be made for the patient to receive IMP injections at the study site as unscheduled visits, or for qualified site personnel and/or a professional caregiver to administer IMP at home at q2w intervals.
- Perform urine pregnancy test (for women of childbearing potential).
- Obtain urine for urinalysis (dipstick).
- Remind patient to continue the background therapy.
- Schedule appointment for next visit and remind patient to the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours and withholding the last dose of LABA for at least 12 hours (ultra-LABA like vilanterol should be withheld for at least 24 hours) and withholding the last dose of LAMA for at least 24 hours prior to the next visit.
- Remind patients for the next visit in fasting state.
- Perform monthly telephone contact with patient after Week 24 (Visit 11) to collect safety information.

10.1.1.16 Visit 17 (End-of-Treatment: Month 24, Week 96)

End-of-Treatment Visit is scheduled 2 weeks after the last IMP administration.

- Record all medication use with start dose in e-CRF including starting dose.
- Inquire about AEs/SAEs and background asthma therapy tolerability.
- Measure vital signs (blood pressure, heart rate, respiration rate, body temperature, weight).
- Perform physical examination.
- Administer health care resource utilization utilization questionnaire.
- Perform spirometry
  - Spirometry will be performed after withholding the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours and withholding the last dose of LABA for at least 12 hours (ultra-LABA like vilanterol should be withheld for at least 24 hours) and withholding the last dose of LAMA for at least 24 hours prior to administration of investigational product. This will be verified before performing the measurements.
- Perform 12-lead ECG.
- Perform blood sampling for:
  - Clinical laboratories.
  - Serum sample (predose) for PK and anti-dupilumab antibody analysis.
  - Hepatitis B viral load testing: For patients in Japan (or other countries/regions if there is local regulatory requirement) who were HBsAg negative and HBsAb positive at screening during the parent study, or at the additional test due to Local Amendment 03 (Japan).
- [redacted]
- Perform urine pregnancy test (for women of childbearing potential).
- Obtain urine for urinalysis (dipstick).
- Call IVRS/IWRS to register the EOT date.
- Schedule appointment for next visit and remind patient to withhold the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours and withholding the last dose of LABA for at least 12 hours (ultra-LABA like vilanterol should be withheld for at least 24 hours) and withholding the last dose of LAMA for at least 24 hours prior to the next visit.
- Remind patient to continue the background therapy.
- Remind patients to arrive for next visit in fasting state.
- Perform monthly telephone contact with patient after Week 24 (Visit 11) to collect safety information.

10.1.1.17 Visit 18 (End-of-Study: Month 27, Week 108)

End-of-Study (EOS) visit is scheduled 12 weeks after EOT.

- Record all medication use with start dose in e-CRF including starting dose.
- Inquire about AEs/SAEs and background asthma therapy tolerability.
- Measure vital signs (blood pressure, heart rate, respiration rate, body temperature, weight).
- Perform physical examination.
- Administer health care resource utilization questionnaire.
- Perform spirometry:
  - Spirometry will be performed after withholding the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours and withholding the last dose of LABA for at least 12 hours (ultra-LABA like vilanterol should be withheld for at least 24 hours) and withholding the last dose of LAMA for at least 24 hours prior to administration of investigational product. This will be verified before performing the measurements.
- Perform 12-lead ECG.
- Perform blood sampling for:
  - Clinical laboratories.
  - Serum sample (predose) for PK and anti-dupilumab antibody analysis.
- Perform urine pregnancy test (for women of childbearing potential).
- Obtain urine for urinalysis (dipstick).
- Call IVRS/IWRS to register the EOS date.

10.1.2 For patients enrolled after Amendment 04

The visit schedule for patients enrolled after Amendment 04 are shown in the study flowchart in Section 1.3.

10.1.2.1 Enrollment: Combined V1/V2 Visit (Start-of-Treatment, Week 0, D1)

Eligible patients from parent studies are considered to be candidates for the LTS12551 study. Following a discussion of participation in the clinical trial, the informed consent (and assent in case of adolescents) must be obtained before any protocol related investigations.

This study is using a central laboratory for blood tests assessments.

For patients coming from PDY14192, EFC13579, and EFC13691 studies:

- Visit 1 and Visit 2 should be combined with *the end-of-treatment visit of the PDY14192, EFC13579 or EFC13691 parent studies*. The majority of the Combined V1/V2 Visit

assessments and laboratory procedures for this study correspond to the EOT Visit in the PDY14192, EFC13579 and EFC13691 studies.

The following activities are performed at the Enrollment (Combined V1/V2) Visit:

- Obtain the signature of the informed consent for participation in LTS12551.
- Review inclusion and exclusion criteria to assess eligibility.
- If the patient meets all inclusion and does not meet any exclusion criteria: Contact IVRS/IWRS to register the visits, confirm the patient's number and receive the first treatment kit number assignment.
- Collect patient's demographic information, asthma history (including allergy history and smoking habits), eligibility module, other medical and surgical history (including significant prior and concurrent illnesses), prior and concomitant medications, ICF, chest imaging, and IMP administration (via e-CRF pages).
- Commence AE reporting from the time of the signature of the informed consent for participation in LTS12551 (anticipated to be at the Combined V1/V2 Visit).
- Record all medication use with start dose in the e-CRF.
- Inquire about background asthma therapy tolerability.
- Instruct the patient to continue the background ICS/LABA or ICS and controller therapy stabilized during the parent study.
- Perform chest imaging (X-ray, MRI, or HRCT scan) if no chest imaging within the previous 12 months is available[2].
- Dispense and administer IMP (see Section 8.1.3):
  - For those patients willing to perform self-injection, the Investigator or delegate will train the patient (or parent or caregiver) regarding preparation and injection of IMP and may inject the study medication, or the patient (or parent or caregiver) may perform the injection under the supervision of the Investigator or delegate if the patient is already self-injecting from the parent study.
  - Document the training/supervision for IMP self-injection in the patient's study file.
  - 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 and remind patient to withhold bronchodilators according to their action duration, for example, withholding the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours and withholding the last dose of LABA for at least 12 hours (ultra-LABA like vilanterol should be withheld

[2] Chest X-ray, MRI or HRCT will be performed only if no chest imaging results within the previous 12 months are available. At the Investigator's discretion (and based on local regulations) chest imaging may be performed during the study (eg, 1 year after the last chest imaging assessment or after a year's treatment).

for at least 24 hours) and withholding the last dose of LAMA for at least 24 hours prior to the next visit.

- Reminder: Sexually active female patients of reproductive potential are required to practice an acceptable contraception (as defined in E18 or local protocol amendment in case of specific local requirement) during the entire study duration, while taking dupilumab and for 12 weeks after the last IMP dose. Study sites should counsel all study patients, with special attention towards adolescent patients, regarding the importance of practicing responsible and effective contraception during the study and 12 weeks after the last dose.

The following will be obtained from the *end-of-treatment visit in the parent study* (PDY14192, EFC13579, and EFC13691 studies) and do not have to be repeated in LTS12551:

- Measure vital signs [blood pressure, heart rate, respiration rate, body temperature, weight (kg), height (cm)].
- Perform physical examination including major body systems exam, Administer paper ACQ-5, AQLQ(S) and health care resource utilization questionnaire. Note: For patients coming from Study PDY14192, AQLQ(S) is not obtained from the parent study so patients from the PDY14192 study will have to complete the questionnaire at the Combined V1/V2 Visit in the LTS12551 study.
- Spirometry:
  - Spirometry will be performed after withholding the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours and withholding the last dose of LABA for at least 12 hours (ultra-LABA like vilanterol should be withheld for at least 24 hours) and withholding the last dose of LAMA for at least 24 hours and prior to administration of investigational product. This will be verified before performing the measurements.
- Perform 12-lead ECG.
- Collect blood samples for the following (fasting - overnight fast or minimum of 8 hours fast):
  - Hematology: Blood count (erythrocytes, hemoglobin, hematocrit, leukocytes), differential blood count (neutrophils, lymphocytes, monocytes, eosinophils, basophils), and platelets.
  - Serum chemistry: Total bilirubin (in case of values above the normal range, differentiation in conjugated and non-conjugated bilirubin), ALT, AST, ALP, total protein, albumin, total cholesterol, CPK, glucose, creatinine, BUN, uric acid, bicarbonate and electrolytes (sodium, potassium, chloride).
  - Serology: HBsAg, hepatitis B surface antibody (HBsAb), HBcAb, total HBcAb, HCV Ab, HIV screen (Anti-HIV-1 and HIV-2 antibodies) and ANA; (these tests were scheduled at the visit prior to the end-of-treatment visit of parent study). In addition, results from hepatitis B virus DNA (HBV DNA) testing and HCV RNA testing should be collected for those patients who were HBsAg negative and HBcAb positive, and/or

HCV Ab positive; also anti-double-strand DNA antibody results for patients with ANA positive (≥1:160 titer).

- Serum sample for PK and ADA (before dose of IMP).
- Eosinophil count (derived from clinical laboratory test).
- [redacted]
- Urine for urinalysis (dipstick) (see Section 9.2.1.4).
- Urine pregnancy test (for women of childbearing potential).
- Schedule appointment for next visit.

10.1.2.2 Visit 3 (Week 2)

- Record all medication use with start dose in e-CRF including starting dose.
- Inquire about AEs/SAEs and background asthma therapy tolerability.
- Measure vital signs (blood pressure, heart rate, respiration rate, body temperature, weight).
- Perform spirometry:
  - Spirometry will be performed after withholding the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours and withholding the last dose of LABA for at least 12 hours (ultra-LABA like vilanterol should be withheld for at least 24 hours) and withholding the last dose of LAMA for at least 24 hours. This will be verified before performing the measurements.
- Call IVRS/IWRS to register visit and obtain next treatment kit number (up to Visit 7, 1 kit to be dispensed at each visit).
- Dispense and administer IMP:
  - 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 the parent study.
- Schedule appointment for next visit and remind patient to withhold the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours and withholding the last dose of LABA for at least 12 hours (ultra-LABA like vilanterol should be withheld for at least 24 hours) and withholding the last dose of LAMA for at least 24 hours prior to the next visit.
- Remind patient to come for the next visit in fasting state.

10.1.2.3 Visit 4 (Month 1, Week 4)

- Record all medication use with start dose in e-CRF including starting dose.
- Inquire about AEs/SAEs and background asthma therapy tolerability.
- Measure vital signs (blood pressure, heart rate, respiration rate, body temperature, weight).

- Perform spirometry:
  - Spirometry will be performed after the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours and withholding the last dose of LABA for at least 12 hours (ultra-LABA like vilanterol should be withheld for at least 24 hours) and withholding the last dose of LAMA for at least 24 hours prior to administration of investigational product. This will be verified before performing the measurements.
- Perform blood sampling for:
  - Clinical laboratories.
  - Serum sample (predose) for PK.
- Perform urine pregnancy test (for women of childbearing potential).
- Call IVRS/IWRS to register visit and obtain treatment kit number.
- Dispense and administer IMP:
  - Patients will be monitored at the study site for a minimum of 30 minutes after the injection.
- Remind patient to continue the background therapy and schedule appointment for next visit.

10.1.2.4 Visit 5 (Week 6)

- Record all medication use with start dose in e-CRF including starting dose.
- Inquire about AEs/SAEs and background asthma therapy tolerability.
- Measure vital signs (blood pressure, heart rate, respiration rate, body temperature, weight).
- Perform urine pregnancy test (for women of childbearing potential).
- Call IVRS/IWRS to register visit and obtain treatment kit number.
- Dispense and administer IMP:
  - Patients will be monitored at the study site for a minimum of 30 minutes after the injection.
- Remind patient to continue the background therapy.
- Schedule appointment for next visit and remind patient to withhold the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours and withholding the last dose of LABA for at least 12 hours (ultra-LABA like vilanterol should be withheld for at least 24 hours) and withholding the last dose of LAMA for at least 24 hours prior to the next visit.

10.1.2.5 Visit 6 (Month 2, Week 8)

- Record all medication use with start dose in e-CRF including starting dose.
- Inquire about AEs/SAEs and background asthma therapy tolerability.

- Measure vital signs (blood pressure, heart rate, respiration rate, body temperature, weight).
- Perform spirometry:
  - Spirometry will be performed after withholding the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours and withholding the last dose of LABA for at least 12 hours (ultra-LABA like vilanterol should be withheld for at least 24 hours) and withholding the last dose of LAMA for at least 24 hours prior to administration of investigational product. This will be verified before performing the measurements.
- Perform urine pregnancy test (for women of childbearing potential).
- Call IVRS/IWRS to register visit and obtain treatment kit number.
- Dispense and administer IMP:
  - Patients will be monitored at the study site for a minimum of 30 minutes after the injection.
- Remind patient to continue the background therapy and schedule appointment for next visit.

10.1.2.6 Visit 7 (Week 10)

- Record all medication use with start dose in e-CRF including starting dose.
- Inquire about AEs/SAEs and background asthma therapy tolerability.
- Measure vital signs (blood pressure, heart rate, respiration rate, body temperature, weight).
- Perform urine pregnancy test (for women of childbearing potential).
- Call IVRS/IWRS to register visit and obtain treatment kit number.
- Dispense and administer IMP:
  - Patients will be monitored at the study site for a minimum of 30 minutes after the injection.
- Remind patient to continue the background therapy.
- Schedule appointment for next visit and remind patient to withhold the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours and withholding the last dose of LABA for at least 12 hours (ultra-LABA like vilanterol should be withheld for at least 24 hours) and withholding the last dose of LAMA for at least 24 hours prior to the next visit. This will be verified before performing the measurements.
- Remind patients for the next visit in fasting state.

10.1.2.7 Visit 8 (Month 3, Week 12)

- Record all medication use with start dose in e-CRF including starting dose.
- Inquire about AEs/SAEs and background asthma therapy tolerability.
- Measure vital signs (blood pressure, heart rate, respiration rate, body temperature, weight).

- Perform physical examination.
- Administer health care resource utilization questionnaire.
- Perform spirometry:
  - Spirometry will be performed after withholding the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours and withholding the last dose of LABA for at least 12 hours (ultra-LABA like vilanterol should be withheld for at least 24 hours) and withholding the last dose of LAMA for at least 24 hours prior to administration of investigational product. This will be verified before performing the measurements.
- Perform blood sampling for:
  - Clinical laboratories.
  - Serum sample (predose) for PK and anti-dupilumab antibody analysis.
  - Hepatitis B viral load testing: For patients in Japan (or other countries/regions if there is local regulatory requirement) who were HBsAg negative and HBsAb positive at screening during the parent study, or at the additional test due to Local Amendment 03 (Japan).
- Perform urine pregnancy test (for women of childbearing potential).
- Obtain urine for urinalysis (dipstick).
- Call IVRS/IWRS to register visit and obtain treatment kits' numbers.
- Dispense and administer IMP
  - Patients will be monitored at the study site for a minimum of 30 minutes after the injection.
  - After Week 12, for patients (or parents caregivers) unable or unwilling to self-administer IMP, arrangements must be made for the patient to receive IMP injections at the study site as unscheduled visits, or for qualified site personnel and/or a professional caregiver to administer IMP at home at q2w intervals.
- Remind patient to continue the background therapy and schedule appointment for next visit.

10.1.2.8 Visit 9 (Month 4, Week 16)

- Record all medication use with start dose in e-CRF including starting dose.
- Inquire about AEs/SAEs and background asthma therapy tolerability.
- Measure vital signs (blood pressure, heart rate, respiration rate, body temperature, weight).
- Perform urine pregnancy test (for women of childbearing potential).
- Call IVRS/IWRS to register visit and obtain treatment kits' numbers.
- Dispense and administer IMP:

- Patients will be monitored at the study site for a minimum of 30 minutes after the injection.
- After Week 12, for patients (or parents caregivers) unable or unwilling to self-administer IMP, arrangements must be made for the patient to receive IMP injections at the study site as unscheduled visits, or for qualified site personnel and/or a professional caregiver to administer IMP at home at q2w intervals.

- Remind patient to continue the background therapy and schedule appointment for next visit.

10.1.2.9 Visit 10 (Month 5, Week 20)

- Record all medication use with start dose in e-CRF including starting dose.
- Inquire about AEs/SAEs and background asthma therapy tolerability.
- Measure vital signs (blood pressure, heart rate, respiration rate, body temperature, weight).
- Perform urine pregnancy test (for women of childbearing potential).
- Call IVRS/IWRS to register visit and obtain treatment kits' numbers.
- Dispense and administer IMP:
  - Patients will be monitored at the study site for a minimum of 30 minutes after the injection.
  - After Week 12, for patients (or parents caregivers) unable or unwilling to self-administer IMP, arrangements must be made for the patient to receive IMP injections at the study site as unscheduled visits, or for qualified site personnel and/or a professional caregiver to administer IMP at home at q2w intervals.
- Remind patient to continue the background therapy.
- Schedule appointment for next visit and remind patient to withhold the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours and withholding the last dose of LABA for at least 12 hours (ultra-LABA like vilanterol should be withheld for at least 24 hours) and withholding the last dose of LAMA for at least 24 hours prior to the next visit.
- Remind patients for the next visit in fasting state.

10.1.2.10 Visit 11 (Month 6, Week 24)

- Record all medication use with start dose in e-CRF including starting dose.
- Inquire about AEs/SAEs and background asthma therapy tolerability.
- Measure vital signs (blood pressure, heart rate, respiration rate, body temperature, weight).
- Perform physical examination.
- Administer paper ACQ-5, AQLQ(S), and health care resource utilization questionnaire.
- Perform spirometry:

- Spirometry will be performed after withholding the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours and withholding the last dose of LABA for at least 12 hours (ultra-LABA like vilanterol should be withheld for at least 24 hours) and withholding the last dose of LAMA for at least 24 hours prior to administration of investigational product. This will be verified before performing the measurements.

- Perform 12-lead ECG.
- Perform blood sampling for:
  - Clinical laboratories.
  - Serum sample (predose) for PK and anti-dupilumab antibody analysis.
  - Hepatitis B viral load testing: For patients in Japan (or other countries/regions if there is local regulatory requirement) who were HBsAg negative and HBsAb positive at screening during the parent study, or at the additional test due to Local Amendment 03 (Japan).
- Perform urine pregnancy test (for women of childbearing potential).
- Obtain urine for urinalysis (dipstick).
- Call IVRS/IWRS to register visit and obtain treatment kits' numbers.
- Dispense and administer IMP:
  - Patients will be monitored at the study site for a minimum of 30 minutes after the injection.
  - After Week 12, for patients (or parents caregivers) unable or unwilling to self-administer IMP, arrangements must be made for the patient to receive IMP injections at the study site as unscheduled visits, or for qualified site personnel and/or a professional caregiver to administer IMP at home at q2w intervals.
- Remind patient to continue the background therapy and schedule appointment for next visit.
- Perform monthly telephone contact with patient after Week 24 (Visit 11) to collect safety information.

10.1.2.11 Visit 12 (Month 9, Week 36)

- Record all medication use with start dose in e-CRF including starting dose.
- Inquire about AEs/SAEs and background asthma therapy tolerability.
- Measure vital signs (blood pressure, heart rate, respiration rate, body temperature, weight).
- Perform urine pregnancy test (for women of childbearing potential).
- Call IVRS/IWRS to register visit and obtain treatment kits' numbers.
- Dispense and administer IMP:

  - Patients will be monitored at the study site for a minimum of 30 minutes after the injection.
  - After Week 12, for patients (or parents caregivers) unable or unwilling to self-administer IMP, arrangements must be made for the patient to receive IMP injections at the study site as unscheduled visits, or for qualified site personnel and/or a professional caregiver to administer IMP at home at q2w intervals.
- Remind patient to continue the background therapy.
- Schedule appointment for next visit and remind patient to withhold the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours and withholding the last dose of LABA for at least 12 hours (ultra-LABA like vilanterol should be withheld for at least 24 hours) and withholding the last dose of LAMA for at least 24 hours prior to the next visit.
- Remind patients for the next visit in fasting state.
- Perform monthly telephone contact with patient after Week 24 (Visit 11) to collect safety information.

Note: Patient's next visit will be Visit 17 (EOT: Month 12, Week 48)

10.1.2.12 Visit 17 (End-of-Treatment: Month 12, Week 48)

End-of-Treatment visit is scheduled 2 weeks after the last IMP administration.

- Record all medication use with start dose in e-CRF including starting dose.
- Inquire about AEs/SAEs and background asthma therapy tolerability.
- Measure vital signs (blood pressure, heart rate, respiration rate, body temperature, weight).
- Perform physical examination.
- Administer paper ACQ-5 and AQLQ(S).
- Administer health care resource utilization questionnaire.
- Perform spirometry:
  - Spirometry will be performed after withholding the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours and withholding the last dose of LABA for at least 12 hours (ultra-LABA like vilanterol should be withheld for at least 24 hours) and withholding the last dose of LAMA for at least 24 hours prior to administration of investigational product. This will be verified before performing the measurements.
- Perform 12-lead ECG.
- Perform blood sampling for:
  - Clinical laboratories.
  - Serum sample (predose) for PK and anti-dupilumab antibody analysis.
  - Hepatitis B viral load testing: For patients in Japan (or other countries/regions if there is local regulatory requirement) who were HBsAg negative and HBsAb positive at

screening during the parent study, or at the additional test due to Local Amendment 03 (Japan).

- [redacted]
- Perform urine pregnancy test (for women of childbearing potential).
- Obtain urine for urinalysis (dipstick).
- Call IVRS/IWRS to register the EOT date.
- Schedule appointment for next visit and remind patient to withhold the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours and withholding the last dose of LABA for at least 12 hours (ultra-LABA like vilanterol should be withheld for at least 24 hours) and withholding the last dose of LAMA for at least 24 hours prior to the next visit.
- Remind patient to continue the background therapy.
- Remind patients to arrive for next visit in fasting state.
- Perform monthly telephone contact with patient after Week 24 (Visit 11) to collect safety information.

10.1.2.13 Visit 18 (End-of-Study: Month 15, Week 60)

End-of-Study Visit is scheduled 12 weeks after EOT.

- Record all medication use with start dose in e-CRF including starting dose.
- Inquire about AEs/SAEs and background asthma therapy tolerability.
- Measure vital signs (blood pressure, heart rate, respiration rate, body temperature, weight).
- Perform physical examination.
- Administer health care resource utilization questionnaire.
- Perform spirometry:
  - Spirometry will be performed after withholding the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours and withholding the last dose of LABA for at least 12 hours (ultra-LABA like vilanterol should be withheld for at least 24 hours) and withholding the last dose of LAMA for at least 24 hours prior to administration of investigational product. This will be verified before performing the measurements.
- Perform 12-lead ECG.
- Perform blood sampling for:
  - Clinical laboratories.
  - Serum sample (predose) for PK and anti-dupilumab antibody analysis.
- Perform urine pregnancy test (for women of childbearing potential).
- Obtain urine for urinalysis (dipstick).

- Call IVRS/IWRS to register the EOS date.

10.2 DEFINITION OF SOURCE DATA

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

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

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 should be fully documented in the e-CRF. In any case, the patient should remain in the study as long as possible.

10.3.1 Temporary treatment discontinuation with investigational medicinal product(s)

The following conditions will be causes for temporary treatment discontinuation:

- Infections or infestations that do not respond to medical treatment.
- Any laboratory abnormality that meets temporary treatment discontinuation criteria as per Appendix D.

In addition, temporary treatment discontinuation may be considered by the Investigator because of suspected AEs. Re-initiation 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 AE is sufficiently resolved and unlikely to recur after resuming therapy with IMP, that the responsibility of the IMP in the occurrence of the concerned event was unlikely, and that the selection criteria for the study are still met (see Section 7.1 and Section 7.2).

For all temporary treatment discontinuations, the Investigator should record injections that are missed in the e-CRF IMP pages.

10.3.2 Permanent treatment discontinuation with investigational medicinal product(s)

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

In case permanent treatment discontinuation, the patient should be scheduled for the EOT Visit and procedures and continue the 12-week follow-up period for safety evaluation.

10.3.3 List of criteria for permanent treatment discontinuation

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

Any abnormal laboratory value or ECG parameter should be immediately rechecked for confirmation (within 24 hours) before making a decision of permanent discontinuation of the IMP for the concerned patient. Threshold values for the discontinuation of IMP are defined in collaboration with Global Pharmacovigilance and Epidemiology (see Appendix D).

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 also safety 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 I).
- Serum ALT >3 Upper Limit of Normal (ULN) concurrent with Total Bilirubin >2 ULN (see Appendix D).
- Serum ALT >5 ULN if baseline ALT < 2 ULN or ALT >8 ULN if baseline ALT >2 ULN (Appendix D).

Note: Any abnormal laboratory value or ECG parameter will be immediately rechecked for confirmation before making a decision of permanent discontinuation of the IMP for the concerned patient.

10.3.4 Handling of patients after permanent treatment discontinuation

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

After the permanent discontinuation of dupilumab, the patients will be assessed using the procedure normally planned for the EOT Visit. After 12 weeks follow-up time, the patients will be asked to return for the EOS assessments.

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

10.3.5 Procedure and consequence for patient withdrawal from study

The patients may withdraw from the study before study completion if they decide to do so, at any time and irrespective of the reason.

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

If possible, the patients are assessed using the procedures normally planned for the EOT Visit, including a PK sample, if appropriate.

A patient should only be designated as lost to follow-up if the site is unable to establish contact with the patient after 3 documented attempts via 2 different methods (phone, text, e-mail, certified letter, etc).

Patients who have withdrawn from the study cannot be re-enrolled (treated) in the study. Their inclusion and treatment numbers must not be reused. The statistical analysis plan (SAP) will specify how these patients lost to follow-up for their primary endpoints will be analyzed. The patients may withdraw from the study before study completion if they decide to do so, at any time and irrespective of the reason.

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.

Asthma exacerbation events are collected as secondary efficacy endpoints via the "Asthma Exacerbation Event Form". These events should not be reported as AEs unless they fulfill a seriousness criterion.

For this study, asthma exacerbations should be managed by the Investigators based on their medical judgment and applicable national / international asthma management guidelines.

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, or
- 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 as a medically important event. The list is not intended to be exhaustive:

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

- Bullous cutaneous eruptions.
- Cancers diagnosed during the study or aggravated during the study (only if judged unusual/significant by the Investigators in oncology studies).
- Chronic neurodegenerative diseases (newly diagnosed) or aggravated during the study (only if judged unusual/significant by the Investigators in studies assessing specifically the effect of a study drug on these diseases).

10.4.1.3 Adverse event of special interest

An AESI is an AE (serious or non-serious) of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and 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 or removed during a study by protocol amendment.

For these AESIs, the Sponsor will be informed immediately (ie, within 24 hours), per SAE notification described in Section 10.4.3, even if not fulfilling a seriousness criterion, using the corresponding pages/screens in the e-CRF.

- Anaphylactic reactions or systemic allergic reactions that are related to IMP and require treatment (see Appendix H for Definition of Anaphylaxis).
- Severe injection site reactions that last longer than 24 hours.
- Any infection meeting at least one of the following criteria (see Section 10.6.3):
  - Any serious infection (SAE).
  - Requires parenteral (intravenous, intramuscular, SC) antimicrobial therapy.
  - Requires oral antimicrobial therapy for longer than 2 weeks.
  - Is a parasitic infection.
  - Is an opportunistic infection (see Appendix I).

  Note: Antimicrobial therapy refers to antibiotic, antiviral, and antifungal agents.
- Significant ALT elevation:
  - ALT >5 x the ULN in patients with baseline ALT ≤2 x ULN; or
  - ALT >8 x ULN if baseline ALT >2 x ULN.
- Pregnancy:
  - 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 discontinued.
  - Follow-up of the pregnancy in a female participant or in a female partner of a male participant is mandatory until the outcome has been determined (see Section 9.2.1.4.1).

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

10.4.2 General guidelines for reporting adverse events

- All AEs, regardless of seriousness or relationship to IMP/Non-IMP, spanning from the signature of the informed consent form until the end of the study as defined by the protocol for that patient, are to be recorded on the corresponding page(s) or screen(s) of the e-CRF.
- 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, should be followed until resolution, stabilization, or death and related data will be collected.
- When treatment is prematurely discontinued, the patient's observations will continue until the end of the study as defined by the protocol for that patient.
- Laboratory, vital signs or ECG abnormalities are to be recorded as AEs only if:
  - Symptomatic 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.

Table 5 summarizes the reporting timelines.

Table 5 - Adverse event/laboratory abnormality reporting timelines

Adverse event / laboratory abnormality		Reporting timeline
Serious adverse event (SAE)		Within 24 hours
Adverse event (non-SAE, non-AESI)		Routine
Pregnancy		Within 24 hours
Overdose	Symptomatic	Within 24 hours
	Asymptomatic	Routine
ALT elevation		
ALT >5 ULN if baseline ALT is ≤2 ULN		Within 24 hours
ALT >8 ULN if baseline ALT is >2 ULN		Within 24 hours
ALT >3 ULN plus total bilirubin >2 ULN		Within 24 hours
Anaphylactic reactions or acute allergic reactions that require immediate treatment		Within 24 hours
Severe injection site reactions that last longer than 24 hours		Within 24 hours
Infections, as defined in Section 10.4.1.3		Within 24 hours

Abbreviations: AESI = Adverse event of special interest; ALT= Alanine Aminotransferase; SAE = serious adverse event; ULT= Upper limit of normal.

10.4.3 Instructions for reporting serious adverse events

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

- ENTER (within 24 hours) the information related to the SAE in the appropriate screens of the e-CRF; the system will automatically send a notification to the monitoring team after approval of the Investigator within the e-CRF or after a standard delay.
- SEND (preferably by fax or e-mail) a photocopy of all examinations carried out and the dates on which these examinations were performed, to the representative of the monitoring team whose name, fax number, and email address appear on the clinical trial protocol. Care should be taken to ensure that the patient's identity is protected and the patient's identifiers in the clinical trial are properly mentioned on any copy of a source document provided to the Sponsor. For laboratory results, include the laboratory normal ranges.
- All further data updates should be recorded in the e-CRF as appropriate, and further documentation as well as additional information (for laboratory data, concomitant medications, patient status, etc) should be sent (by fax or e-mail) to the monitoring team within 24 hours of knowledge. In addition, every effort should be made to further document any SAE that is fatal or life threatening within a week (7 days) of the initial notification.
- A back-up plan (using a paper CRF process) is available and should be used when the e-CRF system does not work.

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

10.4.4 Guidelines for 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 pages/screens in the e-CRF. Instructions for AE reporting are summarized in Table 6.

10.4.5 Guidelines for management of specific laboratory abnormalities

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

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

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

In addition, on treatment eosinophil counts >3000 cells/µL (3.0 giga/L) are to be reported as AEs.

NOTE: Increase in ALT is considered as an AESI (see Section 10.4.1.3).

Appropriate reporting according to categories will appear in the CRF instructions/completion guide.

Table 6 - Summary of adverse event reporting instructions

EVENT CATEGORY	REPORTING TIMEFRAME	SPECIFIC EVENTS IN THIS CATEGORY	CASE REPORT FORM COMPLETION		
			AE form	Safety Comple-mentary Form	Other specific forms
AE (non-SAE, non-AESI)	Routine	Any AE that is not SAE or AESI	Yes	No	No
SAE (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)	As per Section 10.4.1.3	Yes	Yes	No

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

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 (ie, a Serious Unexpected Serious Adverse Reaction [SUSAR]), to the regulatory authorities, Institutional Review Boards / Institutional Ethics Committees (IRBs/IECs) 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.

In this study 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 (see the Investigator's Brochure).

Any other AE not listed as an expected event in the Investigator's Brochure or in this protocol will be considered unexpected.

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

10.6 SAFETY INSTRUCTIONS

During the study, all patients will be closely monitored.

In addition, any problems related to dupilumab injection administration should be documented in the patient's home dosing diary and in the specific e-CRF pages 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 H "Definition of Anaphylaxis", which describes the clinical criteria for the diagnosis of anaphylaxis.

Patients should be monitored for at least 30 minutes after each study-site administered investigational product administration for any signs or symptoms of a hypersensitivity reaction. Trained personnel and medications should be available to treat anaphylaxis or any severe allergic reaction if it occurs. Furthermore, the patients will be advised, when the IMP is administered at home, to self-monitor for potential signs and symptoms that may suggest a hypersensitive reaction for 30 minutes after administration.

Anaphylactic reactions or systemic allergic reactions that are related to IMP and require treatment must be reported as an AESI (within 24 hours, for further details, see AESI definition in Section 10.4.1.3) and study medication must be permanently discontinued. ADA and PK samples will be collected near the onset and resolution of the AESI for any additional analysis.

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. ADA and PK samples will be collected near the onset and resolution of the AESI for any additional analysis.

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 slum areas, lack of running water, consumption of uncooked, undercooked, or otherwise potentially contaminated food, close contact with carriers and vectors, etc). Subsequent medical assessments (eg, stool exam, blood tests, etc) must be performed in order to rule out parasitic infection/infestation. Patients with

confirmed parasitic infections during the study should be reported as AESI with immediate notification.

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 I), patients must be permanently discontinued from IMP.

10.6.4 Elevated liver function tests

No preclinical or clinical data have suggested any hepatic toxicity of dupilumab; however, as general consideration of clinical development, the administration of immunosuppressant or immunomodulating agents may represent an additional risk factor for hepatotoxicity.

In order to closely follow liver function tests (LFT), assessment of total protein, albumin, total bilirubin, ALT, AST, and ALP are measured as part of the clinical laboratory testing. Clinical laboratory testing also includes a hepatitis screen for HBsAg, HBcAb-IgM, HCVAb. Patients who are total-HBcAb positive and HBsAg negative must undergo HBV DNA testing to determine eligibility. Furthermore, it is recommended that patients who are receiving potentially immunosuppressive therapy and are HBcAb positive and HBV DNA negative undergo surveillance HBV DNA every 1 to 3 months depending upon the individual potential therapeutic risk and comorbidities. If necessary, a hepatologist should be consulted on a case-by-case basis.

Note: Japanese patients who have rolled over from DRI12544 study should be retested for hepatitis B (HBsAg, HBsAb, and HBcAb) after Visit 1, at any time during the LTS12551 study via the earliest scheduled study visit, after IRB approval for Local Amendment 03 (Japan). Japanese patients with HBsAg negative and HBsAb positive at any time during the parent study or at the additional test due to Local Amendment 03 (Japan) do not need to discontinue the study. In Japan (or other countries/regions if there is local regulatory requirement), hepatitis B viral load (HBV DNA) will be tested for patients who are HBsAg negative and HBsAb positive at screening during the parent study or at the additional test due to Local Amendment 03 (Japan).

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

10.7 ADVERSE EVENTS MONITORING

All events will be managed and reported in compliance with all applicable regulations, and included in the final CSR.

11 STATISTICAL CONSIDERATIONS

11.1 DETERMINATION OF SAMPLE SIZE

The primary objective of the study is to evaluate the long-term safety and tolerability of dupilumab in patients with asthma who participated in previous dupilumab asthma clinical trials. Hence, the maximal number of patients to participate in this extension study will be the number corresponding to the total randomized in those studies.

11.2 DISPOSITION OF PATIENTS

Screened patients are defined as any patients who signed the informed consent form.

Enrolled patients consist of all the patients who signed informed consent and had a treatment kit number allocated and recorded in IVRS/IWRS 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 LTS12551 study.

11.3 ANALYSIS POPULATIONS

11.3.1 Efficacy populations

Efficacy population is the same as the safety population.

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 in the LTS12551 study.

The treatment-emergent period is defined as the time from the first dose of dupilumab in LTS12551 up to the last dose of dupilumab plus 2 weeks (corresponding to one dose interval) plus 12 weeks (follow-up period duration). The pre-treatment period is defined as the time from the starting of AE reporting in LTS12551 study up to the first dose of dupilumab in LTS12551.

11.3.3 Pharmacokinetics population

The PK population (the systemic drug concentration population) will consist of all the patients in the safety population with at least one non-missing and evaluable predose serum concentration value after the first dose of dupilumab in the LTS12551 study.

11.3.4 Anti-drug antibody population

The ADA population will consist of all the patients in the safety population with at least one predose sample that was assayed successfully using the ADA assay after the first dose of dupilumab in the LTS12551 study.

11.4 STATISTICAL METHODS

11.4.1 Extent of study treatment exposure and compliance

Extent of study treatment exposure and compliance will be summarized on 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. No imputation will be made for patients with missing or incomplete data.

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 planned to take during the treatment period).

Treatment compliance will be summarized descriptively (number, mean, SD, median, minimum and maximum). The percentage of patients with compliance <80% will be summarized.

11.4.2 Analyses of efficacy endpoints

There will be no confirmatory analysis for the efficacy variables. All analyses will be done descriptively on the safety population in observed case, as appropriate. The baseline value for the applicable efficacy parameters is the original baseline from the parent studies.

For the continuous efficacy variables, descriptive statistics (number, mean, SD, median, minimum and maximum) will be presented for the parameter and its change from baseline over visits. In addition, a figure of mean change from baseline (with corresponding standard error) will be presented for the continuous efficacy parameter over visits.

For the categorical efficacy variables, the number and percentage will be presented over time for all patients who have data available at that time point.

For severe exacerbation events, the total number of severe exacerbation events, total patient-years, unadjusted annualized severe exacerbation event rate, and individual patient annualized severe exacerbation event rate (number, mean, SD, median, minimum and maximum) during the treatment period will be summarized.

More details about the efficacy analysis can be found in the SAP.

11.4.3 Analyses of safety data

All safety analysis will be performed on the safety population. The baseline value for the applicable safety parameters is the original baseline from the parent studies.

11.4.3.1 Adverse events

Adverse event reported in this study will be coded using the version of the Medical Dictionary for Regulatory Activities (MedDRA) 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

Treatment-emergent AE incidence tables will be presented by system organ class (SOC) (sorted by internationally agreed order), high level group term (HLGT), high level term (HLT) and preferred term (PT) sorted in alphabetical order, the number (n) and percentage (%) of patients experiencing a TEAE. Multiple occurrences of the same event in the same patient will be counted only once in the tables. The denominator is 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 relation to the study drug. Adverse events that are not treatment-emergent will be summarized separately.

11.4.3.1.2 Adverse Events of Special Interest

The following summaries will be generated:

- Incidence of each AESI will be tabulated.
- The time-to-first event analyzed using Kaplan-Meier methods and displayed as Kaplan-Meier plots (cumulative incidence [%] versus time based on Kaplan-Meier estimates) will be provided to depict the course of onset over time. Number of treatment-emergent AESIs per 100 patient-years (total number of events adjusted for the total duration of exposure) will be presented by decreasing incidence of PT.
- An overview summary of the number (%) of patients with:
  - Any TEAE.
  - Any serious AE (regardless of treatment-emergent status).

- Any treatment-emergent SAE.
- Any AE leading to death.
- Any TEAE leading to permanent study drug discontinuation.
- Any TEAE by maximum intensity, corrective treatment, and final outcome.
- Cumulative incidence (Kaplan-Meier estimates) up to specified time points.

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

11.4.3.1.3 Death

The following summaries of deaths will be generated:

- Number (%) of patients who died by study period (TEAE, on-study) and reasons for death summarized on the safety population.
- TEAE leading to death (death as an outcome on the AE CRF page as reported by the Investigator) by primary SOC, HLGT, HLT, and PT showing number (%) of patients sorted by internationally agreed order of SOC and alphabetic order of HLGT, HLT, and PT.

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

11.4.3.1.4 Clinical laboratory evaluation, vital signs, and electrocardiogram data

Results and change from baseline for the parameters will be summarized for baseline and each post-baseline time point, endpoint, minimum and maximum value. Summary statistics will include number of patients, mean, SD, median, lower and upper quartiles, minimum and maximum.

The proportion of patients who had at least one incidence of potentially clinically significant abnormality (PCSA) at any time during the TEAE period will be summarized by biological category. Shift tables showing changes with respect to baseline and Week 0 (predose) status will be provided.

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

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

- The PCSA values are defined as abnormal values considered medically important by the Sponsor according to predefined criteria/thresholds based on literature review and defined by the Sponsor for clinical laboratory tests, vital signs, and ECG.
- PCSA criteria will determine which patients had at least 1 PCSA during the on-treatment period, taking into account all evaluations performed during the on-treatment period,

including unscheduled or repeated evaluations. The number of all such patients will be the numerator for the on-treatment PCSA percentage.

11.4.4 Analyses of pharmacokinetic and pharmacodynamic variables

11.4.4.1 Pharmacokinetic analysis - (drug concentration analyses)

The PK analyses will be performed on the PK (systemic drug concentration) population. The baseline value of each applicable PK variable is the original baseline from the parent studies.

Serum concentrations of functional dupilumab will be summarized using arithmetic and geometric means, SD, standard error of the mean (SEM), coefficient of variation, median, minimum and maximum per visit.

11.4.4.2 Anti-drug antibodies analysis

The ADA analyses will be performed on the ADA population. The baseline value of each applicable ADA variable is the original baseline from the parent studies.

The incidence of positivity in the ADA assay will be assessed as absolute occurrence (n) and percent of patients (%). Listing of ADA titer levels will be provided for patients positive in the ADA assay. Samples that are positive in the ADA assay will be further characterized for the presence of anti-dupilumab neutralizing antibodies, if applicable. Assessment of the potential impact of ADA on safety, efficacy, and PK may be provided. The ADA analyses will be detailed in SAP.

11.4.4.3 Pharmacodynamics

The biomarker analyses will be applied to the safety population. The baseline value for the applicable pharmacodynamic (PD) variables is the original baseline from the parent studies. For all PD parameters, the descriptive statistics (number, mean, median, SD, lower and upper quartiles, minimum and maximum) will be summarized over time for the raw measurements, the change from baseline and percentage change from baseline. Summary plots (mean±SEM) over time on the raw measurements, change from baseline and percentage change from the baseline will be presented for the PD parameters.

All parameters will be summarized in descriptive statistics.

11.4.5 Analyses of patient reported outcomes (health-related quality of life / health economics variables)

Change from baseline in the following variables: global measure of AQLQ(S) and the four domains, the quantitative variables of the EQ-5D-3L (single index utility) will be summarized in the same way as described previously for the continuous efficacy variables.

11.5 INTERIM ANALYSIS

Interim study reports may be prepared to support regulatory submissions of an indication in the dupilumab project or other purposes. No alpha adjustment is needed for the final CSR.

12 ETHICAL AND REGULATORY CONSIDERATIONS

12.1 ETHICAL AND REGULATORY STANDARDS

This clinical trial will be conducted by the Sponsor, the Investigator, delegated Investigator staff and Subinvestigator, in accordance with the principles laid down by the 18th World Medical Assembly (Helsinki, 1964) and all applicable amendments laid down by the World Medical Assemblies, and the International Council on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use 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 of all pertinent aspects of the clinical trial including the written information giving approval/favorable opinion by the Institutional Review Board / Institutional Ethics Committee (IRB/IEC). All participants should be informed to the fullest extent possible about the study, in language and terms they are able to understand.

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

A copy of the signed and dated written informed consent form will be provided to the patient (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 for pediatric patients. 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 IRB/IEC approved standard practice for pediatric participants at each participating center (age of assent to be determined by the IRB/IEC or be consistent with the local requirements):

- Pediatric participants who can read the assent form will do so before writing their name and dating or signing and dating the form.
- Pediatric participants who can write but cannot read will have the assent form read to them before writing their name on the form.

If informed consent is obtained under special circumstances (emergency, from a guardian, minor, etc), the method should be specified following the ICH requirements.

12.3 INSTITUTIONAL REVIEW BOARD / INDEPENDENT ETHICS COMMITTEE

As required by local regulation, the Investigator or the Sponsor must submit this clinical trial protocol to 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, informed consent form, Investigator's Brochure, Investigator's curriculum vitae, etc) and the date of the review should be clearly stated on the written IRB/IEC approval/favorable opinion.

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

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

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 INVESTIGATOR(S)

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

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

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

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

13.2 RESPONSIBILITIES OF THE SPONSOR

The Sponsor of this clinical trial is responsible to 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 CRFs. Thus, the main duty of the monitoring team is to help the Investigator and the Sponsor maintain a high level of ethical, scientific, technical and regulatory quality in all aspects of the clinical trial.

At regular intervals during the clinical trial, the study 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 CRF entries against the source documents, except for the pre-identified source data directly recorded in the CRF. The informed consent form will include a statement by which the patient allows the Sponsor's duly authorized personnel, the IRB/IEC, and the regulatory authorities to have direct access to original medical records, which support the data on the CRFs (eg, patient's medical file, appointment books, original laboratory records, etc). These personnel, bound by professional secrecy, must maintain the confidentiality of all personal identity or personal medical information (according to confidentiality and personal data protection rules).

13.4 USE AND COMPLETION OF CASE REPORT FORMS AND ADDITIONAL REQUEST

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

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

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

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

13.5 USE OF COMPUTERIZED SYSTEMS

The complete list of computerized systems used for the study is provided in a separate document which is maintained in the Sponsor and Investigator study files.

Computerized systems planned to be used during the different steps of the study are:

- For screening and enrollment activities, IVRS/IWRS.
- For data management activities, Medidata Rave.
- For statistical activities, SAS, query Advisor 6.01.
- For pharmacovigilance activities, AWARE.
- For investigational product ordering/tracking, SmartSupplies PMD.
- For monitoring activities, IMPACT, POLARIS, CTI, I/J review, SmartSupplies RAR.
- For medical writing activities, DOMASYS.
- CT-fast for IMP forecasts.

External data loading is planned for this clinical trial.

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 Investigator's Brochure and the results obtained during the course of the clinical trial, is confidential, prior to the publication of results. The Investigator and any person under his/her authority agree to undertake to keep confidential and not to disclose the information to any third party without the prior written approval of the Sponsor.

However, the submission of this clinical trial protocol and other necessary documentation to the 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.
- Patient’s race or ethnicity will be collected in this study because these data are required by several regulatory authorities.
- The data collected in this study will only be used for the purpose(s) of the study and to document the evaluation of the benefit/risk ratio, efficacy and safety of the product(s). They may be further processed if they have been anonymized.

14.6 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 IRBs/IECs 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 study 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.

14.9 CLINICAL TRIAL RESULTS

The Sponsor will be responsible for preparing a CSR 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 study 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 study 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).

Sanofi is free to publish, and to communicate the recommendations made by the DMC, using all existing or future means of communication with an agreement between both parties.

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 of the clinical trial protocol without agreement by the Sponsor and prior review and documented approval/favorable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to clinical trial patients, or when the change(s) involves only logistical or administrative aspects of the trial. Any change agreed upon will be recorded in writing, the written amendment will be signed by the Investigator and by the Sponsor and the signed amendment will be filed with this clinical trial protocol.

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

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

15.1 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 study site, for any reason whatsoever, the appropriate IRB/IEC and regulatory authorities should be informed according to applicable regulatory requirements.

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17 APPENDICES

Appendix A. List of prohibited live, attenuated vaccines

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

This list is indicative and not exhaustive.

Appendix B. Examples of commonly used asthma controller therapies

Controller groups	Medications
ICS	Beclomethasone dipropionate CFC
ICS	Beclomethasone dipropionate HFA
ICS	Budesonide
ICS	Ciclesonide
ICS	Fluticasone propionate
ICS	Mometasone furoate
ICS	Triamcinolone acetonide
ICS	Fluticasone furoate
ICS/LABA	Fluticasone Propionate / Salmeterol
ICS/LABA	Fluticasone Propionate / Formoterol
ICS/LABA	Fluticasone Furoate / Vilanterol
ICS/LABA	Budesonide /Formoterol
ICS/LABA	Mometasone Furoate / Formoterol
ICS/LABA	Beclometasone Dipropionate/ Formoterol
LABA	Salmeterol
LABA	Formoterol
LABA	Bambuterol
LABA	Clenbuterol
LABA	Tulobuterol
LABA	Vilanterol
LABA	Olodaterol
LABA	Indacaterol
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

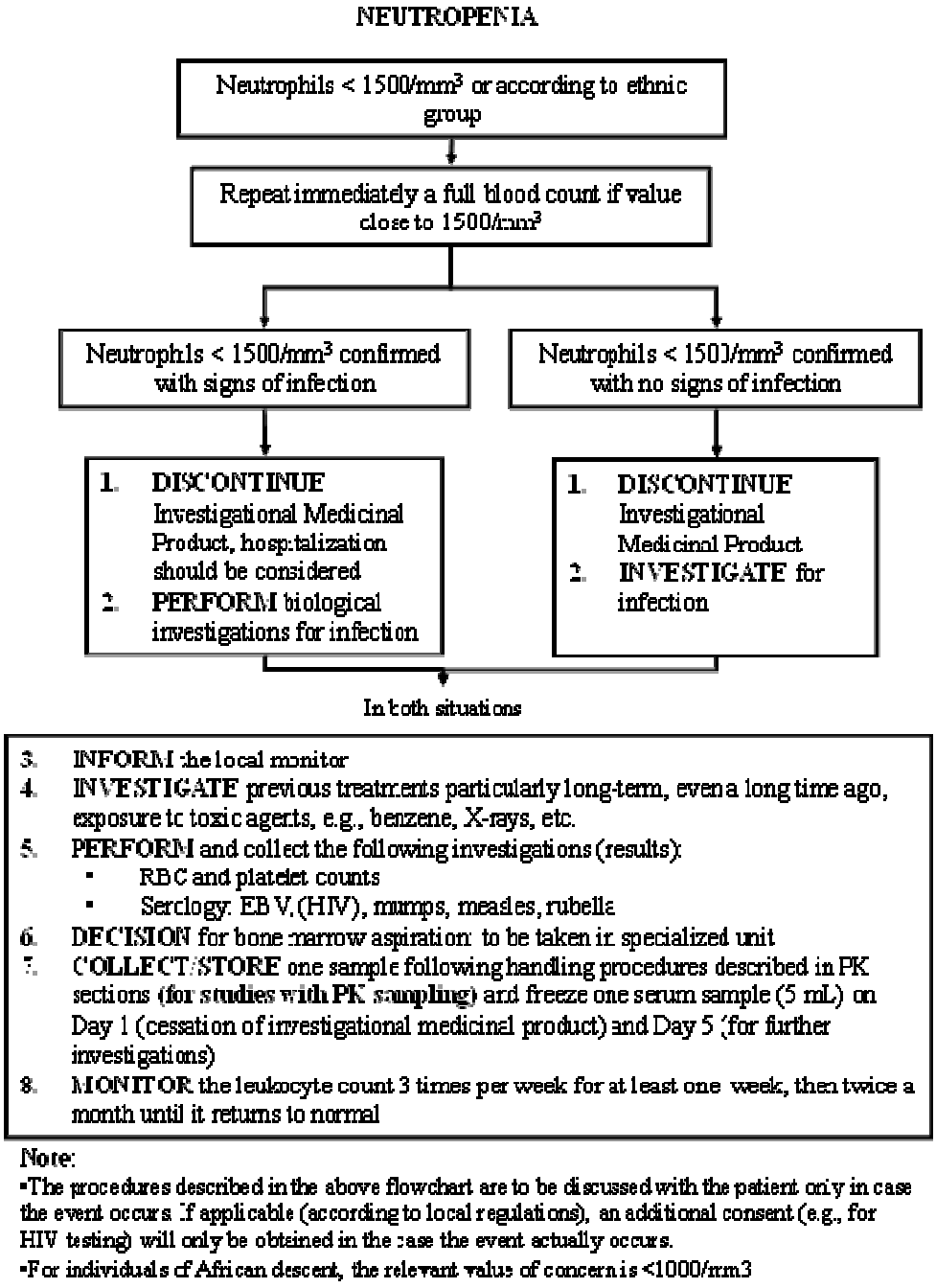
This list is indicative and not exhaustive.

Appendix C. Examples[1] of CYP substrates with narrow therapeutic range

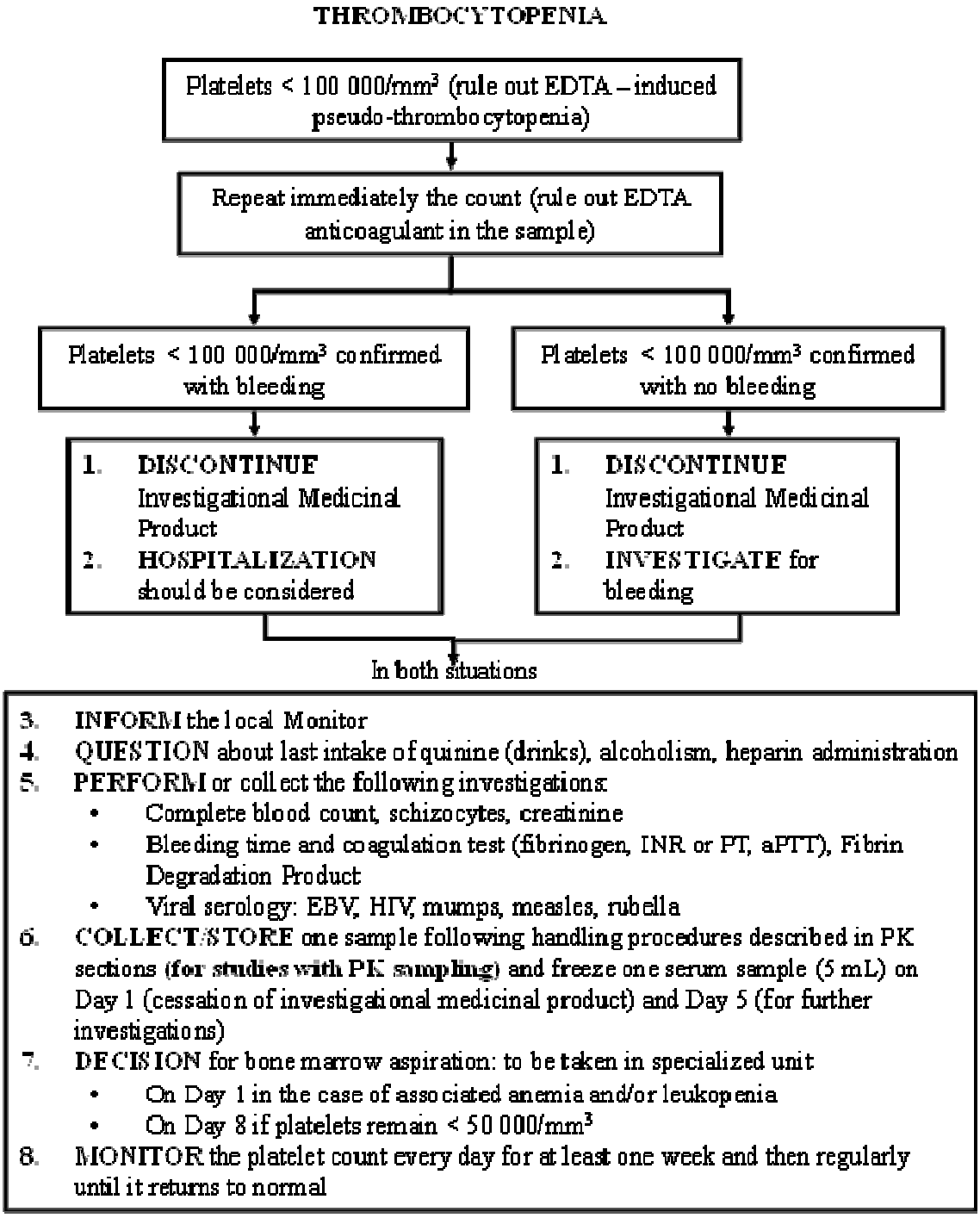
CYP enzymes	Substrates with narrow therapeutic range[2]
CYP1A2	Theophylline, tizanidine
CYP2C8	Paclitaxel
CYP2C9	Warfarin, phenytoin
CYP2C19	S-mephenytoin
CYP3A[3]	Alfentanil, astemizole[4] cisapride, [4] cyclosporine [5], dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus [5], terfenadine[4]
CYP2D6	Thioridazine

1) Note that this is not an exhaustive list. For an updated list, see the following link: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm
(2) CYP *substrates with narrow therapeutic range* refers to drugs whose exposure-response relationship indicates that small changes in their exposure levels by the concomitant use of CYP inhibitors or inducers may lead to either serious safety concerns (eg, Torsades de Pointes) or loss of therapeutic effect.
(3) Because a number of CYP3A substrates (eg, darunavir, maraviroc) are also substrates of P-gp, the observed increase in exposure could be due to inhibition of both CYP3A and P-gp.
(4) Withdrawn from the United States market because of safety reasons
(5) Prohibited medication during the study

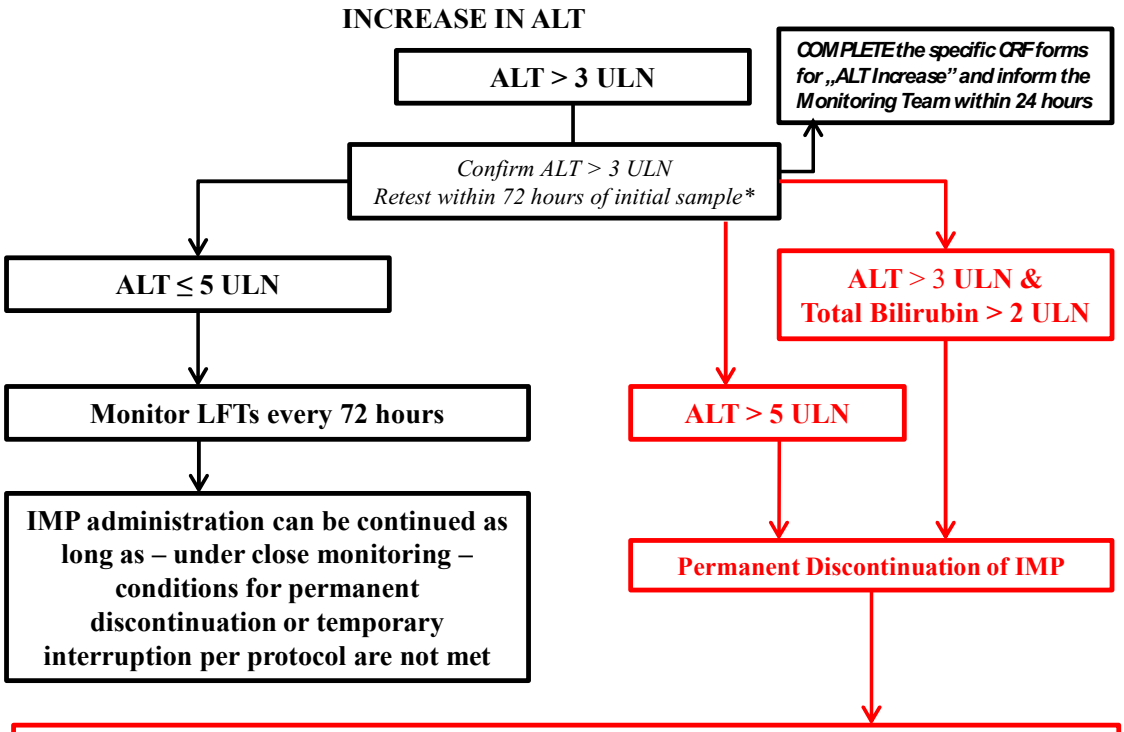
Appendix D. General guidance for the follow-up of laboratory abnormalities by sanofi



Neutropenia is to be recorded as AE only if at least one of the criteria listed in the General guidelines for reporting AEs in Section 10.4.2 is met.



Thrombocytopenia is to be recorded as AE only if at least one of the criteria listed in the General guidelines for reporting AEs in Section 10.4.2 is met.



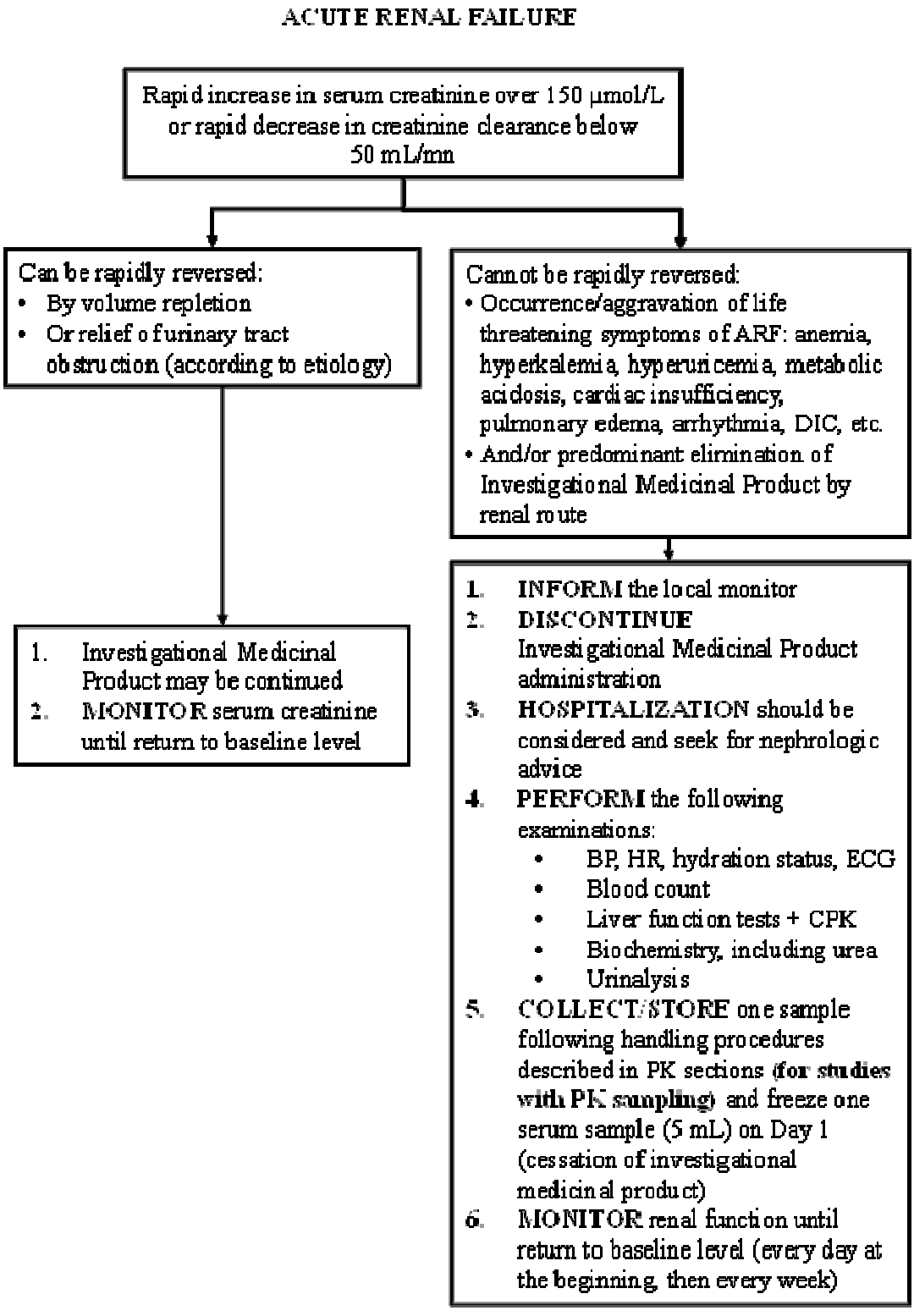
In ANY CASE, FOLLOW the instructions listed in the box below:

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

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

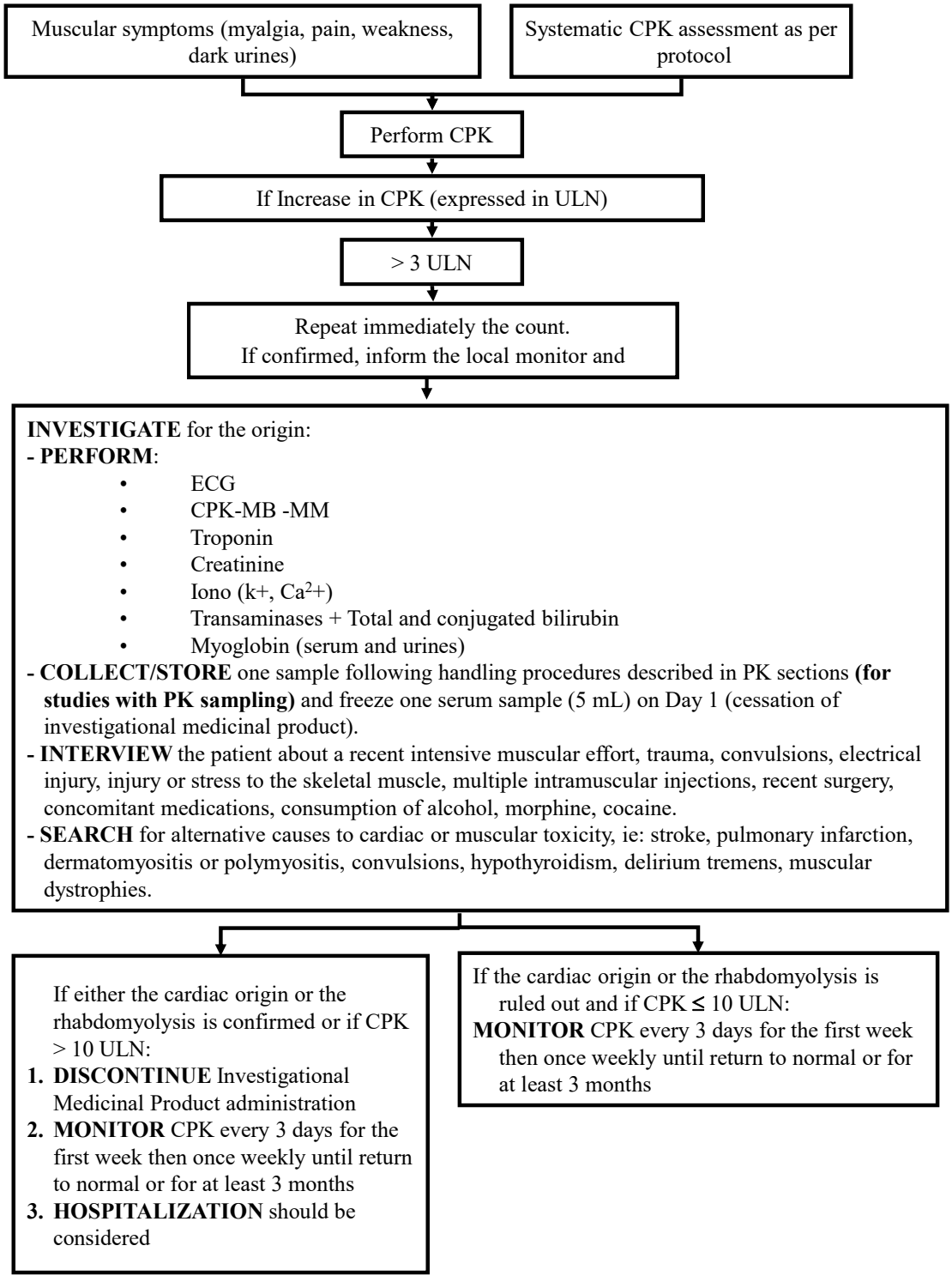
Note:

- "Baseline" refers to ALT sampled at baseline visit; or if baseline value unavailable, to the latest ALT sampled before the baseline visit. The algorithm does not apply to the instances of increase in ALT during screening.
- See Section 10.4 for guidance on safety reporting.
- Normalization is defined as ≤ULN or baseline value, if baseline value is >ULN.



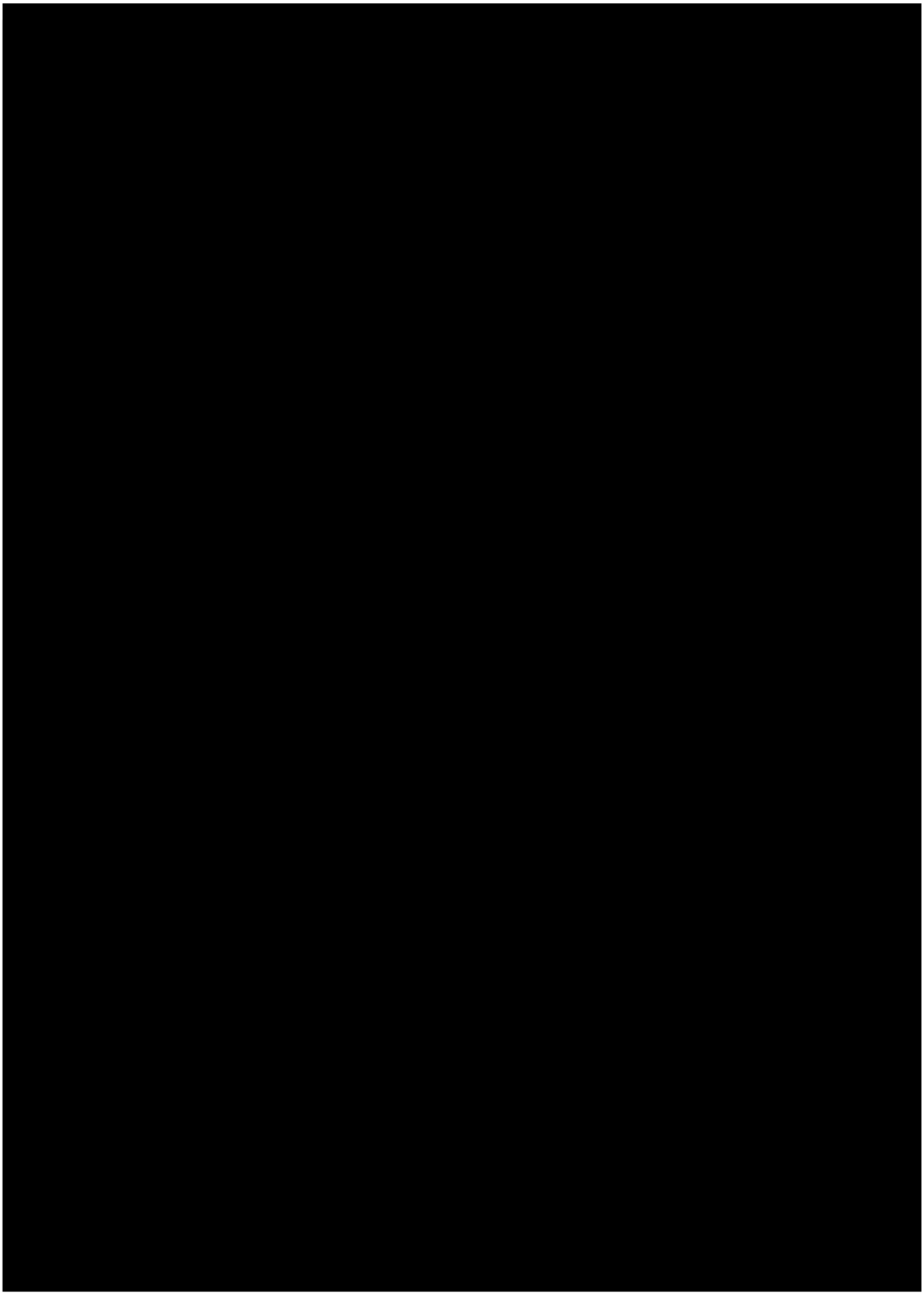
Acute renal failure is to be recorded as AE only if at least one of the criteria listed in the General guidelines for reporting AEs in Section 10.4.2 is met.

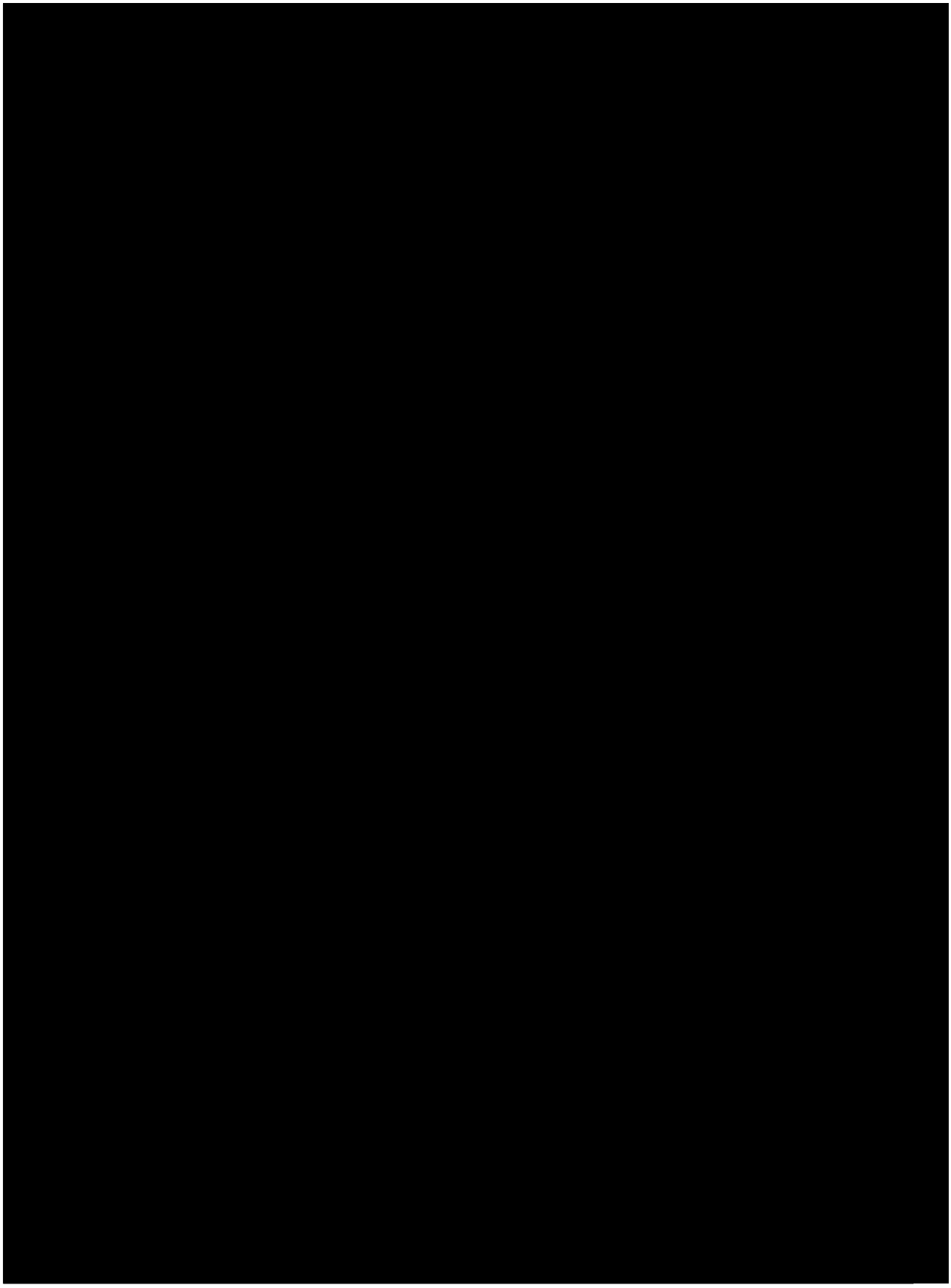
SUSPICION OF RHABDOMYOLYSIS

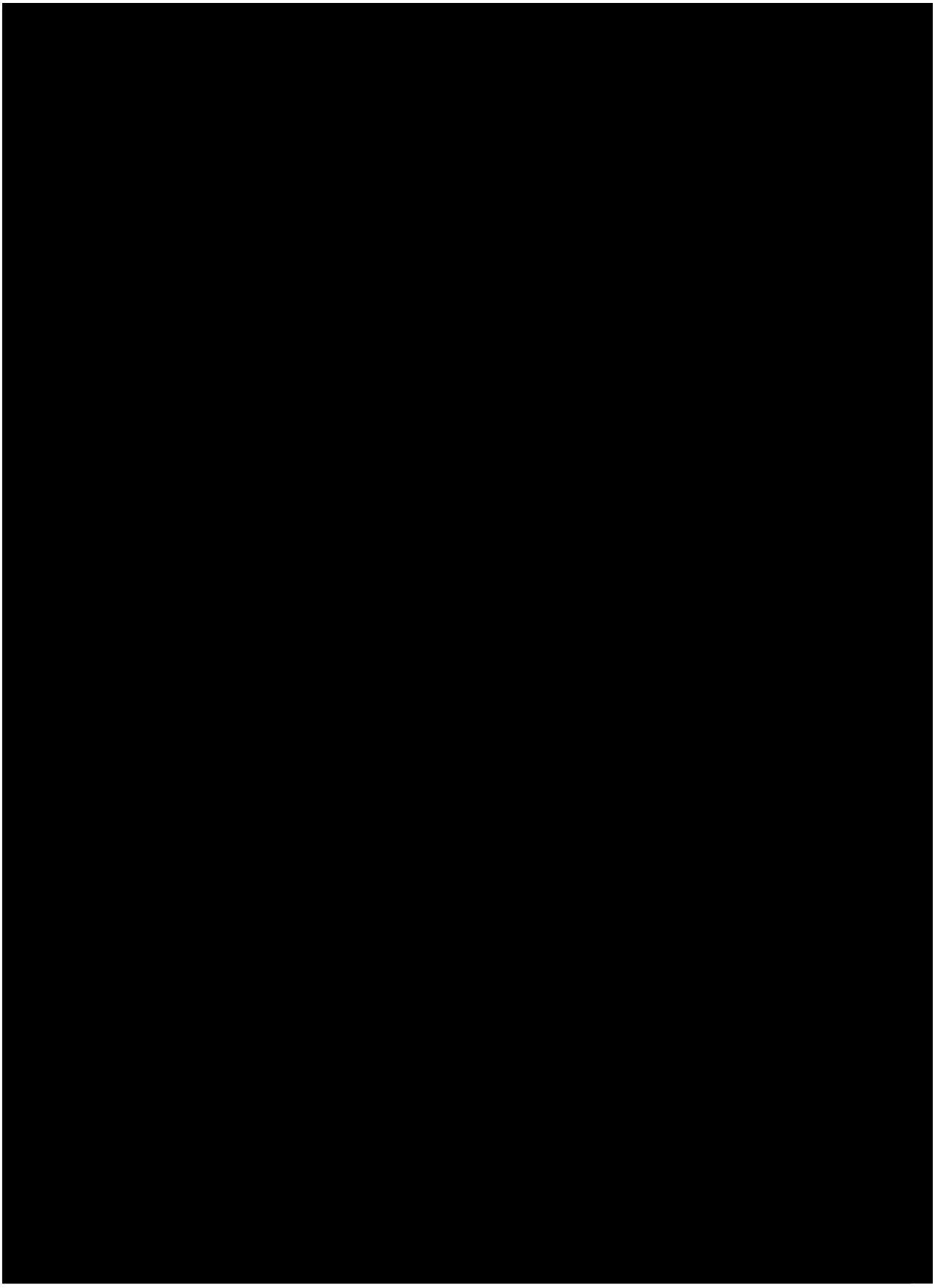


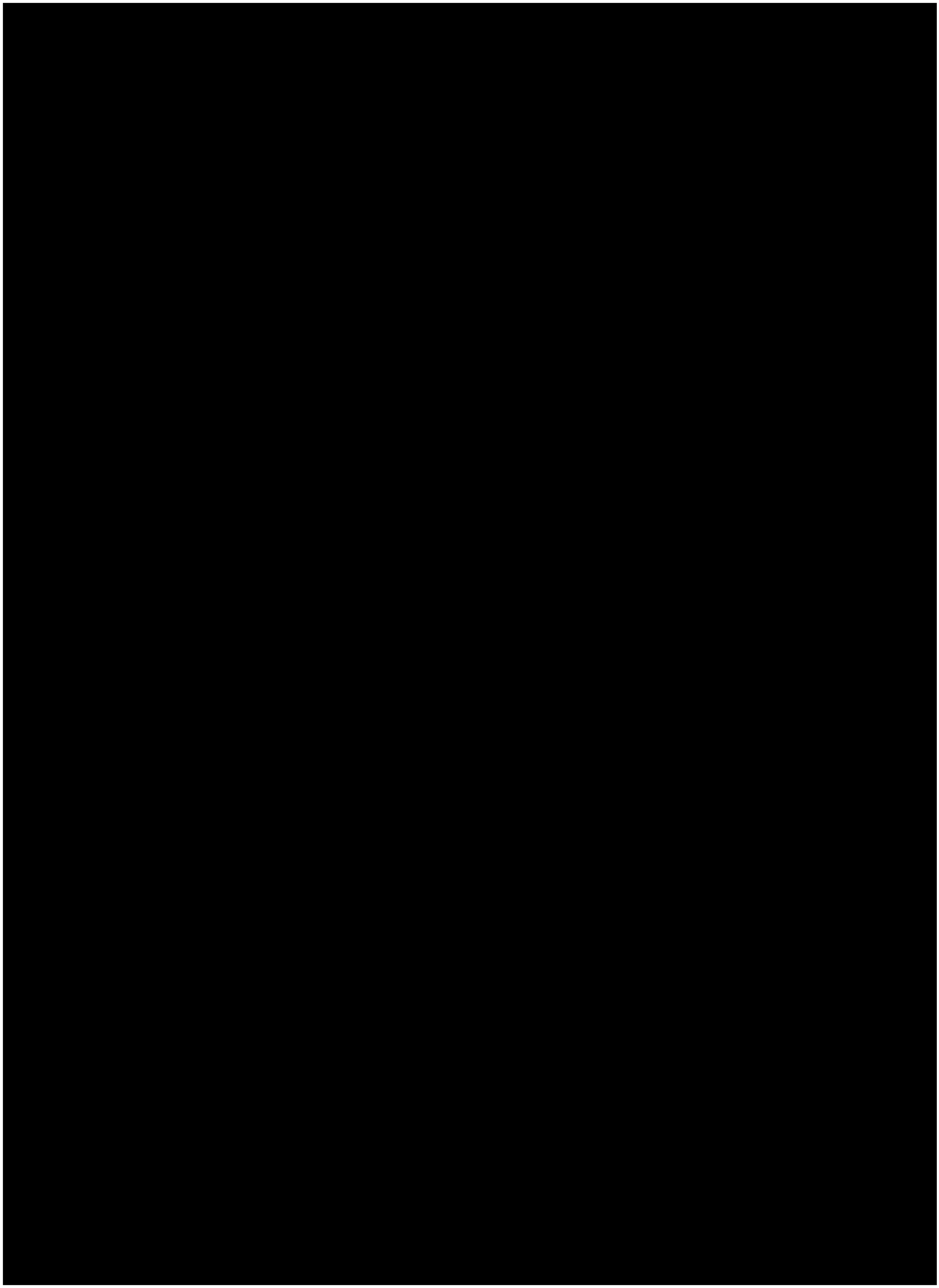
Suspicion of rhabdomyolysis is to be recorded as AE only if at least one of the criteria in the General guidelines for reporting AEs in Section 10.4.2 is met.

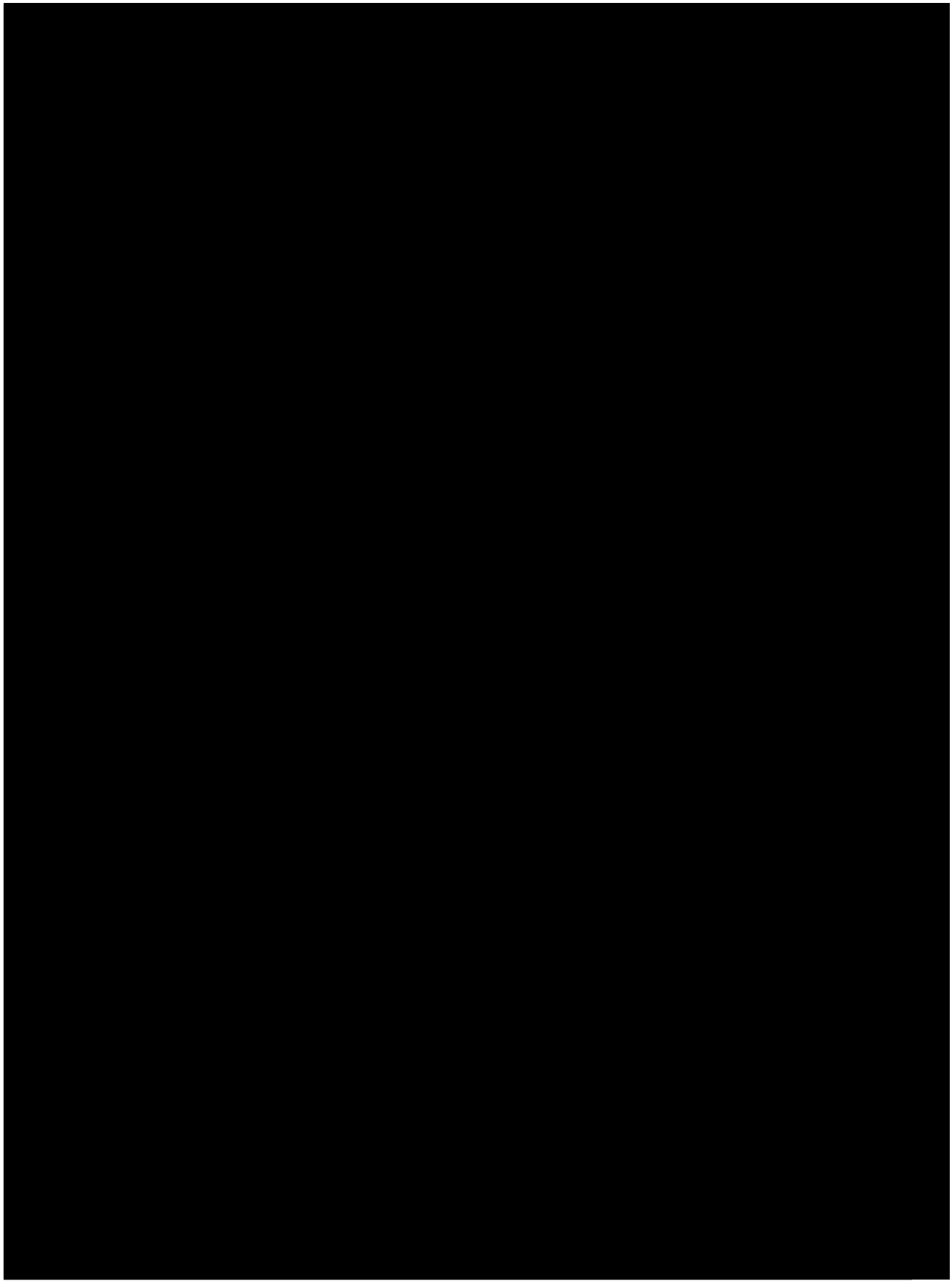
Appendix E. Asthma Quality of Life Questionnaire AQLQ(S)

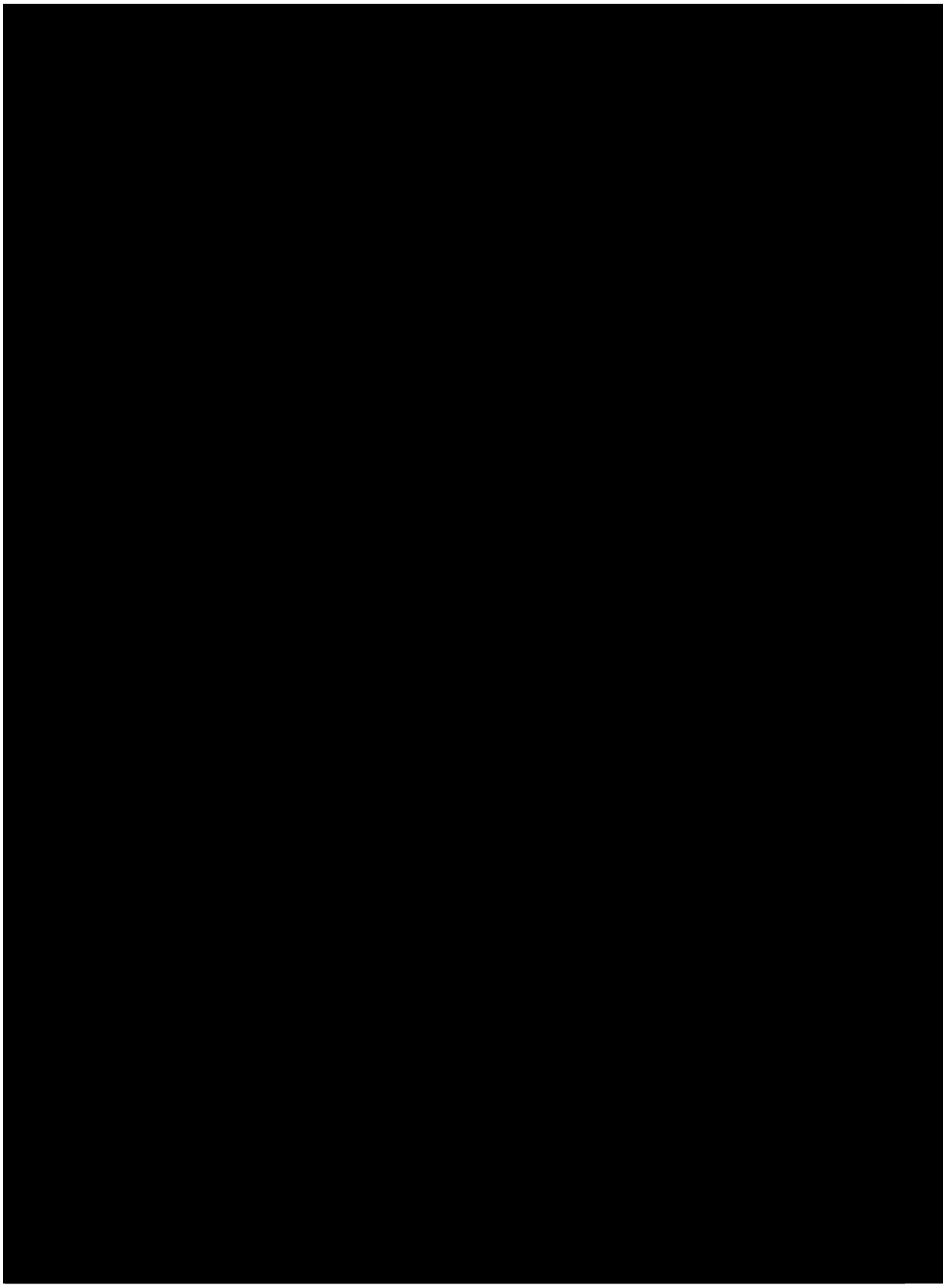




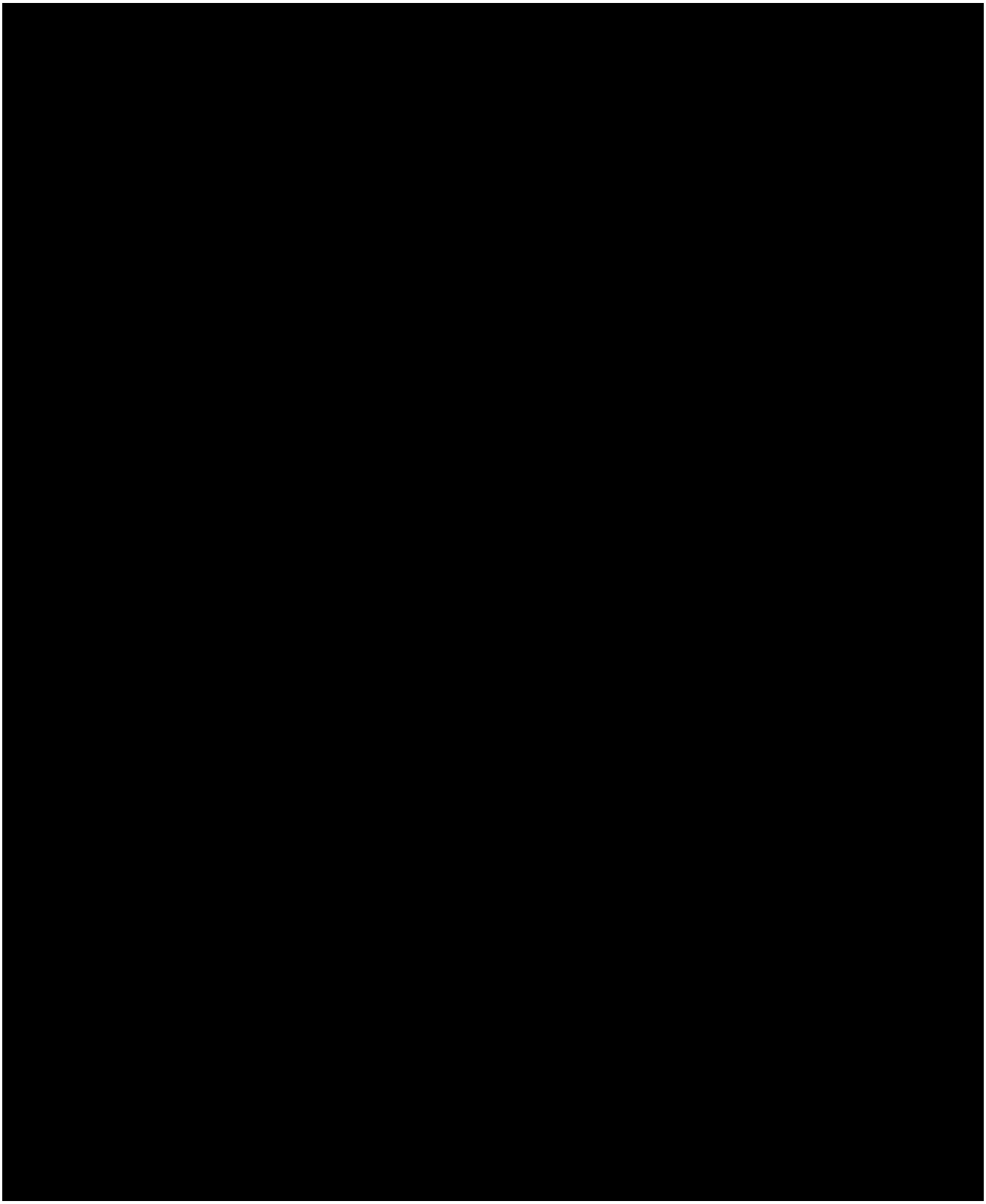




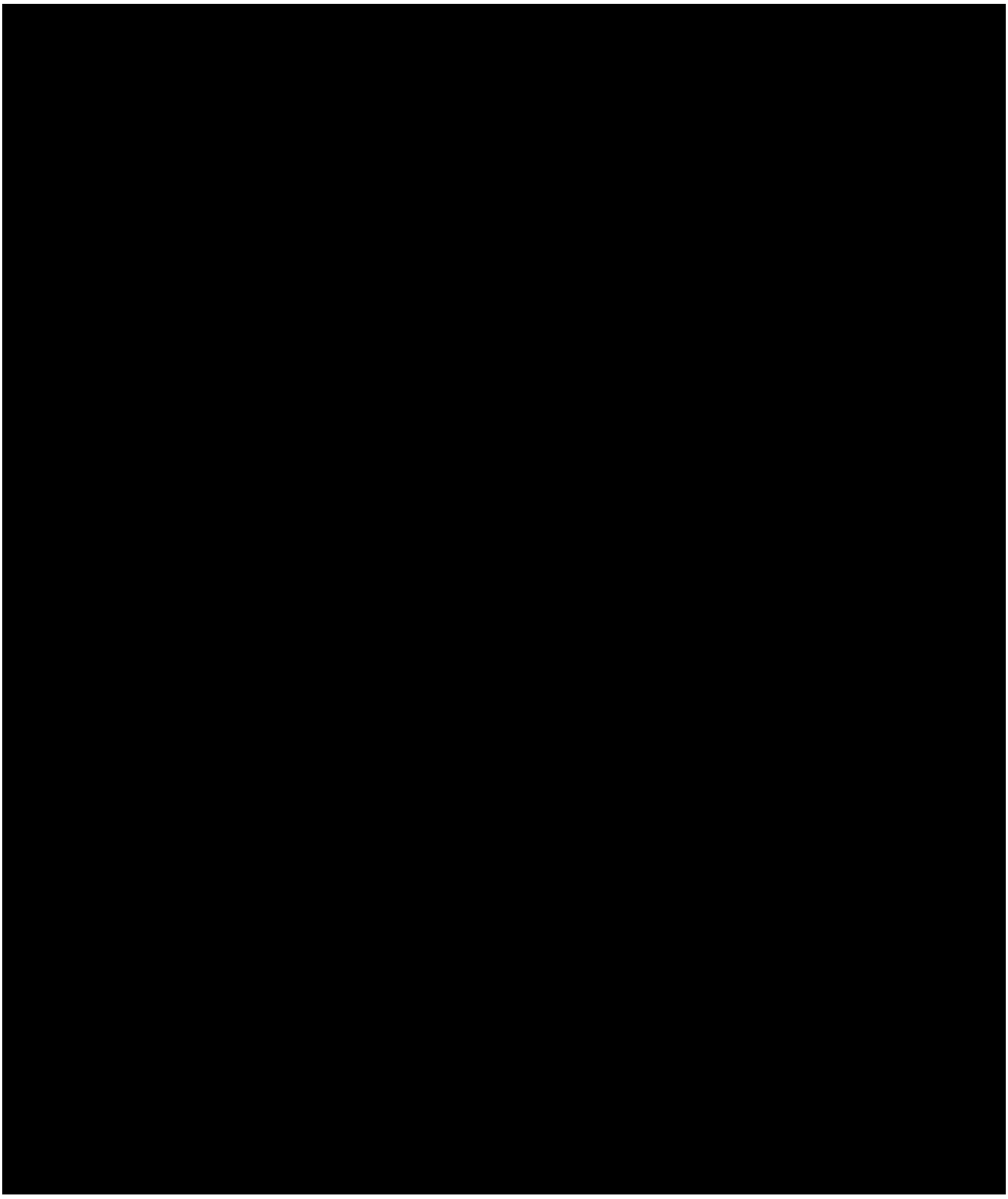


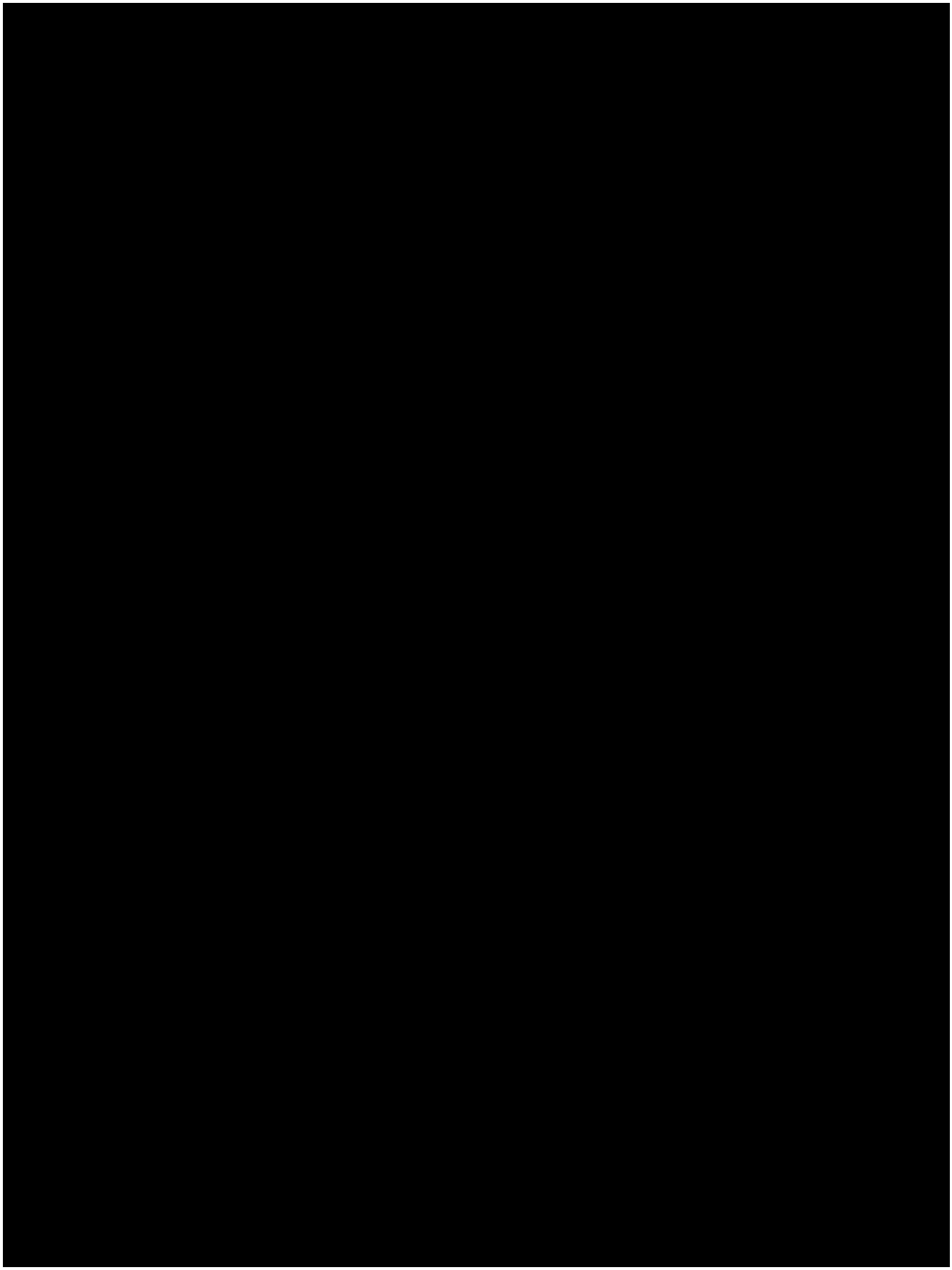


Appendix F. Asthma Control Questionnaire, 5-question Version (ACQ-5)



Appendix G. EuroQUAL Questionnaire (EuroQol 5 dimensions questionnaire, 3-Level Version [EQ-5D-3L])





Appendix H. 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: 391-397)*

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.

Appendix I. List of opportunistic infections

- 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 or more dermatomes)
- Histoplasmosis (pulmonary or disseminated; most common tropical areas Tennessee-Ohio-Mississippi river basins)
- Listeriosis

Mycobacterium avium

- Nontuberculosis mycobacteria
- Pneumocystis pneumonia (PCP).

This list is indicative and not exhaustive.

lts12551-amended-protocol02

ELECTRONIC SIGNATURES

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