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STATISTICAL ANALYSIS PLAN

An 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

SAR231893-LTS12551

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ACQ-5	Asthma Control Questionnaire 5-item scale
ADA	Anti-drug Antibodies
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Aminotransferase
ANA	Antinuclear Antibodies
ATS	American Thoracic Society
COPD	Chronic Obstructive Pulmonary Disease
CRFs	Case Report Forms (CRFs)
CV	Curriculum Vitae
CV%	Coefficient of Variation
CYP	Cytochrome P
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
DRF	Discrepancy Resolution Form
ECG	Electrocardiogram/Electrocardiography
EOS	End-of-Study
EOT	End-of-treatment
e-CRF	Electronic Case Report Form
ELISA	Enzyme-Linked Immunosorbent Assay
EQ	EuroQual
FEV_1	Forced Expiratory Volume in one second
GCP	Good Clinical Practice
HBcAb-IgM	Hepatitis B IgM Core Antibody
HBsAg	Hepatitis B Surface Antigen
HCAb	Hepatitis C Core Antibody
HLGT	High-Level Group Term
HLT	High Level Term
HIV	Human Immunodeficiency Virus
ICH	International Conference on Harmonization

ICS	Inhaled Corticosteroid
LABA	Long-Acting Beta Agonist
LAMA	Long-Acting Muscarinic Antagonist
LTRA	Leukotriene Receptor Antagonist
IgE	Immunoglobulin E
IL-4	Interleukin 4
IL-4Rα	Interleukin 4 Receptor Alpha Subunit
IL-13	Interleukin 13
IMP	Investigational Medicinal Product
IRB/IEC	Institutional Review Board / Institutional Ethics Committee
IVRS/IWRS	Interactive Voice Response System/Interactive Web Response System
LFT	Liver Function Test
MDI	Metered Dose Inhaler
MMR	Measles, Mumps, Rubella
MMRV	Measles, Mumps, Rubella, Varicella
Non-IMP	Non-investigational Medicinal Product
PCSA	Potentially Clinically Significant Abnormalities
PEF	Peak expiratory flow
PK	Pharmacokinetics
q2w	Once every 2 weeks
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SEM	Standard Error of the Mean
SC	Subcutaneously
SD	Standard Deviation
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
Th2	T-helper 2
ULN	Upper Limit of Normal
VAS	Visual Analogue Scale

1 OVERVIEW AND INVESTIGATIONAL PLAN

1.1 STUDY DESIGN AND RANDOMIZATION

LTS12551 is a multinational, multicenter, 1-year (48 weeks) or 2-year (96 weeks) single arm extension study to evaluate the long-term safety and tolerability of dupilumab in patients with asthma, who completed the treatment and follow-up period in the DRI12544 study, or who completed the treatment period in the EFC13579, EFC13691 or PDY14192 studies.

In the LTS12551 study, dupilumab 300 mg is administered subcutaneously (SC) every 2 weeks (q2w), as an add-on therapy to a variety of allowable combinations between inhaled corticosteroid (ICS) and other controller medications as maintained during the parent study, including the oral corticosteroids (OCS) medication for the patients from the EFC13691 study. The LTS12551 consists of three periods:

- Screening Period (0-3 weeks, if applicable)
- Treatment Period (48 weeks open-label period for the patients enrolled after the protocol amendment 4, or 96 weeks open-label period for the patients enrolled before the protocol amendment 4)
- Post-treatment Period (12 weeks, dupilumab-free follow-up period)

The 4 parent studies are described briefly as follows:

DRI12544: A phase 2b, randomized, double-blind, placebo-controlled, dose ranging, parallel group study comparing different doses and regimens of dupilumab SC for 24 weeks in patients with moderate to severe, uncontrolled asthma. Patients were randomized in ratio of 1:1:1:1:1 into 5 arms, dupilumab 200 mg every 4 weeks (q4w), dupilumab 300 mg q4w, dupilumab 200 mg q2w, dupilumab 300 mg q2w, and placebo. Patients were allowed to administer moderate- or high-dose inhaled corticosteroid (ICS) in combination with long-acting beta agonist (LABA) as follows: mometasone furoate / formoterol, budesonide / formoterol, and fluticasone propionate / salmeterol in the treatment period, and continued with the stable dosage of controller medications in the 16-week post-treatment follow-up period. There were 776 patients enrolled in DRI12544.

EFC13579: A phase 3, randomized, double blind, placebo-controlled, parallel group study to evaluate the efficacy and safety of dupilumab SC for 52 weeks in patients with persistent asthma. Patients were randomized in ratio of 2:2:1:1 into the following regimens, dupilumab 200 mg q2w, dupilumab 300 mg q2w, placebo matching 200mg q2w and placebo matching 300 mg q2w. In the treatment period, patients are allowed to administer a stable background therapy of medium to high dose of inhaled corticosteroid (ICS) in combination with a second controller medication (for example, long-acting beta agonist [LABA], leukotriene receptor antagonist [LTRA], theophylline, and etc.), and potentially plus a third controller medication. There were in total 1902 patients randomized for EFC13579.

EFC13691: A phase 3, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of dupilumab 300 mg q2w SC for 24 weeks in patients with severe oral corticosteroid dependent asthma. Patients are randomized in a ratio of 1:1 to dupilumab 300 mg q2w and matching placebo, which will be given on top of standard of care and of oral corticosteroids. During the course of the study, the oral corticosteroid (OCS) [prednisone/prednisolone] doses will be adjusted to the dose required for the maintenance of asthma control. In the screening period, patients experience an OCS dose optimization process. In the treatment period, patients continue with the optimized OCS doses in the first 4 weeks, then have the OCS dose down-titrated till Week 20, and at last maintain on the Week 20 OCS dose for the rest 4 weeks. In the meantime, patients are also allowed to be on a stable dose of high dose ICS with a second controller medication (LABA, LTRA, theophylline, etc), and potentially plus a third controller medication per requested by patients. There were in total 210 patients randomized for EFC13691.

PDY14192: A phase 2a, exploratory, randomized, double-blind, placebo-controlled study of the effects of dupilumab 300 mg q2w SC for 12 weeks on airway inflammation of adults with persistent asthma. Patients are randomized in a ratio of 1:1 to dupilumab 300 mg q2w and placebo q2w. Patients undergo two bronchoscopy procedures respectively before treatment and at the end of treatment period, each of which is followed with an oral prednisone 40 mg daily treatment for 3 (up to 5) days. Patients are allowed to administer a background therapy of medium to high dose ICS in combination with a second controller medication (LABA), and potentially plus a third controller medication (eg, LAMA, LTRA). There are in total 42 patients planned for PDY14192.

Parent study	Sample size	Treatment arms	Treatment duration
DRI12544	776	Dupilumab 300 mg q2w, Dupilumab 200 mg q2w, Dupilumab 300 mg q4w, Dupilumab 200 mg q4w, Placebo q2w (2 mL in matched 5 mL vials)	24 weeks
EFC13579	1902	Dupilumab 300 mg q2w, Placebo q2w matching 300 mg q2w (2 mL in matched pre-filled syringe), Dupilumab 200 mg q2w, Placebo q2w matching 200 mg q2w (1.14 mL in matched pre-filled syringe)	52 weeks
EFC13691	210	Dupilumab 300 mg q2w, Placebo q2w (2 mL in matched pre-filled syringe)	24 weeks
PDY14192	42	Dupilumab 300 mg q2w, Placebo q2w (2 mL in matched pre-filled syringe)	12 weeks

Patients from DRI12544 who completed the 24-week treatment period and 16-week follow-up period might be eligible for enrolling into LTS12551 at the end of study (EOS) visit of DRI12544 or thereafter. The screening period (Visit 1 and Visit 2) of LTS12551, and a 600 mg loading dose on Day 1 were only applicable for patients coming from DRI12544, as those patients experienced a gap in dosing for at least 16 weeks. According to the original protocol of LTS12551, patients coming from DRI12544 (non-US) could combine the EOS visit of DRI12544 with Visit 1/Visit 2 of LTS12551; according to the amended protocol 1, Visit 1 and Visit 2 of LTS12551 should be independent from the EOS visit of DRI12544. Thus, after the protocol amendment 1 became effective in LTS12551, patients from DRI12544 should be screened starting at Visit 1 (for 7 to 21 days) in LTS12551 before dosing started at Visit 2.

Patients from EFC13579, EFC13691 or PDY14192 who complete the entire planned treatment period may be eligible for enrolling into LTS12551 immediately at the end of treatment (EOT) visit of the parent study. In other words, for patients coming from these 3 studies, the end of treatment visit of parent study should be combined with Visit 1 and Visit 2 of LTS12551, so there is no gap in dosing, and screening and loading dose at Day 1 are not applicable.

1.2 OBJECTIVES

1.2.1 Primary objectives

The primary objective of this study is to evaluate the long-term safety and tolerability of dupilumab in patients with asthma who participated in a previous dupilumab asthma clinical study (DRI12544, EFC13579, EFC13691 or PDY14192).

1.2.2 Secondary objectives

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

To evaluate dupilumab in patients with asthma who participated in a previous dupilumab asthma clinical study (DRI12544, EFC13579, EFC13691 or PDY14192), with regards to:

- Systemic exposure
- Anti-drug antibodies
- Biomarkers

1.3 DETERMINATION OF SAMPLE SIZE

The study size is predicated on the overall size of the parent studies; hence, the maximum number of patients to participate will be the number corresponding to the sum of the total enrolled in DRI12544, PDY14192, EFC13579, and EFC13691 studies. Based on the actual patient number of

DRI12544 study and the planned patient numbers of EFC13579, EFC13691 and PDY14192 studies, the maximum number of patients of LTS12551 can be estimated as 2930.

1.4 STUDY PLAN

LTS12551 study consists of three periods, using an add-on therapy approach to inhaled corticosteroid (ICS) in combination with other acceptable controller medications maintained during the parent study, including the oral corticosteroids for the patients from the EFC13691 study.

Screening Period (0-3 weeks)

Patients are to be stabilized on their background dose of moderate or high-dose ICS for ≥1 month prior to Visit 1 and continue the stable dose during the screening period.

- The screening period is applicable for the patients from the DRI12544 study only.
- Eligible patients in PDY14192, EFC13579 or EFC13691 studies are to rollover into LTS12551 on the same day as the end of treatment visit in the parent study. Visit 1 and Visit 2 of LTS12551 study are combined with the end of treatment visit in the parent study for the patients enrolled from PDY14192, EFC13579 or EFC13691 studies, who start directly with the treatment period in the LTS12551 study.

Open-label Treatment Period (48 or 96 weeks)

During the open-label treatment period, patients continue their background controller therapy as maintained during the parent study or as modified based on investigator's judgment, including the oral corticosteroids for the patients from the EFC13691 study.

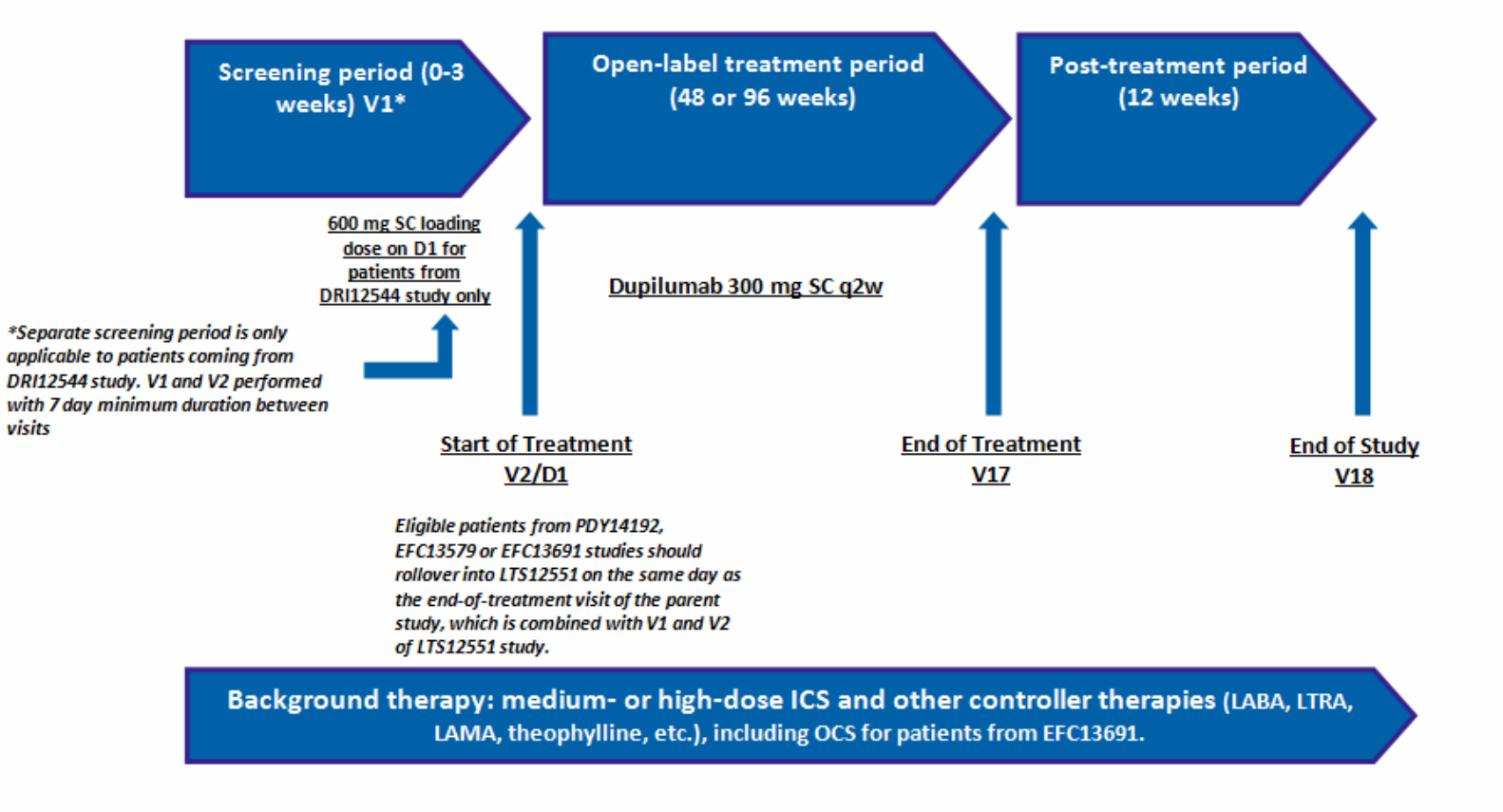
Post-treatment Period (12 weeks)

Upon completion of the open-label treatment period (or following early discontinuation of IMP) patients continue into the post-treatment period. During this period, patients continue with the background controller therapies as maintained during the open-label treatment period or as modified based on investigator's judgment.

Reliever Medications

Over the course of LTS12551 study, patients may receive salbutamol / albuterol hydrofluoroalkane pressurized MDI or levosalbutamol / levalbuterol hydrofluoroalkane pressurized MDI as reliever medication as needed. Nebulizer solutions with either albuterol / salbutamol or levalabuterol / levosalbutamol may be used as an alternative delivery method.

1.4.1 Graphical Study Design



1.5 MODIFICATIONS TO THE STATISTICAL SECTION OF THE PROTOCOL

Table 1 - Protocol amendment statistical changes

Amendment Number	Date Approved	Rationale	Description of statistical changes
4	31-Oct-2016	Based on the data defining the safety profile of dupilumab to date (as determined in multiple clinical trials performed across the AD, Asthma and NP indications), data from a 1 year asthma OLE study is anticipated to be sufficient to support the asthma program.	The open-label treatment duration is amended to 48 weeks (1 year), for patients providing consents after the implementation of the protocol amendment 4.
4	31-Oct-2016	The DRI12544 study showed that the median dupilumab concentration at 12 weeks post-last-dose (at PK steady-state) was below the limit of quantitation (78 ng/mL) for the group of patients on 300 mg every 2 weeks (q2w). Given this, the duration of study participation can be minimized by reducing the post-treatment period by 1 month. The follow-up duration for all the ongoing dupilumab asthma studies has been harmonized as 12 weeks.	The post-treatment period is shortened to 12 weeks for all patients in the LTS12551 study.
4	31-Oct-2016	The patient population from study EFC13691 is a different population from the patient population from the other parent studies. The patients from	Three efficacy endpoints linked to the prescribed oral corticosteroids (OCS) dose and corresponding analyses have been added only for the patients from the EFC13691.

Amendment Number	Date Approved	Rationale	Description of statistical changes
		EFC13691 are more severe at the baseline of the parent study and are using a different background controller medication. The endpoints linked to the reduction of the OCS dose are only used in EFC13691, in addition to the other efficacy endpoints shared in common with the patients from the other parent studies.	

1.6 STATISTICAL MODIFICATIONS MADE IN THE STATISTICAL ANALYSIS PLAN

This statistical analysis plan (SAP) version 3.0 is based on the LTS12551 amended protocol 2 (protocol amendment 4) dated October 31st, 2016, and is the third version of SAP for LTS12551.

Table 2 - Statistical analysis plan statistical changes

SAP version number	Date approved	Rationale	Description of statistical changes
2	23-Nov-2016	Protocol amendment 4 shortens the open-label treatment period to 48 weeks.	The open-label treatment duration is amended to 48 weeks for patients providing consents after the implementation of the protocol amendment 4.
2	23-Nov-2016	Protocol amendment 4 drops the electronic diary, PEF meter, EQ-5D-3L, serum immunoglobulins, and serum total IgE for all the patients in LTS12551 study. Before the protocol amendment 4 becomes effective, the patients from	The analyses for AM/PM PEF, AM/PM asthma symptom score, number of reliever uses, number of nocturnal awakenings, EQ-5D-3L score, serum immunoglobulins and serum total IgE in LTS12551 study will be restricted to the patients from the DRI12544 study and performed to the data observed up

SAP version number	Date approved	Rationale	Description of statistical changes
		DRI12544 study have data collection for the aforementioned endpoints for more than one year, while only a few of patients from EFC13579, EFC13691 or PDY14192 studies have limited amount of data collected for those endpoints.	to the end of their collection. The compliance for background controller medications will be calculated using the data observed up to the end of the electronic diary collection.
2	23-Nov-2016	Protocol amendment 4 adds three efficacy endpoints linked to the prescribed OCS dose for the patients from the EFC13691 study only. They are the percentage change from baseline in the OCS dose, the proportion of patients achieving a reduction of 50% or greater in the OCS dose compared with the baseline, and the proportion of patients whose background OCS are completely tapered off. The baseline OCS dose is defined as the original baseline value of the parent study.	The proportion of patients whose background OCS are completely tapered off and its analysis have been added to this version of SAP, and the other two endpoints linked to the OCS dose and their corresponding analyses have already existed in the SAP 1.0.
2	23-Nov-2016	Protocol amendment 4 reduces the frequency of assessments for the ACQ-5, AQLQ, clinical laboratories, ECG and ADA variables for all patients in the LTS12551 study.	The scheduled visits and corresponding analysis windows for the endpoints of ACQ-5, AQLQ, clinical laboratories, ECG and ADA are adjusted accordingly per the reduced scheduled visits in the protocol amendment 4.
2	23-Nov-2016	The patient population from study EFC13691 is expected to be different from the	All the planned analyses in LTS12551 study will be performed and presented separately for the

SAP version number	Date approved	Rationale	Description of statistical changes
		patient population from the DRI12544, EFC13579 or PDY14192 studies. The patients from EFC13691 are more severe at the baseline of the parent study and are using a different background controller medication, and thus potentially have different safety profiles in general from the patient population from the other parent studies.	patients from EFC13691 study and the patients from DRI12544, EFC13579 or PDY14192 studies, except for the endpoints that are particularly collected for the patients from EFC13691 study only.
3	This version	The layouts of all outputs are changed to avoid potential confounding introduced by between-study variation.	The treatment category (Naïve, Re-treated, Interrupted treatment, and Continuously treated) is removed. The layouts of all outputs are changed to: For the patients from EFC13691 study, results of each planned analysis will be presented by "Placebo/Dupilumab, Dupilumab/Dupilumab, and All" (see Section 2.3.2). For the patients from DRI12544/EFC13579/PDY14192 studies, results of each planned analysis will be presented by the parent study and "All", and by "Placebo/Dupilumab and Dupilumab/Dupilumab" within each parent study (see Section 2.3.2).
3	This version	To be consistent with ISS SAP	The definition of AESI and other selected AE groupings are updated in Section 2.1.4.1

SAP version number	Date approved	Rationale	Description of statistical changes
3	This version	To be consistent with ISS SAP by including the combined PCSA criteria for adult and adolescents	PCSA criteria in Appendix A are updated
3	This version	To be consistent with the amended protocol #2 of LTS12551 study	The lab test parameters lactate dehydrogenase, low-density lipoprotein, high-density lipoprotein, and triglycerides are removed according to the amended protocol #2 of LTS12551 study
3	This version	To be consistent with EFC13579 / EFC13691 studies	The definition of persistent ADA response is updated in Section 2.1.6
3	This version	To be consistent with EFC13579 / EFC13691 studies	The definitions of Comorbidity history and Atopic Medical History are updated in Section 2.1.1
3	This version	Add additional subgroup analyses	The subgroup defined by the eosinophil count at baseline of parent study is added to the subgroup analysis for key efficacy endpoints in Section 2.4.4.1. The subgroup defined by the Ethnicity at baseline of parent study is added to the subgroup analysis for key safety endpoints in Section 2.4.5.6.

2 STATISTICAL AND ANALYTICAL PROCEDURES

2.1 ANALYSIS ENDPOINTS

In general, the baseline values of endpoints in LTS12551 are correspondingly defined as the original baselines of the parent studies, unless otherwise specified. In addition to the baselines, the pre-dose measurements at Week 0 of LTS12551 are defined as follows. For patients enrolled from DRI12544, the measurements at Week 0 are obtained from the EOS visit of DRI12544 if available, regardless of whether the EOS visit in DRI12544 was combined with Visit 1/Visit 2 in LTS12551; otherwise, Week 0 value will be the last available measurement prior to the first IMP dose in LTS12551 study. For patients enrolled from EFC13579, EFC13691 or PDY14192, the measurements at Week 0 are obtained from the EOT visit of the parent studies if available; otherwise, Week 0 value will be the last available measurement prior to the first IMP dose in LTS12551 study.

2.1.1 Demographic and baseline characteristics

Demographic characteristics

The following demographic characteristics will be summarized:

Age (years)

Age group (age <18, 18≤ age <65, 65≤ age <75, 75≤ age < 85, age ≥85 years)

Gender (Male, Female)

Region (Asia, Latin America, East Europe, Western Countries) following the classification in the parent study

Territory (North America: Canada and USA; European Union: France, Germany, Hungary, Italy, Poland, Spain and United Kingdom; Rest of World: Argentina, Australia, Brazil, Colombia, Chile, Japan, Mexico, Russia, South Africa, South Korea, Taiwan, Turkey and Ukraine)

Race (Caucasian/White, Black, Asian/Oriental, American Indian or Alaska native, Native Hawaiian or other Pacific Islander, Other)

Ethnicity (Hispanic, Not Hispanic)

Height (cm)

Weight (kg)

Weight group (weight <50, 50≤ weight <100, weight ≥100 kg)

BMI (kg/m^2)

BMI group (BMI<25, 25≤ BMI <30, BMI≥30 kg/m^2)

Alcohol drinking frequency (Never, At least monthly, At least weekly and At least daily) and number of standard alcohol drinks on a typical day when drinking (1 or 2, >2)

The data for demographic characteristics will be obtained from the original baselines of the parent studies.

Medical or surgical history

Medical or surgical history includes all the relevant medical (or surgical) history during the lifetime of the patient. This information will be coded to a "Lower Level Term (LLT)", "Preferred Term (PT)", "High Level Term (HLT)", "High Level Group Term (HLGT)", and associated primary "System Organ Class (SOC)" using the version of Medical Dictionary for Regulatory Activities (MedDRA) currently in effect at Sanofi at the time of database locks.

Comorbidity history will be summarized separately. The following comorbid diseases will be summarized.

Atopic dermatitis history (Yes, Ongoing condition)

Allergic conjunctivitis history (Yes, Ongoing condition)

Allergic rhinitis history (Yes, Ongoing condition)

Allergic conjunctivitis history and/or allergic rhinitis history (Yes, Ongoing condition)

Chronic rhinosinusitis history (Yes, Ongoing condition)

Nasal polyposis history (Yes, Ongoing condition)

Eosinophillic esophagitis history (Yes, Ongoing condition)

Food allergy history (Yes, Ongoing condition)

Hives history (Yes, Ongoing condition)

A patient will be considered to have an atopic medical condition if the patient has any of the following: atopic dermatitis, allergic conjunctivitis or allergic rhinitis, eosinophilic esophagitis, food allergy, hives; or has baseline (parent study) total IgE ≥100 IU/mL and at least one aeroantigen specific IgE is positive (≥0.35 IU/mL) at baseline of parent study.

The data of medical or surgical history will be obtained from the original baselines of the parent studies.

Disease characteristics at baseline

The following baseline disease characteristics will be summarized:

- Prior ICS (medium, high as defined in Appendix C) in combination with allowable controller therapy
- Age of asthma onset
- Time since first diagnosis of asthma (years)

  (Year of randomization in parent study – Year of first diagnosis of asthma) + (month of randomization in parent study – month of first diagnosis of asthma)/12
- Smoking history (Never, Former)
  - For former smokers,
    - Time since cessation of smoking for former smokers (months) to be derived as (Year of randomization in parent study – Year of cessation)×12 + (month of randomization in parent study – month of cessation)
    - Smoking quantity (Pack-year)
- Time since last asthma exacerbation (months)

  (Year of randomization in parent study – Year of last asthma exacerbation)×12 + (month of randomization in parent study – month of last asthma exacerbation)
- Number of asthma exacerbations experienced 1 year before Visit 1 of the parent study
- Number of asthma exacerbations required hospitalization or urgent medical care 1 year before Visit 1 of the parent study
- FEV_1 (L)
- ACQ-5 score

The data of baseline disease characteristics will be obtained from the original baselines of the parent studies, unless otherwise specified. Any technical detail related to computation, dates, and imputation for missing dates is described in Section 2.5.

2.1.2 Prior or concomitant medications

- Prior medications are any treatments taken by patient prior to the first IMP administration in the parent study. Prior medications can be discontinued before the first IMP administration in parent study or can be maintained during treatment phase in parent study.

- Concomitant medications in parent study are any treatments received by patient concomitantly to the IMP in the parent studies, from (on/after) the first administration of IMP to the end of post-treatment follow-up period.
- Concomitant medications are any treatments received by patient concomitantly to the IMP in the LTS12551 study, from (on/after) the first administration of IMP to the end of post-treatment follow-up period. A given medication can be classified both as a prior medication and as a concomitant medication.

All medications taken at any time either prior to the first IMP administration or on/after the first IMP dose till the end of follow-up period in the parent study are reported in the case report form and obtained from the parent studies. All medications obtained from the parent studies will be coded using the World Health Organization-Drug Dictionary (WHO-DD) using the version currently in effect at Sanofi at the time of database locks.

All medications taken at any time during the LTS12551 study, from the time of first IMP administration to the end of follow-up period, including inhaled corticosteroid (ICS) in combination with other allowable controller therapies (LABA, LTRA, LAMA, theophylline, etc.), albuterol or levalbuterol reliever medications, and the background oral corticosteroids medication (for patients from the EFC13691 study only) are to be reported in the case report form.

All medications collected during the LTS12551 will be coded using the World Health Organization-Drug Dictionary (WHO-DD) using the version currently in effect at Sanofi at the time of database locks.

2.1.2.1 Salbutamol/albuterol or levosalbutamol/levalbuterol reliever medication

Patients may administer salbutamol/albuterol hydrofluoroalkane pressurized 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 are to convert salbutamol/albuterol nebulizer and levosalbutamol/levalbuterol nebulizer use as shown by the following table:

Salbutamol/Albuterol Nebulizer Solution -Total Daily Dose (mg)	Number of Puffs*
2.5	4
5.0	8
7.5	12
10	16
*Conversion factor: salbutamol/albuterol nebulizer solution (2.5 mg) corresponds to 4 puffs	

- Example of salbutamol/albuterol nebulizer-to-puff conversion: patient received 3 salbutamol/albuterol nebulizer treatments (2.5 mg/treatment) between 7 and 11 AM. Total = 7.5 mg → 12 puffs.

Levosalbutamol/Levalbuterol Nebulizer Solution -Total Daily Dose (mg)	Number of Puffs*
1.25	4
2.5	8
3.75	12
5	16
*Conversion factor: salbutamol/albuterol nebulizer solution (2.5 mg) corresponds to 4 puffs	

- 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 = 3.75 mg → 12 puffs.

Any technical details related to computation, dates, imputation for missing dates are described in Section 2.5.

2.1.3 Efficacy endpoints

Efficacy endpoints are secondary endpoints of this study. The following efficacy endpoints will be analyzed:

- Number and Annualized rate of severe exacerbation events during the treatment period
- Forced expiratory volume in one second (FEV1)
- Other spirometry endpoints: Percent Predicted FEV1, Forced Vital Capacity (FVC), Forced Expiratory Flow (FEF) 25-75%
- Asthma control questionnaire 5-question version (ACQ-5) score and responder status
- Asthma quality of life questionnaire (AQLQ) score and responder status
- EuroQoL questionnaire (EQ-5D-3L) score
- Morning and evening peak expiratory flow (PEF)
- Morning evening asthma symptom scores
- Number of inhalations / day of salbutamol / albuterol or levosalbutamol / levalbuterol for symptom relief
- Number of Nocturnal awakenings due to asthma symptoms

- Endpoints linked to the prescribed oral corticosteroids (OCS) dose for the patients from the EFC13691 study:
  - Percentage change from baseline in OCS dose, where the baseline OCS dose is the original baseline from EFC13691
  - Proportion of patients achieving a reduction of 50% or greater in OCS dose compared with the original baseline in the parent study
  - Proportion of patients whose background OCS are completely tapered off

For the above efficacy endpoints, except for the number of severe exacerbations, ACQ-5/AQLQ responder, and the three endpoints particularly for the patients from EFC13691, the change from baseline over time will also be analyzed. The baseline values are the original baselines from the parent study.

2.1.3.1 Severe Exacerbation Events

A severe exacerbation event during the study is defined as any of the following:

- Use of systemic corticosteroids for ≥ 3 days.
  - At least double the dose of systemic corticosteroids for patients enrolling from EFC13691 who are currently on systemic corticosteroids.
- Or, hospitalization or emergency room visit because of asthma, requiring a systemic corticosteroid treatment.

The severe exacerbation events are collected on eCRF page “Asthma exacerbations event”. Only events confirmed on eCRF page will be used in the analysis.

Both number and annualized rate of severe exacerbation events will be analyzed. The annualized event rate is defined as the number of severe exacerbation events per patient-year. Number and annualized rate will also be analyzed for severe exacerbation with use of systemic corticosteroids for ≥3 days only, and that with hospitalization or with emergency room visit only. The mean duration of a severe exacerbation will also be summarized.

For the treatment period, total number of events and standardized on-treatment duration will be calculated for each patient:

- The total number of events is defined as the number of events that are onset between the date of first IMP dose in LTS12551 study and the date of last IMP dose in LTS12551 study + 14 days;

The standardized on-treatment duration (in years) is calculated by (the date of last IMP dose in LTS12551 study – the date of first IMP dose in LTS12551 study + 14 days)/365.25.

2.1.3.2 Forced expiratory volume in one second (FEV1) and other spirometry assessments

The forced expiratory volume in one second (FEV1) is part of the spirometry assessment that will be performed at Visit 1, Visit 3 (Week 2), Visit 4 (Week 4), Visit 6 (Week 8), Visit 8 (Week 12), Visit 11 (Week 24), Visit 13 (Week 48; if applicable), Visit 15 (Week 72; if applicable), Visit 16 (Week 84; if applicable), Visit 17 (End-of-Treatment) and Visit 18 (End-of-Study). The other parts of the spirometry assessment, including the percent predicted FEV1, Forced Vital Capacity (FVC) and Forced Expiratory Flow (FEF) 25-75%, will be performed at the same visits as above.

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 (1). 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.

Pulmonary function tests will be measured in the sitting position and the highest measure will be recorded in liters for FEV_1.

2.1.3.3 Asthma control questionnaire, 5-question version (ACQ-5)

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. 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.

In addition, the minimal clinically important difference at patient level (pMCID) is the smallest treatment efficacy that would lead to a change in a patient's management; and, the minimal clinically important difference at group mean level (gMCID) is the smallest treatment efficacy that would lead to a change in a group's management. The threshold of gMCID is usually published or calculated based on the Cohen's rule (2). Based on the gMCID and the condition that absolute

value of pMCID is greater than or equal to the absolute value of gMCID, the value of pMCID is derived out. The pMCID for ACQ-5 is derived as -0.5.

- Definition of ACQ-5 responder (based on pMCID): a patient is considered to be a "responder" if his/her change in ACQ-5 score from the baseline in parent study is equal to or greater than the minimal clinically important difference at patient level (pMCID):

  Responder = Yes, if change from baseline in ACQ-5 score ≤ pMCID;

  Responder = No, if change from baseline in ACQ-5 score > pMCID.

Measurement properties such as reliability, ability to detect change have been documented in the literature (3).

Based on the manual of ACQ (4), any more than one missing value is not acceptable. If more than one of the questions have missing value, the global score is invalid and will be considered as missing. If only one question has missing value, it will be interpolated (pro-rated) using the completed questionnaires from the previous visit. For instance, answer to question 5 is missing at Visit 2, and all questions are completed at Visit 1. Then the question 5 score at Visit 2 is interpolated as: (total score at Visit 2/sum of scores of question 1 to question 4 at Visit 1) × score of question 5 at Visit 1. If the questionnaire from the previous visit is not complete either, the missing value will be imputed as the average of the completed questions within the current visit.

2.1.3.4 Asthma quality of life questionnaire (AQLQ)

The AQLQ was designed to measure the functional impairments that are most troublesome to adults (17 to 70 years) as a result of their asthma (see Appendix G). The instrument is comprised of 32 items, each rated on a 7-point scale from 1 (severely impaired) to 7 (not impaired). The AQLQ 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)

The instrument has been used in many clinical trials, and it has been shown to be reliable, valid (patient interviews), and sensitive to change.

Individual items are equally weighted. The overall score is the mean of response to each of the 32 questions. The score of each domain is the mean of response to each question in that domain. Higher scores indicate better quality of life. An MCID is available: the pMCID is approximated to be 0.5 (5).

- Definition of AQLQ responder (based on pMCID): a patient is considered to be a "responder" if his/her change in AQLQ overall score from the baseline in parent study is equal to or greater than the minimal clinically important difference at patient level (pMCID):

  Responder = Yes, if change from baseline in AQLQ overall score ≥ pMCID;

  Responder = No, if change from baseline in AQLQ overall score < pMCID.

To have a valid overall score, it is not acceptable to have more than three missing responses or more than one missing response per domain. For the symptoms and activity limitation domain score, only one missing value per domain is acceptable. For the emotional function and environmental stimuli domain scores, no missing value is acceptable. For responses with intolerable amount of missing value(s), the overall or the domain score will be considered as missing. For the other case, the missing score will be interpolated using the previous completions of the questionnaire following the similar algorithm used for ACQ-5.

The analysis for AQLQ in LTS12551 study will exclude the patients enrolled from the PDY14192 study, as the AQLQ is not assessed in the PDY14192 study.

2.1.3.5 EuroQoL questionnaire (EQ-5D-3L)

EQ-5D-3L is a standardized health-related quality of life questionnaire developed by the EuroQol Group in order to provide a simple, generic measure of health for clinical and economic appraisal (6). EQ-5D-3L is designed for self-completion by patients.

The EQ-5D essentially consists of 2 pages – the EQ-5D descriptive system and the EQ VAS (See Appendix H). The EQ-5D descriptive system comprises 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 3 levels: no problem, some problems, and severe problems.

The 5 dimensional 3-level systems are converted into a single index utility score. Values for the 243 theoretically possible health states defined by the EuroQol classification are calculated using a regression model and weighted according to the social preferences of the UK population (7). The minimum value for the single index utility score is -0.594, which corresponds to a level 3 (severe problems) for mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The maximum value for this index is 1.0, which corresponds to a full health (level 1 (no problem) for mobility, self-care, usual activities, pain/discomfort and anxiety/depression).

The EQ Visual Analogue Scale (VAS) records the respondent's self-rated health on a vertical visual analogue scale. The EQ VAS 'thermometer' has endpoints of 100 (Best imaginable health state) at the top and 0 (Worst imaginable health state) at the bottom. Appendix I provides the SAS code to derive the index utility score using UK based population.

The collection of the EQ-5D-3L will be stopped after the approval of protocol amendment 4. The analyses for the EQ-5D-3L endpoints in LTS12551 study will be restricted to the patients from DRI12544 study and performed to the data observed up to the end of collection.

2.1.3.6 Daily efficacy assessments

On a daily basis before the approval of protocol amendment 4, the patient uses 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 nocturnal awakenings

The use of the electronic diary/PEF meter will be stopped after the approval of protocol amendment 4. The analyses in LTS12551 study for the above four daily efficacy endpoints in this section will be restricted to the patients from DRI12544 study and performed to the data observed up to the end of collection.

2.1.3.6.1 Peak expiratory flow

At Visit 1, patients are issued an electronic PEF meter to record morning (AM) and evening (PM) PEF, daily salbutamol/albuterol or levosalbutamol/levalbuterol, morning and evening asthma symptom scores, and number of nighttime awakenings due to asthma symptoms that require reliever medications. Patients are instructed on the use of the device, and written instructions on the use of the electronic PEF meter are provided to the patients. In addition, the investigator instructs 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 AM) prior to taking any salbutamol/albuterol or levosalbutamol/levalbuterol
- PM PEF performed in the evening (between 5:30 PM and 10 PM) prior to taking any salbutamol/albuterol or levosalbutamol/levalbuterol
- Patients should try to withhold salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours prior to measuring their PEF
- Three PEF efforts are performed by the patient; all 3 values will be recorded by the electronic PEF meter, and the highest value will be used for evaluation and it is called PEF maximum (MAX). If more than 3 PEF readings are captured, the highest value of 3 readings closest to the Diary start date and time is the PEF MAX. If only 2 PEF readings are captured, the maximum of the 2 PEF readings captured is the PEF MAX. If only 1 PEF readings is captured, the PEF MAX is treated as missing.

Baseline AM/PM PEF is calculated based on the original baseline values from the parent studies. Baseline AM PEF is the mean AM PEF MAX measurements from the 7 morning diaries

(minimum of 4) prior to randomization in parent study, including the morning diary completed on the randomization day prior to the first dose of IMP. Out of the 7 diaries, if less than 4 have missing PEF value, the baseline AM PEF is the mean of the completed AM PEF MAX within the 7 diaries. If 4 or more diaries have missing AM PEF MAX value, the baseline AM PEF is the mean of the 4 AM PEF MAX prior to and closest to randomization during the whole screening period in parent study.

Baseline PM PEF is the mean PM PEF maximum (MAX) measurement from the 7 evening diaries (minimum of 4) prior to randomization in parent study. Out of the 7 diaries, if less than 4 have missing PEF value, the baseline PM PEF is the mean of the completed PM PEF MAX within the 7 diaries. If 4 or more diaries have missing PM PEF MAX value, the baseline PM PEF is the mean of 4 PM PEF MAX prior to and closest to randomization during the whole screening period in parent study.

In addition to the original baselines from parent study, the pre-dose AM/PM PEF at Week 0 of LTS12551 study is to be presented separately, and is calculated in the same way as for the original baseline AM/PM PEF of parent studies.

2.1.3.6.2 Asthma Symptom Score

Patients record overall symptom scores twice a day prior to measuring PEF. The patient's overall asthma symptoms experienced during the waking hours will be recorded in the evening (PM symptom score). Symptoms experienced during the night will be recorded upon arising (AM symptom score). Patients will be 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

The baseline AM/PM symptom score is from the original baselines of parent study, and will be computed following the same algorithm used for baseline AM/PM PEF. An MCID of 0.35 is being used (8).

2.1.3.6.3 Reliever use

The number of salbutamol/albuterol or levosalbutamol/levalbuterol inhalations is recorded daily by the patients in an electronic diary/PEF meter. In the case that Nebulizer solutions are used as an alternative delivery method, the nebulizer dose is converted to number of puffs according to Section 2.1.2.1. Each patient should be reminded that salbutamol/albuterol or levosalbutamol/levalbuterol should be used only as needed for symptoms, not on a regular basis or prophylactically.

A diary day is defined as the period beginning with an Evening diary, and ending with the following day's Morning Diary. The baseline reliever med use is obtained from the original baselines of parent studies, and will be calculated as follows:

The mean of reliever puffs taken in each of the 7 diary days (minimum 4 diary days) prior to randomization, including the diary day that ends with the morning diary completed on the randomization day.

A diary day cannot be included in the calculation if it is not complete, meaning if an evening or morning diary is missing for that diary day. Out of the 7 diary days, if less than 4 are incomplete, the baseline reliever use is the mean of reliever puffs in each of the complete dairy days. If 4 or more diary days are incomplete, the baseline reliever use is the mean of reliever puffs taken in the closest 4 diary days with complete reliever use information prior to randomization.

2.1.3.6.4 Nocturnal awakenings

The number of nocturnal awakening because of asthma symptoms is recorded every morning by the patients in an electronic diary. The baseline number of nocturnal awakenings is obtained from the original baselines of parent studies, and is computed following the same algorithm used for AM PEF.

2.1.3.7 Endpoints linked to the prescribed OCS dose

For the patients from the EFC13691 study only, the following three efficacy endpoints are derived using the prescribed dose of the background oral corticosteroids (OCS) medications. The baseline OCS dose is the original baseline value from the EFC13691 study.

- Percentage change from baseline in the OCS dose

- Proportion of patients achieving a reduction of 50% or greater in the OCS dose compared with the baseline
- Proportion of patients whose background OCS are completely tapered off

2.1.4 Safety endpoints

The primary endpoint of this study is the number (n) and percentage (%) of patients experiencing any treatment-emergent adverse events (TEAE). Adverse Events (AEs), Serious Adverse Events (SAEs), Adverse Events of Special Interest (AESI), adverse events leading to treatment discontinuation are collected at each visit from the time of informed consent signature to the end of study. The safety analysis will be based on the reported adverse events and other safety information, such as clinical laboratory data, vital signs, and ECG.

Observation period

The observation period will be divided into 4 epochs:

- The **screening** epoch is defined as the time period prior to the date/time of the first dose of IMP in LTS12551.
- The **treatment** epoch is defined as the time period from the date/time of the first dose of IMP to the date/time of the last dose of IMP + 14 days.
- The **follow-up** epoch is defined as the time period from the date/time of the last dose of IMP + 15 days to the end date of 12-week post-treatment follow-up period.
- The **post-study** epoch is defined as the time period from the end date of 12-week post-treatment follow-up period + 1 day.

The **treatment - emergent adverse event period** will include both the **treatment** epoch and **follow-up** epoch. If applicable, the **post-treatment-emergent adverse event period** will be the post-study epoch.

The **pre-treatment adverse event period** will be from starting time of AE reporting up to the first dose of IMP in the LTS12551 study. For all the periods aforementioned, both date and time shall be used in the determination of the periods, as long as they will be available.

2.1.4.1 Adverse events variables

Adverse event observation period

- Pre-treatment adverse events are adverse events that develop or worsen or become serious during the pre-treatment adverse event period.
- Treatment-emergent adverse events are adverse events that develop or worsen or become serious during the treatment-emergent adverse event period.

- Post-treatment-emergent adverse events are adverse events that develop or worsen or become serious during the post-treatment-emergent adverse event period.

All adverse events (including serious adverse events and adverse events of special interest) will be coded to a lower-level term (LLT), preferred term (PT), high-level term (HLT), high-level group term (HLGT), and associated primary system organ class (SOC) using the version of Medical Dictionary for Regulatory Activities (MedDRA) currently in effect at Sanofi at the time of database lock.

The occurrence of all adverse events (regardless of seriousness or relationship to IMP/NIMP) is recorded from the time of signed informed consent for patients from DRI12544 and from the time of the first IMP dose in LTS12551 study for patients from EFC13579, EFC13691 and PDY14192, until the end of the study as defined by the protocol for that patient.

Adverse events of special interest (AESI) and other selected AE groupings will be searched based on the criteria in Table 3

Table 3 - Criteria for adverse events of special interest and other selected AE groupings

AE Grouping	Criteria
AESI	
Anaphylactic reaction	Anaphylactic reaction algorithmic approach (*Introductory Guide for Standardised MedDRA Queries (SMQs) Version 18.1*): includes anaphylactic reaction narrow SMQ (20000021) terms; for selection based on occurrence of multiple symptoms, the symptoms must have occurred within 24 hours of each other
Hypersensitivity (medically reviewed)	Hypersensitivity narrow SMQ (20000214) and [AE corrective treatment/therapy='Y' or Action taken with IMP='Drug withdrawn' or Action taken with IMP='Drug interrupted'] followed by medical review (documented process) for selection of relevant systemic hypersensitivity events
Severe injection site reactions that last longer than 24 hours or serious injection site reaction	HLT = 'Injection site reaction' and either with serious status, or with severe status and (AE end date/time –AE start date/time) ≥ 24 hours or ongoing
Severe or serious infection	Primary SOC = 'infections and infestations' and with severe or serious status
Parasitic infection	The Infection Type 'Parasitic' was checked on the eCRF page "Infection Defined as AESI Complementary Form"
Opportunistic infection	The Infection Type 'Opportunistic' was checked on the eCRF page "Infection Defined as AESI Complementary Form"

AE Grouping	Criteria
Drug-related hepatic disorder	Drug-related hepatic disorders - Comprehensive search narrow SMQ (20000006)
Pregnancy	Primary SOC = 'Pregnancy, puerperium and perinatal conditions', or PT in (Aborted pregnancy, False negative pregnancy test, Pregnancy test positive, Pregnancy test urine positive, Ectopic pregnancy termination)
Symptomatic overdose with IMP	The question "Is the event a Symptomatic Overdose with IMP?" is answered "Yes" on the eCRF page "Adverse Event"
Symptomatic overdose with non-IMP	The question "Is the event a Symptomatic Overdose with non-IMP?" is answered "Yes" on the eCRF page "Adverse Event"
Other selected AE grouping	
Injection site reaction	HLT = 'Injection site reaction'
Malignancy	Sub-SMQ (20000091) – Malignant or unspecified tumors
Suicidal behavior	PT in (Completed suicide, Suicidal ideation, Depression suicidal, Suicidal behavior, Suicide attempt)
Partner pregnancy	PT in (Pregnancy of partner, Miscarriage of partner)
Conjunctivitis (narrow)	PT in (Conjunctivitis, Conjunctivitis allergic, Conjunctivitis bacterial, Conjunctivitis viral, Atopic keratoconjunctivitis)
Conjunctivitis (broad)	PT in (Conjunctivitis, Conjunctivitis allergic, Conjunctivitis bacterial, Conjunctivitis viral, Atopic keratoconjunctivitis, Blepharitis, Dry eye, Eye irritation, Eye pruritus, Lacrimation increased, Eye discharge, Foreign body sensation in eyes, Photophobia, Xerophthalmia, Ocular hyperaemia, Conjunctival hyperaemia)
Hypereosinophilia	HLT = 'Eosinophilic disorders' or PT = 'Eosinophil count increased'

2.1.4.2 Deaths

The deaths observation period are per the observation periods defined above.

2.1.4.3 Laboratory safety variables

Clinical laboratory data consists of blood analysis, including hematology, clinical chemistry, and urinalysis. Clinical laboratory values will be converted to standard international units and analyzed in standard international units; international units will be used in all listings and tables. Baseline values for clinical laboratory variables will be the original baseline from the parent study.

Blood samples for clinical laboratories will be collected at Visit1, Visit 4 (Week 4), Visit 8 (Week 12), Visit 11 (Week 24), Visit 13 (Week 48; if applicable), Visit 15 (Week 72; if applicable), 17 (End-of-Treatment), 18 (End-of-Study) and/or early termination, unless otherwise specified. The laboratory parameters will be classified as follows:

- Hematology:
  - **Red blood cells and platelets and coagulation:** hemoglobin, hematocrit, platelet count and total red blood cell count.
  - **White blood cells:** total white blood cell count, with five-part differential count (neutrophils, lymphocytes, monocytes, basophils, eosinophils).
- Clinical chemistry
  - **Metabolism**: glucose, total cholesterol, total protein, creatine phosphokinase.
  - **Electrolytes**: sodium, potassium, chloride, bicarbonate
  - **Renal function**: creatinine, creatinine clearance, blood urea nitrogen, uric acid
  - **Liver function**: alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, total bilirubin, albumin
  - **Pregnancy test**: A serum pregnancy test (β-human chorionic gonadotrophin) performed at screening (Visit 1) in women of childbearing potential will be applicable to patients coming from DRI12544.
  - **Hepatitis screen**: A hepatitis screen (hepatitis B surface antigen [HBsAg], Hepatitis B IgM core antibody [HBcAb-IgM], hepatitis C antibodies [HC Ab]) will be performed at Visit 1.
  - **HIV screen**: HIV screen (Anti-HIV-1 and HIV-2 antibodies) will be performed at Visit 1.
  - **Antibody**: anti-nuclear antibody (ANA) at Visit 1. Note: Anti-double-strand DNA antibody will be tested if ANA is positive (≥1:160 titer).
- Serum immunoglobulin quantitative immunoassays (IEP) (IgG, IgG subclasses 1-4 subtypes, IgM, and IgA). The collection for serum immunoglobulin will be stopped after the approval of protocol amendment 4. The analyses for IgG, IgG subclasses 1-4 subtypes, IgM, and IgA in LTS12551 study will be restricted to the patients from DRI12544 study and performed to the data observed up to the end of collection.

Urine samples will be collected as follows:

- **Urinalysis** - Quantitative analyses: 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. Testing is performed at Visit 1, Visit 8 (Week 12), Visit 11 (Week 24), Visit 13 (Week 48; if applicable), Visit 15 (Week 72; if applicable), Visit 16 (Week 84; if applicable), Visit 17 (End-of-Treatment) and Visit 18 (End-of-Study).

- **Pregnancy test**: Qualifying pregnancy test for patients coming from EFC13579, EFC13691 and PDY14192 studies will be the urine pregnancy test performed at the combined EOT/V1/V2 visit. The urine pregnancy test will be performed at visit 2 (Day 1) and every scheduled visit from Visit 4 (Week 4) to Visit 18 (End-of-Study).

Technical formulas are described in Section 2.5.1.

2.1.4.4 Vital signs variables

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 visit. Height (cm) will be measured at Visit 1 only. Vital signs will be measured in the sitting position using the same arm at each visit, and will be measured prior to receiving investigational product at the study visits. Baseline values for vital signs will be the original baseline from the parent studies.

2.1.4.5 Electrocardiogram variables

ECG results will be from an independent central lab. Baseline values for ECG will be the original baseline from the parent study.

One recording of a standard 12-lead ECG will be performed at Visit 1, Visit 11 (Week 24), Visit 13 (Week 48; if applicable), Visit 17 (End-of-Treatment) and Visit 18 (End-of-Study). A minimum of 3 complexes in an appropriate lead (lead II) will be averaged to determine the PR-interval, QT/QTcF/QTcB interval, QRS-complex and heart rate will be measured for each ECG. At the post-enrollment visits, ECGs will be performed prior to investigational product administration. All ECGs will be performed with the subject in a reclined position.

2.1.5 Pharmacokinetic variables

Blood samples of serum functional dupilumab are collected at Visit 1, Visit 4 (Week 4), Visit 8 (Week 12), Visit 11 (Week 24), Visit 13 (Week 48; if applicable), Visit 15 (Week 72; if applicable), Visit 17 (End-of-Treatment), Visit 18 (End-of-Study) and/or early termination, and before the IMP administration at corresponding scheduled visits that are specified in the protocol. The pre-dose serum dupilumab concentration will be collected at the scheduled visits in LTS12551 study. The baseline values for PK variables are the original baselines from the parent studies.

2.1.6 Anti-drug antibody (ADA) variables

Samples for anti-drug antibodies (ADAs) are collected at various time points throughout the study. ADA samples collected at Visit 1, Visit 8 (Week 12), Visit 11 (Week 24), Visit 13 (Week 48; if applicable), Visit 15 (Week 72; if applicable), Visit 17 (End-of-Treatment), Visit 18 (End-of-Study) and/or early termination will be analyzed for ADA. The baseline used to define ADA variables refers to the baseline value in the parent study.

In response to AE's of special interest like anaphylaxis or hypersensitivity additional ADA samples closer to the event may be analyzed, based on the judgment of the medical investigator and/or medical monitor.

The ADA variables include ADA status (positive or negative) and titer as follows:

- Number of patients with pre-existing immunoreactivity

  Pre-existing immunoreactivity is defined as either an ADA positive response in the assay at baseline of the parent study with all post first dose ADA results negative in the current study, or an ADA positive response at baseline of the parent study with all post first dose ADA results in the current study less than 4-fold of the baseline titer levels of the parent study.

- Number of patients with treatment-emergent response in the ADA assay

  Treatment-emergent response is defined as a positive response in the ADA assay post first dose in the current study, when baseline status in the parent study is negative or missing. The treatment-emergent response is further characterized as:

  - Persistent response - defined as a treatment-emergent ADA positive response with two or more consecutive ADA positive sampling time points separated by greater than 12-week period (greater than 84 days), with no ADA negative sample in between.
  - Indeterminate response - defined as a treatment-emergent response with only the last collected sample positive in the ADA assay.
  - Transient response – defined as a treatment-emergent ADA positive response that is not considered persistent or indeterminate.

- Number of patients with treatment-boosted response in the ADA assay

  Treatment-boosted response is defined as a positive response in the ADA assay post first dose in the current study that is greater than or equal to 4-fold of the baseline titer levels of the parent studies, when baseline status of the parent studies are positive.

- Titer values (titer value category)
  - Low (titer <1,000)
  - Moderate (1,000 ≤ titer ≤10,000)
  - High (titer >10,000).
- ADA positive samples will be further characterized for the presence of neutralizing antibody (NAb) response

2.1.7 Pharmacodynamic/genomics endpoints

2.1.7.1 Whole blood biomarkers

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.

2.1.7.2 Serum biomarkers

Serum total IgE will be measured with a quantitative method (eg, ImmunoCAP) approved for diagnostic testing at Visit 1, Visit 13 (Week 48), Visit 16 (Week 84), and Visit 17 (End-of-Treatment).

Serum IgM, IgA, IgG and IgG subtypes will be measured with immunoassays at Visit 1, Visit 11 (Week 24), Visit 13 (Week 48), Visit 16 (Week 84), and Visit 17 (End-of-Treatment).

The collection for serum immunoglobulin and serum total IgE will be stopped after the approval of protocol amendment 4. The analyses for the total IgE in LTS12551 study will be restricted to the patients from DRI12544 study and performed to the data observed up to the end of collection.

2.2 DISPOSITION OF PATIENTS

This section describes patient disposition for both patient study status and the patient analysis populations for LTS12551 only, unless otherwise specified.

- Screened patients are defined as the patients who signed the informed consent.
- Enrolled patients are defined as the patients who signed the informed consent and had a treatment kit number allocated and recorded in the IVRS/IWRS database, regardless of whether the treatment kit was used.
- The safety population consists of the patients who actually received at least one dose or part of a dose of the LTS12551 study medication.

For patient study status, the total number of patients in each of the following categories will be presented in the clinical study report via using a summary table:

- Screened patients
- Screen failure patients and reasons for screen failure
- Non-enrolled but treated patients
- Enrolled patients (Overall and by parent study)
- Enrolled but not treated patients

Enrolled and treated patients (by the treatment category and overall, defined in Section 2.3.2)

- Patients who discontinued study treatment by main reason for permanent treatment discontinuation
- Status at last study contact

For all categories of patients (except for the screened and non-enrolled categories), percentages will be calculated using the total number of all enrolled patients as the denominator. Reasons for treatment discontinuation will be supplied in tables giving numbers and percentages. This summary will be provided by the treatment category (see Section 2.3.2) and may also by region/pooled countries.

A patient is considered as lost to follow-up at the end of study if he/she is not assessed at the last protocol planned visit.

All critical or major deviations potentially impacting safety evaluation, drug-dispensing irregularities, and other major or critical deviations will be summarized in tables giving numbers and percentages of deviations by treatment category.

Additionally, the analysis populations for safety, efficacy, PK and Anti-drug antibody will be summarized in a table by number of patients in the enrolled population.

- Safety population (for both safety and efficacy analyses)
- Pharmacokinetics population
- Anti-drug antibody population

2.2.1 Randomization and drug dispensing irregularities

There is no randomization procedure in LTS12551. Drug-dispensing irregularities occur whenever:

- A patient is dispensed an IMP kit not allocated by the IVRS, such as, a) a patient at any time in the study is dispensed a different treatment kit than as assigned, or b) a non-screened patient is treated with IMP reserved for enrolled patients.

Drug-dispensing irregularities will be monitored throughout the study and reviewed on an ongoing basis.

All drug-dispensing irregularities will be documented in the clinical study report. If the number of irregularities is large enough to make a tabular summary useful, the irregularities will be categorized and summarized among enrolled patients (number and percentages). Non-enrolled and treated patients will be described separately.

Drug-dispensing irregularities to be prospectively identified include but are not limited to:

Randomization and drug allocation irregularities
Kit dispensation without IVRS transaction
Erroneous kit dispensation
Kit not available
Subject enrolled twice
Subject switched to another site

2.3 ANALYSIS POPULATIONS

The primary analysis population is the safety population. All safety and efficacy analyses will be performed based on the safety population.

2.3.1 OCS dependent and Non-OCS dependent populations

The OCS dependent population is defined as the patients who participated in EFC13691 study and then subsequently enrolled in the LTS12551 study.

The non-OCS dependent population is defined as the patients who were not on daily chronic OCS therapy and participated in DRI12544, EFC13579 or PDY14192 studies and then enrolled in the LTS12551 study.

The patients from the EFC13691 study are considered as a different patient population from the patients from the DRI12544, EFC13579 or PDY14192 studies. This is because the patients from the EFC13691 study are more severe at the baseline of parent study, are using a different background controller medication, and potentially could have different safety profiles and different efficacy effect from the patients enrolled from the DRI12544, EFC13579 or PDY14192 studies. In addition, for the patients from the EFC13691 study only, LTS12551 study will assess the efficacy endpoints linked to the reduction of the OCS dose.

Furthermore, all analyses planned in LTS12551 will be performed and presented separately for the patients from the EFC13691 study and the patients from the DRI12544, EFC13579 or PDY14192 studies, except for the endpoints (see Section 2.1.3.7) that are collected for the patients from EFC13691 study only.

2.3.2 Safety population

The safety population is defined as the patients who have actually received at least 1 dose or part of a dose of the IMP in LTS12551.

Enrolled patients for whom it is unclear whether they took the IMP or not will be included in the safety population as enrolled.

The treatment category “Placebo/Dupilumab” is defined as the patients who have been in the actual placebo arms of the parent studies and exposed to Dupilumab in LTS12551. The treatment category “Dupilumab/Dupilumab” is defined as the patients who have been in the actual Dupilumab arms of the parent studies and exposed to Dupilumab in LTS12551.

For the OCS dependent patients, results of each planned analysis will be presented by “Placebo/Dupilumab”, “Dupilumab/Dupilumab” and “All”.

For the non-OCS dependent patients, results of each planned analysis will be presented by the parent study and “All”, and further by “Placebo/Dupilumab” and “Dupilumab/Dupilumab” within each parent study.

2.3.3 Efficacy populations

The efficacy analysis population is the same as the safety population.

2.3.4 Pharmacokinetics (PK) population

The PK population will consist of all the patients in the safety population who had at least one non-missing functional dupilumab concentration value after the 1st dose of study drug in the current study.

2.3.5 Anti-drug antibody (ADA) population

ADA Population will consist of all the patients in the safety population who had at least one non-missing ADA result in the ADA assay after the 1st dose of study drug in the current study.

2.4 STATISTICAL METHODS

2.4.1 Demographics and baseline characteristics

The demographics and baseline characteristics will be summarized for the safety population. The data for demographics and baseline characteristics will be obtained from the original baselines of the parent studies. Continuous data will be summarized by the treatment category and overall (see Section 2.3.2), using the number of available data, mean, standard deviation (SD), median, minimum, and maximum. Categorical and ordinal data will be summarized by the treatment category and overall (see Section 2.3.2), using the number and percentage of patients.

Parameters described in Section 2.1.1 will be summarized for the safety population by the treatment category and overall (see Section 2.3.2) using descriptive statistics.

Medical and surgical history will be summarized by the treatment category and overall (see Section 2.3.2), by system organ class (SOC) and preferred term (PT) sorted by internationally agreed order of SOC and by the decreasing frequency of PT within SOC based on the overall group. Comorbidity history and atopic medical history will be summarized separately.

No specific description of the safety/efficacy parameters will be provided at baseline. If relevant, the baseline values will be described along with each safety/efficacy analysis.

2.4.2 Prior or concomitant medications

The prior medications, concomitant medications in parent study, and concomitant medications will be presented for the safety population by the treatment category and overall (see Section 2.3.2). The prior medications are those the patients used prior to the first IMP dose in the parent study. The data of prior medications are obtained from the parent study. Medications will be summarized according to the WHO-DD dictionary, considering the first digit of the ATC class (anatomic category) and the first 3 digits of the ATC class (therapeutic category). All ATC codes corresponding to a medication will be summarized. Patients will be counted once in each ATC category (anatomic or therapeutic) linked to the medication, and therefore patients may be counted several times for the same medication.

The table for prior medications will be sorted by decreasing frequency of ATC followed by all other therapeutic classes based on the overall incidence. In case of equal frequency regarding ATC (anatomic or therapeutic), alphabetical order will be used.

The tables for concomitant medications in parent study will be sorted by decreasing frequency of ATC followed by all other therapeutic classes based on the overall incidence. In case of equal frequency regarding ATCs (anatomic or therapeutic categories), alphabetical order will be used.

The tables for concomitant medications will be sorted by decreasing frequency of ATC followed by all other therapeutic classes based on the overall incidence. In case of equal frequency regarding ATCs (anatomic or therapeutic categories), alphabetical order will be used.

In addition, the ICS in combination with allowable controller medication(s), the salbutamol/albuterol or levosalbutamol/levalbuterol reliever medication, and the OCS medication (for patients from EFC13691 only) will be summarized separately.

2.4.2.1 ICS in combination with allowable controller medication(s)

ICS in combination with allowable controller medications and the OCS medication (for patients from EFC13691 only) taken within 30 days prior to screening of parent study will be summarized by the treatment category and overall (see Section 2.3.2), and will be sorted by decreasing frequency of medication name in the overall category. The data of prior ICS and controller medications and the OCS medication (for patients from EFC13691 only) are sourced from the parent studies.

The prescription of ICS in combination with allowable controller medication(s) at enrollment of LTS12551 will be summarized by the treatment category and overall (see Section 2.3.2). Number (%) of patients will be presented by medication names and also by ICS dose level (medium/high as defined in Appendix C) according to the classification specified in (9). The descriptive summary for the percentage change from baseline in OCS dose will be presented in the efficacy evaluations for patients from EFC13691.

2.4.2.1.1 Compliance for ICS and controller medications

During the LTS12551 study, the prescription of background asthma controller medications is reported on the eCRF, and the daily intake is recorded on the electronic diary by patients. The use of electronic diary will be stopped after the approval of protocol amendment 4 in LTS12551. The compliance for the controller medications with ICS component will be calculated for each patient, based on the data observed up to the end of electronic diary collection.

For a patient from DRI12544 study, a morning/evening dairy is compliant if the number of puffs administered is the same as or greater than what is prescribed. **Percentage of Compliance** is defined as the total number of controller medication puffs taken divided by the total number of expected puffs of controller medication during the treatment period (ie, from the evening dairy of the first IMP dose date in LTS12551 study to the morning dairy of the last IMP dose in LTS12551 study + 14 days). The total number of controller medication puff taken is the sum of the controller medication puffs captured in each morning and evening diary during the treatment period, with each diary being capped at the number of puffs expected per diary, according to the patient's prescribed controller medication dosing regimen.

For a patient from EFC13579, EFC13691 or PDY14192 studies, due to changes in the design of electronic diary logpad, the daily intake of each prescribed asthma controller medication is recorded on the electronic diary every evening. An evening diary is considered as compliant to the prescribed controller medication with ICS component if the actual dose of each controller medication with ICS component is same as or greater than the prescribed dose. **Percentage of Compliance** is defined as the number of days when the patient is compliant to the prescribed controller medication(s) with ICS component divided by the number of days the patient stays in the treatment period (from first dose to last dose + 14 days).

2.4.3 Extent of investigational medicinal product exposure and compliance

The extent of IMP exposure and compliance will be assessed and summarized by the treatment category and overall on the safety population (Section 2.3.2).

2.4.3.1 Extent of investigational medicinal product exposure

The extent of IMP exposure will be assessed by the duration of IMP exposure in LTS12551 study.

Duration of investigational product exposure is defined as: the last IMP dose date in LTS12551 study – the first IMP dose date in LTS12551 study + 14 days, regardless of unplanned intermittent discontinuations (see Section 2.5.3 for calculation in case of missing or incomplete data).

Duration of IMP exposure will be summarized descriptively as a quantitative variable (number, mean, SD, median, minimum, and maximum). In addition, duration of treatment exposure will also be summarized categorically by counts and percentages for each of the following categories and cumulatively according to these categories (the categories exceeding Week 48 may apply to only the patients on the 96-week treatment period who signed the informed consent form before the approval of protocol amendment 4):

≤ 4 week

> 4 and ≤ 12 weeks

> 12 and ≤ 24 weeks

> 24 and ≤ 48 weeks

> 48 and ≤ 72 weeks

> 72 and ≤ 96 weeks

> 96 weeks

Additionally, the cumulative duration of treatment exposure, will be provided in patient years by treatment category and overall (see Section 2.3.2).

Number and percentage of patients will be summarized by total number of injections they received during the LTS12551 study. The number and percentage of patients who receive injection will be summarized by type of administrator (site staff, patient or non-professional care giver, professional care giver at home), by dosing week, and maybe by IMP packaging way (vial or pre-filled syringe).

2.4.3.2 Compliance

A given IMP administration will be considered noncompliant if the patient did not take the planned dose of treatment as required by the protocol. No imputation will be made for patients with missing or incomplete data. An administration is considered compliant if an injection is performed, regardless the actual amount of solution injected.

The loading dose will be considered as two administrations, and the administration of loading dose will be considered compliant if both the two injections are performed. The loading dose on Day 1 of LTS12551 is applied to patients from DRI12544 only, and is not applicable to patients from EFC13579, EFC13691 or PDY14192.

Percentage of compliance for a patient will be defined as the number of administrations that the patient was compliant divided by the total number of administrations that the patient was planned to take during the treatment epoch defined in Section 2.1.4.

Treatment compliance percentages will be summarized descriptively as quantitative variables (number, mean, SD, median, minimum, and maximum). The percentage of patients whose compliance is < 80% will be summarized.

Cases of overdose (at least twice the dose during an interval of less than 11 days) will constitute serious adverse events and will be listed as such. More generally, dosing irregularities will be listed in Section 2.2.1.

2.4.4 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 efficacy parameters is the original baselines from the parent studies.

For severe exacerbation events, the number of patients with one or more severe exacerbation events (number and qualitative variable: Yes/No), number of severe exacerbation events (qualitative variable: 0, 1, 2, 3, ≥4), 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, maximum) will be presented by the treatment category and overall (see Section 2.3.2) during the treatment period. Number and annualized rate will also be analyzed for severe exacerbation with use of systemic corticosteroids for ≥3 days only, and that with hospitalization or with emergency room visit only. The mean duration of a severe exacerbation will also be summarized.

For the continuous efficacy variables listed in Section 2.1.3, descriptive statistics (mean, SD, median, minimum and maximum) will be presented for the parameter and its change from baseline over visits and by the treatment category and overall (see Section 2.3.2). In addition, figure of mean change from baseline (with corresponding standard error) will be presented for the continuous efficacy parameter over visits and by the treatment category and overall (see Section 2.3.2).

For the categorical efficacy variables listed in Section 2.1.3, the number and percentage will be presented over time for all patients who have data available at that time point by the treatment category and overall (see Section 2.3.2).

In addition, particularly for the patients coming from the EFC13691 study, the descriptive statistics (mean, SD, median, minimum and maximum) for the percentage change from baseline in oral corticosteroids (OCS) dose will be presented over time by the treatment category and overall (see Section 2.3.2); and, the proportion of patients achieving a reduction of 50% or greater in their OCS dose compared with the original baseline in parent study, and the proportion of patients whose background OCS are completely tapered off will be presented over time by the treatment category and overall (see Section 2.3.2).

2.4.4.1 Subgroup analyses

Subgroup analyses will be performed for several key efficacy variables (severe exacerbation events, FEV1, ACQ5, and AQLQ) by:

- ICS dose group: patients on the medium or high ICS dose at the original baseline in the parent studies
- Blood eosinophil (Giga/L) groups at baseline of the parent study: ≥0.3, <0.3, ≥0.15, <0.15, ≥0.15 - <0.3, ≥0.3 - <0.5, and ≥0.5

2.4.4.2 Multiplicity issues

Not applicable.

2.4.5 Analyses of safety data

The summary of safety endpoints will be presented by the treatment category and overall (see Section 2.3.2).

General common rules

All safety analyses will be performed on the safety population as defined in Section 2.3.2, unless otherwise specified, using the following common rules:

- The baseline value for safety parameters is defined as the original baseline from the parent studies.
- In addition to the baseline values, the pre-dose measurements at Week 0 in LTS12551 will be presented in the by-visit summary/figure for laboratory, vital signs or ECG parameters. The pre-dose measurements at Week 0 of LTS12551 are defined as follows: for patients enrolled from DRI12544, the measurements at Week 0 are obtained from the EOS visit of DRI12544 if available, regardless whether the EOS visit in DRI12544 was combined with Visit 1/Visit 2 in LTS12551; otherwise, Week 0 value will be the last available measurement prior to the first IMP dose in LTS12551 study. For patients enrolled from EFC13579, EFC13691 and PDY14192, the measurements at Week 0 are obtained from the EOT visit of parent studies if available; otherwise, Week 0 value will be the last available measurement prior to the first IMP dose in LTS12551 study.
- The potentially clinically significant abnormality (PCSA) values are defined as abnormal values considered medically important by the sponsor according to predefined criteria/thresholds based on literature review and defined by the sponsor for clinical laboratory tests, vital signs, and ECG (Appendix A).
- PCSA criteria will determine which patients had at least one PCSA during the treatment-emergent adverse event period, taking into account all evaluations performed during the treatment-emergent adverse event period, including non-scheduled or repeated evaluations.

The number of all such patients will be the numerator for the on-treatment PCSA percentage.

- The treatment-emergent PCSA denominator for a given parameter will be based on the number of patients assessed for that given parameter in the treatment-emergent adverse event period by the treatment category and overall (see Section 2.3.2) on the safety population.
- For quantitative safety parameters based on central laboratory/reading measurements, descriptive statistics will be used to summarize results and change from baseline values by visit and treatment category and overall (see Section 2.3.2). Summaries will include the endpoint value and/or the worst on-treatment value. The endpoint value is commonly defined as the value collected at the date of last IMP dose + 14 days or the end of treatment visit. If this value is missing, this endpoint value will be the closest value prior to the last administration of IMP + 14 days. The worst value is defined as the nadir and /or the peak post-baseline (up to last administration of IMP + 14 days) according to the direction (minimum or maximum) of the abnormality as defined in the PCSA list.
- All of the values including unscheduled measurements will be assigned to the appropriate safety analysis visit window. The safety analysis visit window is defined in Section 2.5.4.
- The analysis of the safety variables will be essentially descriptive and no systematic testing is planned.

2.4.5.1 Analyses of adverse events

Generalities

The primary endpoint of this study is the number (n) and percentage (%) of patients experiencing any treatment-emergent adverse events (TEAE). Pre-treatment (if applicable) adverse events will be described separately.

If an adverse event date/time of onset (occurrence, worsening, or becoming serious) is incomplete, an imputation algorithm will be used to classify the adverse event as pre-treatment or treatment-emergent adverse event. The algorithm for imputing date/time of onset will be conservative and will classify an adverse event as treatment-emergent, unless there is definitive information to determine it is pre-treatment. Details on classification of adverse events with missing or partial onset dates are provided in Section 2.5.

Adverse event incidence tables will be presented by system organ class (SOC), high level group term (HLGT), high level term (HLT) and preferred term (PT) sorted in alphabetical order, to summarize the number (n) and percentage (%) of patients experiencing at least an AE by the treatment category and overall (see Section 2.3.2). Multiple occurrences of the same event in the same patient will be counted only once in the tables within a treatment category. The denominator for computation of percentages is the safety population within each treatment category. In all AE incidence tables, the total patient years (in the unit of 100 patient-years) for each treatment category and overall (see Section 2.3.2) will be presented in the corresponding column headers.

The number of events per 100 patient-years (adjusted for the total duration of exposure) by the treatment category and overall (see Section 2.3.2) will be presented for each AESI during the treatment-emergent period.

The table of all treatment-emergent adverse events presented by SOC and PT will be sorted by the internationally agreed SOC order (from MedDRA) and decreasing frequency of PTs within SOCs. Sorting will be based on the results for the overall patients across treatment categories, unless otherwise specified.

Analysis of all treatment-emergent adverse events

The following treatment-emergent adverse event summaries by the treatment category and overall patients (see Section 2.3.2) will be generated for the safety population. Sorting will be based on the results for the overall patients across treatment categories, unless otherwise specified.

- Overview of treatment-emergent adverse events, summarizing number (%) of patients (including total patient years in column headers) with any
  - Treatment-emergent adverse event
  - Treatment-emergent serious adverse event
  - Treatment-emergent adverse event leading to death
  - Treatment-emergent adverse event leading to permanent treatment discontinuation
- All treatment-emergent adverse events by primary SOC, HLGT, HLT, and PT, showing number (%) of patients (including total patient years in column headers) with at least one treatment-emergent adverse event sorted by the SOC internationally agreed order. The other levels (HLGT, HLT, PT) will be sorted in alphabetical order.
- All treatment-emergent adverse events by primary SOC and PT, showing the number (%) of patients (including total patient years in column headers) with at least one treatment-emergent adverse event, will be presented by the internationally agreed SOC order and by decreasing incidence of PTs within each SOC.
- All treatment-emergent adverse events by primary SOC, showing the number (%) of patients (including total patient years in column headers) with at least one treatment-emergent adverse event, will be presented by the internationally agreed SOC order.
- All possibly drug-related TEAEs by primary SOC and PT, showing number (%) of patients (including total patient years in column headers) with at least one TEAE, will be presented by SOC internationally agreed order and by decreasing incidence of PTs within each SOC.
- All TEAEs by maximal severity, presented by primary SOC and PT, showing the number (%) of patients (including total patient years in column headers) with at least one TEAE by severity (ie, mild, moderate, or severe), sorted by the order defined above.

- Number (%) of patients (including total patient years in column headers) experiencing TEAE(s) presented by primary and secondary SOC, HLGT, HLT, and PT sorted by SOC internationally agreed order. The other level (HLGT, HLT, PT) will be presented in an alphabetic order.

Analysis of all treatment emergent serious adverse event(s)

- All treatment-emergent serious adverse events by primary SOC, HLGT, HLT, and PT, showing the number (%) of patients (including total patient years in column headers) with at least one treatment-emergent serious adverse event, will be presented by the internationally agreed SOC order. The other levels (HLGT, HLT, PT) will be presented in alphabetical order.

- All treatment-emergent serious adverse events by primary SOC and PT, showing number (%) of patients (including total patient years in column headers) with at least one TEAE, will be presented by SOC internationally agreed order and decreasing incidence of PTs within SOC.

Analysis of all treatment-emergent adverse event(s) leading to treatment discontinuation

- All TEAEs leading to treatment discontinuation, by primary SOC, HLGT, HLT, and PT, showing the number (%) of patients (including total patient years in column headers) will be presented by the internationally agreed SOC order. The other levels (HLGT, HLT, PT) will be presented in alphabetical order.

- All TEAEs leading to treatment discontinuation, by primary SOC and PT, showing number (%) of patients (including total patient years in column headers) with at least one TEAE, will be presented by SOC internationally agreed order and by decreasing incidence of PTs within each SOC.

Analysis of adverse events of special interest (AESI) and other selected AE groupings

Summaries of AESI defined by the search criteria:

- All treatment emergent AESIs and other selected AE groupings identifiable by MedDRA terms or by laboratory values (as in ALT elevation), by AESI category and PT, showing the number (%) of patients (including total patient years in column headers), will be presented by decreasing incidence of PT within each AESI category.
- An overview summary within each treatment-emergent AESI and other selected AE groupings will include:
  - Number (%) of patients with any TEAE
  - Number (%) of patients with any SAE (regardless of treatment-emergent status)
  - Number (%) of patients with any treatment-emergent SAE
  - Number (%) of patients with any AE leading to death

- Number (%) of patients with any TEAE leading to permanent treatment discontinuation
- Number (%) of patients with any TEAE by maximum intensity, corrective treatment, and final outcome
- Number (%) of patients with any possibly related TEAE
- Kaplan-Meier plot (cumulative incidence (%) versus time up to Week 60 based on K-M estimate) for time-to-onset of the first TEAE
- Cumulative incidence (K-M estimates) up to specified time points (Week 4, Week 12, Week 24, Week 48, Week 60)

Notes for the last two bullets: when TEAE start date or worsening date is partially available, the maximum of the earliest possible TEAE start date and the treatment start date will be used. When TEAE start date or worsening date is completely missing, the treatment start date will be used.

- Number of treatment-emergent AESIs and other selected AE groupings per 100 patient-years (total number of events adjusted for the total duration of exposure) will be presented by decreasing incidence of PT within each AESI and other selected AE groupings category.

Analysis of pre-treatment adverse events

- All pre-treatment AEs by primary SOC and PT, showing the number (%) of patients (including total patient years in column headers) with at least one pre-treatment AE, will be presented by the internationally agreed SOC order and by decreasing incidence of PTs within each SOC.

- All pre-treatment SAEs by primary SOC and PT, showing the number (%) of patients (including total patient years in column headers) with at least one pre-treatment SAE, will be presented by the internationally agreed SOC order and by decreasing incidence of PTs within each SOC.

- All pre-treatment adverse events leading to study discontinuation by primary SOC and PT, showing the number (%) of patients (including total patient years in column headers), will be presented by the internationally agreed SOC order and by decreasing incidence of PTs within each SOC.

Analysis of adverse events

- All pre-treatment, treatment-emergent, or post-treatment-emergent AEs by primary SOC and PT, showing the number (%) of patients (including total patient years in column headers) with at least one AE, will be presented by the internationally agreed SOC order and by decreasing incidence of PTs within each SOC.

2.4.5.2 Deaths

The following death summaries will be generated on the safety population, unless otherwise specified.

- Number (%) of patients (including total patient years in column headers) who died by primary SOC and PT for death
- Deaths in non-enrolled patients or enrolled but not treated patients
- TEAE leading to death (death as an outcome on the AE CRF page as reported by the Investigator) by primary SOC and PT showing number (%) of patients (including total patient years in column headers) sorted by internationally agreed SOC order, and by alphabetical order of PT within each SOC.
- All pre-treatment AE leading to death by primary SOC and PT, showing the number (%) of patients (including total patient years in column headers), sorted by the internationally agreed SOC order and by decreasing incidence of PTs within each SOC.
- Listing of deaths showing parent study, treatment category, patient identifier, gender, race, age, duration of exposure, date of death (if relevant), reason of death.

2.4.5.3 Analyses of laboratory variables

The baseline value of all laboratory variables is the original baseline from the parent studies. The pre-dose measurement at Week 0 of LTS12551 will be separately presented in the summaries or plots over time. This section will be organized by biological function as in Section 2.1.4.3.

The summary statistics (including number, mean, median, standard deviation, Q1, Q3, minimum and maximum) of all laboratory variables (central laboratory values and changes from baseline) will be calculated for each visit or study assessment (baseline, each post-baseline time point, and endpoint) by the treatment category and overall (see Section 2.3.2).

For all laboratory variables, the mean change from baseline with corresponding standard error at each visit will be plotted by the treatment category and overall (see Section 2.3.2).

For all laboratory variables, the summary statistics over visits for either measurements or mean change from baseline, and the plot of mean change from baseline over visits should use the centralized data only, and should include the measurements obtained at either scheduled or unscheduled visits.

The incidence of PCSAs (list provided in Appendix A) at any time during the treatment-emergent adverse event period will be summarized by biological function, and by the treatment category and overall (see Section 2.3.2), regardless of the baseline level and/or according to the following status at baseline of parent study and at Week 0 of LTS12551 study, respectively:

- Normal/missing

- Abnormal according to PCSA criterion or criteria

For parameters for which no PCSA criterion is defined, similar table(s) using the normal range will be provided.

For PCSA analyses, the laboratory measurements obtained at either scheduled or unscheduled visits should be used; and, both the centralized and local test results should be used, as long as their available dates/time is different from each other's. Centralized data will be used preferentially to the local measures in the PCSA analyses when measurements are performed on the same date and at the same time for a given laboratory test.

A listing of patients with at least one post-baseline PCSA will be provided and will display the whole profile over time of all parameters of the corresponding biological function. In this listing, baseline, endpoint value and individual values will be flagged when lower or higher than the lower or upper laboratory limits and/or when reaching the absolute limit of abnormality criteria.

Drug-induced liver injury

Additional analysis of liver-related adverse events will be performed if necessary.

2.4.5.4 Analyses of vital sign variables

The baseline value of all vital sign variables is the original baseline from the parent studies. The pre-dose measurement at Week 0 of LTS12551 will be separately presented in the summaries or plots over time.

The summary statistics (including number, mean, median, standard deviation, Q1, Q3, minimum and maximum) of all vital signs variables (measurements and changes from baseline) will be calculated for each visit or study assessment (baseline, each post-baseline time point, and endpoint) by the treatment category and overall (see Section 2.3.2).

For all vital sign variables, the mean change from baseline with corresponding standard error at each visit will be plotted by the treatment category and overall (see Section 2.3.2).

For all vital sign variables, the summary statistics over visits for either measurements or mean change from baseline, and the plot of mean change from baseline over visits should include the measurements obtained at either scheduled or unscheduled visits.

The incidence of PCSAs at any time during the treatment-emergent adverse event period will be summarized by the treatment category and overall (see Section 2.3.2), irrespective of the baseline level and/or according to the following status at baseline of parent study and at Week 0 of LTS12551 study, respectively:

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

For PCSA analyses, the vital sign measurements obtained at either scheduled or unscheduled visits should be used.

2.4.5.5 Analyses of electrocardiogram variables

The baseline value of all ECG variables is the original baseline from the parent studies. The pre-dose measurement at Week 0 of LTS12551 will be separately presented in the summaries or plots over time.

The summary statistics (including number, mean, median, standard deviation, Q1, Q3, minimum and maximum) of all ECG variables (measurements and changes from baseline) will be calculated for each visit or study assessment (baseline and each post-baseline time point, and endpoint) by the treatment category and overall (see Section 2.3.2).

For all ECG parameters, the mean change from baseline with corresponding standard error at each visit will be plotted by the treatment category and overall (see Section 2.3.2).

For all ECG variables, the summary statistics over visits for either measurements or mean change from baseline, and the plot of mean change from baseline over visits should use the centralized data only, and should include the measurements obtained at either scheduled or unscheduled visits.

The incidence of PCSAs at any time during the treatment-emergent adverse event period will be summarized by treatment category and overall (see Section 2.3.2) irrespective of the baseline level and/or according to the following status at baseline of parent study and at Week 0 of LTS12551 study, respectively:

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

For PCSA analyses, the ECG measurements obtained at either scheduled or unscheduled visits should be used; and, both the centralized and local ECG results should be used, as long as their available dates/time is different from each other's. Centralized data will be used preferentially to the local measures in the PCSA analyses when measurements are performed on the same date and at the same time.

2.4.5.6 Subgroup analyses

Subgroup analyses will be performed for several key safety variables (treatment-emergent AE/SAE/AESI/AE leading to permanent treatment discontinuation) by:

- ICS dose group: patients on the medium or high ICS dose at the original baseline in parent studies
- Age group (< 18, 18-64, ≥ 65 years)
- Race (Caucasian/White, Black/of African descent, Asian/Oriental, all the other)
- Sex (Female, Male)
- Ethnicity (Hispanic, Not Hispanic)

2.4.6 Analyses of pharmacokinetic and pharmacodynamic variables

The baseline value of PK and PD variables is the original baseline from the parent studies.

2.4.6.1 Pharmacokinetic analysis

The PK analyses will be performed on the PK population (Section 2.3.4). Serum concentrations of dupilumab will be summarized using arithmetic and geometric means, SD, standard error of the mean (SEM), coefficient of variation (CV), minimum, median and maximum by visit. If date and/or time of the drug intake and/or sampling are missing, then the concentration will not be taken into account. For the patients from the Dupilumab arms of EFC13579, EFC13691 or PDY14192 studies,, if the pre-dose concentration values at Week 0 of LTS12551 are below the lower limit of quantitation (LLOQ = 78 ng/ml), one-half of LLOQ will be used; for the patients from the Dupilumab arms of DRI12544 study, the pre-dose concentration value at Week 0 of LTS12551 should use 0; for the patients from the Placebo arms of parent studies, the pre-dose concentration value at Week 0 of LTS12551 should use 0. Values will be expressed in the tables with no more than three significant figures.

2.4.6.2 Pharmacodynamics

For all biomarkers noted in the Pharmacodynamics (PD) section of the protocol, the biomarker analyses will be applied to the safety population. The collection for serum immunoglobulin and serum total IgE will be stopped after the approval of protocol amendment 4. The analyses for serum immunoglobulin and serum total IgE in LTS12551 study will be restricted to the patients from DRI12544 study and performed to the data observed up to the end of collection.

For eosinophil count and serum total IgE, IgM, IgA, IgG and IgG subtypes, descriptive statistics (including number, mean, median, standard deviation, Q1, Q3, minimum and maximum), change from baseline and percentage change from baseline over visits will be presented by the treatment category and overall (see Section 2.3.2). In addition, the mean, mean change from baseline, mean percentage change from baseline with corresponding standard error will be plotted across visits by the treatment category and overall (see Section 2.3.2). For biomarkers showing substantial skewness, the geometric means will also be presented.

For eosinophil count, with subgrouping the patients into original baseline EOS ≤0.5 Giga/L and >0.5 Giga/L, the mean change from baseline will be plotted over visits for each of the two subgroups and overall. And table showing number (%) of patients who have peak post-baseline EOS count ≥1 Giga/L, ≥3 Giga/L and ≥5 Giga/L will be presented for each of the two subgroups and overall.

2.4.7 Analyses of ADA variables

The baseline value used to define ADA variables is the original baseline from the parent studies. The ADA analyses will be performed on the ADA population (Section 2.3.5). The ADA variables described in Section 2.1.6 will be summarized using descriptive statistics in the ADA analysis set. Frequency tables of the proportion of patients developing ADA positivity in the ADA assay, neutralizing antibody status in the NAb assay, pre-existing immunoreactivity, treatment-emergent, treatment-boosted, persistent, indeterminate, transient ADA responses and titers will be presented. Listing of all ADA peak titer levels and neutralizing antibody status will be provided for ADA positive patients.

2.4.7.1 Status in the ADA assay at baseline of the parent study

The following summary will be provided based on the ADA population (Section 2.3.5):

- Number (%) of patients negative in the ADA assay at baseline of parent study
- Number (%) of patients positive in the ADA assay at baseline of parent study
  - The summary statistics (including number, median, Q1, Q3, minimum and maximum) of the titer for the patients positive in the ADA assay at baseline of the parent study
  - Number (%) of patients with neutralizing antibody status (negative or positive in the NAb assay)

2.4.7.2 Status in the ADA assay in the current study

The following summary will be provided based on ADA population (Section 2.3.5):

- Number (%) of patients with ADA status (negative or positive in the ADA assay) at time points analyzed
  - The summary statistics (including number, median, Q1, Q3, minimum and maximum) of the peak post-baseline titer for ADA positive patients

  - ADA titers using descriptive statistics (median, Q1, Q3, minimum and maximum) at ADA time points analyzed
  - Number (%) of patients with neutralizing antibody status (negative or positive in the NAb assay) for the ADA positive patients
- Number (%) of patients with pre-existing immunoreactivity
- Number (%) of patients with treatment-boosted anti-drug antibodies.
  - The summary statistics (including number, median, Q1, Q3, minimum and maximum) of the peak post-baseline titer for treatment-boosted ADA patients
- Number (%) of patients with treatment-emergent ADA.
  - The summary statistics (including number, median, Q1, Q3, minimum and maximum) of the peak post-baseline titer for treatment-emergent positive patients
  - Number (%) of patients in the low, moderate or high titer category with treatment-emergent positive response
  - Number (%) of patients with transient, indeterminate, or persistent treatment-emergent ADA response
- Number (%) of patients with neutralizing antibody results (negative or positive in the NAb assay).

2.4.7.3 Impact of ADA on clinical safety

The safety assessment will focus on the following events:

- Severe injection site reactions last longer than 24 hours or serious injection site reactions
- Hypersensitivity reactions (SMQ hypersensitivity narrow search and confirmed by medical review)
- Anaphylactic reactions (SMQ anaphylactic reaction narrow search)

In response to AE's of special interest like anaphylaxis or hypersensitivity additional ADA samples closer to the event may be analyzed, based on the judgment of the medical investigator and/or medical monitor.

Correlations between ADA variables (eg, ADA peak titers, neutralizing antibody status, treatment-emergent, treatment-boosted, transient, indeterminate and persistent ADA responses) and safety may be explored.

2.4.7.4 Impact of ADA on clinical efficacy

Correlations between ADA variables (eg, ADA peak titers, neutralizing antibody status, treatment-emergent, treatment-boosted, transient, indeterminate and persistent ADA responses) and efficacy endpoints may be explored for each treatment category and overall (see Section 2.3.2):

- Annualized rate of severe exacerbation events
- Change from baseline in FEV1

2.4.7.5 Impact of ADA on PK

Correlations between ADA variables (eg, ADA peak titers, neutralizing antibody status) and descriptive summary of serum concentration of dupilumab may be explored for each treatment category and overall (see Section 2.3.2). Plot of individual serum concentration of functional dupilumab over visits may also be provided by ADA classifications (negative at all time, pre-existing immunoreactivity, treatment-boosted anti-drug antibodies, and treatment-emergent anti-drug antibodies [further separated by NAb status and peak titer category]) for each treatment category and overall (see Section 2.3.2).

2.5 DATA HANDLING CONVENTIONS

2.5.1 General conventions

The following formulas will be used for computation of parameters.

Demographic formulas

Age is calculated as following:

Age = integer part of (informed consent date – birth date)/365.25

Age of onset of asthma is calculated as following:

Age = integer part of (asthma onset date – birth date)/365.25

BMI is calculated as following:

BMI = Weight in kg / (height^2 in meters)

Smoking quantity (pack-year) is calculated as following:

Number of pack-year= (packs smoked per day) × (years as a smoker)

Renal function formulas

Creatinine clearance (CLcr) value will be derived using the equation of Cockroft and Gault:

CLcr (ml/min) = (140 - age) * weight (kg) * (1 - 0.15*sex (0-M, 1-F)) /(0.814*creatinine (µmol/l))

CLcr will be calculated using weight assessed at the same visit that creatinine was assessed and age at the lab sampling date. Here age is calculated as following:

Age = integer part of (lab sampling date – birth date)/365.25

2.5.2 Data handling conventions for secondary efficacy variables

Calculation of salbutamol/albuterol or levosalbutamol/levalbuterol inhalations/day:

A diary day is defined as the period beginning with an Evening diary, and ending with the following day's Morning Diary. The number of salbutamol/albuterol or levosalbutamol/levalbuterol inhalations per day is the sum of number of inhalations recorded in one diary day including the evening diary and the following day's morning diary.

Periodical average of daily efficacy endpoints at designated study days:

For the daily efficacy endpoints, the time period used to calculate the periodical average at each designated study day is summarized in Table 4. The day of the first IMP administration in LTS12551 study is used as the reference start day (day 1). The use of electronic diary and PEF meter will be stopped after the approval of protocol amendment 4, the periodical average calculation will be performed to the data observed within each interval up to the end of using electronic diary/PEF meter in LTS12551.

Table 4 - Periodical average of daily efficacy assessment

		Day 15	Day 29	Day 57	Day 85	Day 169	Day 337	Day 505
	Endpoint	Days used to compute average						
Days used to compute average	morning PEF, asthma symptom score, number of awakenings	2-15	16-29	30-57	58-85	86-169	170-337	338-505
	evening PEF, asthma symptom score	1-14	15-28	29-56	57-84	85-168	169-336	337-504
	Number of inhalations/day of salbutamol/albuterol or levosalbutamol/levalbuterol for symptom relief	Diary day[a] 1-14	Diary day 15-28	Diary day 29-56	Dairy day 57-84	Diary day 85-168	Diary day 169-336	Diary day 337-504

a Note: A diary day is defined as the period beginning with an Evening diary, and ending with the following day's Morning Diary. For example, diary day 14 includes the evening dairy on day 14 and the morning dairy on day 15

		Day 589	Day 673
	Endpoint	Days used to compute average	
Days used to compute average	morning PEF, asthma symptom score, number of awakenings	506-589	590-673
	evening PEF, asthma symptom score	505-588	589-672
	Number of inhalations/day of salbutamol/albuterol or levosalbutamol/levalbuterol for symptom relief	Diary day[a] 505-588	Diary day 589-672

a Note: A diary day is defined as the period beginning with an Evening diary, and ending with the following day's Morning Diary. For example, diary day 14 includes the evening dairy on day 14 and the morning dairy on day 15

2.5.3 Missing data

For categorical variables, patients with missing data are not included in calculations of percentages unless otherwise specified. When relevant, the number of patients with missing data is presented.

Handling of computation of treatment duration if investigational medicinal product end of treatment date is missing

For the calculation of the treatment duration, the date of the last dose of IMP is equal to the date of last administration reported on the end-of-treatment case report form page. If this date is missing, the exposure duration should be left as missing.

The last dose intake should be clearly identified in the case report form and should not be approximated by the last returned package date.

Handling of medication missing/partial dates

No imputation of medication start/end dates or times will be performed. If a medication date or time is missing or partially missing and it cannot be determined whether it was taken prior or concomitantly, it will be considered a prior and concomitant medication.

Handling of adverse events with missing or partial date/time of onset

Missing or partial adverse event onset dates and times will be imputed so that if the partial adverse event onset date/time information does not indicate that the adverse event started prior to treatment or after the treatment-emergent adverse event period, the adverse event will be classified as treatment-emergent. No imputation of adverse event end dates/times will be performed. These data imputations are for categorization purpose only and will not be used in listings. No imputation is planned for date/time of adverse event resolution.

Handling of adverse events when date and time of first investigational medicinal product administration is missing

When the date and time of the first IMP administration is missing, all adverse events that occurred on or after the day of randomization should be considered as treatment-emergent adverse events. The exposure duration should be kept as missing.

The last dose intake should be clearly identified in the case report form and should not be approximated by the last returned package date.

Handling of missing assessment of relationship of adverse events to investigational medicinal product

If the assessment of the relationship to IMP is missing, then the relationship to IMP has to be assumed and the adverse event considered as such in the frequency tables of possibly related adverse events, but no imputation should be done at the data level.

Handling of missing severity/grades of adverse events

If the severity/grade is missing for 1 of the treatment-emergent occurrences of an adverse event, the maximal severity on the remaining occurrences will be considered. If the severity is missing for all the occurrences, a “missing” category will be added in the summary table.

Handling of potentially clinically significant abnormalities

If a patient has a missing baseline he will be grouped in the category "normal/missing at baseline."

For PCSAs with 2 conditions, one based on a change from baseline value or a normal range and the other on a threshold value, with the first condition being missing, the PCSA will be based only on the second condition.

For a PCSA defined on a threshold and/or a normal range, this PCSA will be derived using this threshold if the normal range is missing; eg, for eosinophils the PCSA is > 0.5 GIGA/L or >ULN if ULN ≥0.5 GIGA/L. When ULN is missing, the value 0.5 should be used.

Measurements flagged as invalid by the laboratory will not be summarized or taken into account in the computation of PCSA values.

2.5.4 Windows for time points

For the safety assessment, the reference date for the derivation of relative days of events or findings will be the date of first IMP dose injection in LTS12551 study. Selected safety variables will be summarized by the analysis window defined in Table 5 for the by-visit descriptive analysis. For all laboratory/vital sign/ECG variables, the summary statistics over visits for either measurements or mean change from baseline, and the plot of mean change from baseline over visits should use the centralized data only (if applicable), and should include the measurements obtained at either scheduled or unscheduled visits. For PCSA analyses, the measurements of laboratory/vital sign/ECG variables obtained at either scheduled visits or unscheduled visits should be used; and, both the centralized and local test results should be used (if applicable), as long as their available dates/time are different from each other's. All available safety measurements (from either scheduled or unscheduled visit) will be assigned to the appropriate visit window. In the event of multiple measurements of the same test in the same window, the one closest to the targeted visit date will be used for the by-visit summary. If they are at the same distance to the target day, the latest one will be used.

The pre-dose measurements at Week 0 of LTS12551 are defined as follows: for patients enrolled from DRI12544, the measurements at Week 0 are obtained from the EOS visit of DRI12544 if available, regardless whether the EOS visit in DRI12544 was combined with Visit 1/Visit 2 in LTS12551; otherwise, Week 0 value will be the last available measurement prior to the first IMP dose in LTS12551 study. For patients enrolled from EFC13579, EFC13691 and PDY14192, the measurements at Week 0 are obtained from the EOT visit of parent studies if available; otherwise, Week 0 value will be the last available measurement prior to the first IMP dose in LTS12551 study.

Table 5 - Time window for safety variables

Visit	Week	Target day	Vital Signs		ECG		Physical Examination, Urine Analysis		Hematology, Serum Chemistry	
			Minimum days	Maximum days	Minimum days	Maximum days	Minimum days	Maximum days	Minimum days	Maximum days
1 & 2	0	Derived		Up to 1st IMP dose date/time		Up to 1st IMP dose date/time		Up to 1st IMP dose date/time		Up to 1st IMP dose date/time
3	2	15	After 1st IMP dose date/time	21						
4	4	29	22	35					After 1st IMP dose date/time	56
5	6	43	36	49						
6	8	57	50	63						
7	10	71	64	77						
8	12	85	78	98			After 1st IMP dose date/time	126	57	126
9	16	113	99	126						
10	20	141	127	154						
11	24	169	155	210	After 1st IMP dose date/time	252	127	252	127	252
12	36	253	211	294						
13	48	337	295	378	253	504	253	420	253	420
14	60	421	379	462						
15	72	505	463	546			421	546	421	588
16	84	589	547	630			547	630		
17 (EOT)	96	673	631	d*	505	d*	631	d*	589	d*
18 (EOS)	108	757	d*+1		d*+1		d*+1		d*+1	

*Note: d= max (last IMP dose +14 days, EOT date)

Visit	Week	Target day	Pregnancy Test		Serum Immunoglobulin	
			Minimum days	Maximum days	Minimum days	Maximum days
1 & 2	0	Derived		Up to 1st IMP dose date/time		Up to 1st IMP dose date/time
3	2	15				
4	4	29	After 1st IMP dose date/time	35		
5	6	43	36	49		
6	8	57	50	63		
7	10	71	64	77		
8	12	85	78	98		
9	16	113	99	126		
10	20	141	127	154		
11	24	169	155	210	After 1st IMP dose date/time	252
12	36	253	211	294		
13	48	337	295	378	253	462
14	60	421	379	462		
15	72	505	463	546		
16	84	589	547	630	463	630
17 (EOT)	96	673	631	d*	631	
18 (EOS)	108	757	d*+1			

*Note: d= max (last IMP dose +14 days, EOT date)

For the efficacy assessment, the reference date for the derivation of relative days of events or findings will be the day of the first IMP injection in LTS12551 study. And for the endpoints not measured daily, all available values of scheduled measurements will be assigned to the appropriate visit window according to Table 6. In the event of multiple measurements of the same test in the same window, the one closest to the targeted visit date will be used for the by-visit summary. If they are at the same distance to the target day, the latest one will be used. The pre-dose measurements at Week 0 of LTS12551 are defined in the same way as in the paragraph prior to Table 5.

Table 6 - Time window for efficacy variables

Visit	Week	Target day	Spirometry		ACQ-5, AQLQ	
			Minimum days	Maximum days	Minimum days	Maximum days
1 & 2	0	Derived		1st IMP dose date/time (Day 1)		1st IMP dose date/time (Day 1)
3	2	15	2	21		
4	4	29	22	42		
5	6	43				
6	8	57	43	70		
7	10	71				
8	12	85	71	126		
9	16	113				
10	20	141				
11	24	169	127	252	2	252
12	36	253				
13	48	337	253	420	253	
14	60	421				
15	72	505	421	546		
16	84	589	547	630		
17 (EOT)	96	673	631	d*		
18 (EOS)	108	757	d*+1			

*Note: d= max (last dose +14 days, EOT date)

Visit	Week	Target day	EQ-5D, Resource Utilization		Prescribed OCS dose	
			Minimum days	Maximum days	Minimum days	Maximum days
1 & 2	0	Derived		1st IMP dose date/time (Day 1)		1st IMP dose date/time (Day 1)
3	2	15			2	21
4	4	29			22	35
5	6	43			36	49
6	8	57			50	63
7	10	71			64	77
8	12	85	2	126	78	98
9	16	113			99	126
10	20	141			127	154
11	24	169	127	252	155	210
12	36	253			211	294
13	48	337	253	420	295	378
14	60	421			379	462
15	72	505	421	546	463	546
16	84	589	547	630	547	630
17 (EOT)	96	673	631	d*	631	d*
18 (EOS)	108	757	d*+1		d*+1	

*Note: d= max (last dose +14 days, EOT date)

For the pharmacokinetics/pharmacodynamics variables summary, the reference date for the derivation of relative days of measurements will be the date of first IMP dose injection in LTS12551 study. Pharmacodynamics variables will be summarized by the analysis window defined in Table 7 for the by visit descriptive analyses. All available values of scheduled measurements will be assigned to the appropriate visit window. In the event of multiple measurements of the same test in the same window, the one closest to the targeted visit date will be used for the by-visit summary. If they are at the same distance to the target day, the latest one will be used. The pre-dose measurements at Week 0 of LTS12551 are defined in the same way as in the paragraph prior to Table 5.

Table 7 - Time window for pharmacokinetics and pharmacodynamics variables

Visit	Week	Target day	PK sampling, dupilumab concentration		Anti-drug antibodies	
			Minimum days	Maximum days	Minimum days	Maximum days
1 & 2	0	Derived		Up to 1st IMP dose date/time		Up to 1st IMP dose date/time
3	2	15				
4	4	29	After 1st IMP dose date/time	56		
5	6	43				
6	8	57				
7	10	71				
8	12	85	57	126	After 1st IMP dose date/time	126
9	16	113				
10	20	141				
11	24	169	127	252	127	252
12	36	253				
13	48	337	253	420	253	420
14	60	421				
15	72	505	421	588	421	588
16	84	589				
17 (EOT)	96	673	589	d*	589	d*
18 (EOS)	108	757	d*+1		d*+1	

*Note: d= max (last dose +14 days, EOT date)

Visit	Week	Target day	Total IgE	
			Minimum days	Maximum days
1 & 2	0	Derived		Up to 1st IMP dose date/time
3	2	15		
4	4	29		
5	6	43		
6	8	57		
7	10	71		
8	12	85		
9	16	113		
10	20	141		
11	24	169		
12	36	253		
13	48	337	After 1st IMP dose date/time	462
14	60	421		
15	72	505		
16	84	589	463	630
17 (EOT)	96	673	631	
18 (EOS)	108	757		

*Note: d= max (last dose +14 days, EOT date)

2.5.5 Unscheduled visits

Unscheduled visit measurements of laboratory data, vital signs, and ECG will be included in the by-visit summaries and figures, as well as the computation of baseline, worst values, and PCSAs.

2.5.6 Pooling of centers for statistical analyses

Not applicable

2.5.7 Statistical technical issues

None

3 INTERIM ANALYSIS

This is an open-label extension study. Interim analyses/reports may be prepared to support regulatory submission of an indication in the dupilumab project or other purpose.

Interim analysis for non-asthma submission

In general, the analyses for this report will focus on the safety evaluations on the accumulative data in LTS12551 as of the cut-off date. Specifically, the report shall include all safety analyses, demographics, baseline characteristics, patient disposition, exposure to IMP, as well as the prior and concomitant medications.

Interim analysis for asthma submission

All planned analyses in this SAP shall be performed for this report.

4 DATABASE LOCK

At the time of the initial dupilumab marketing authorization application for the treatment of Asthma, an interim database lock will be performed. Additional database snapshots may be performed to support regulatory submission of an indication in dupilumab project, or prior to subsequent marketing authorization applications in major markets, eg, EU. The final database lock is planned to occur 4 weeks after last patient last visit.

5 SOFTWARE DOCUMENTATION

All summaries and statistical analyses will be generated using SAS version 9.4 or higher.

6 REFERENCES

1. Wanger J, Clausen JL, Coates A, Pedersen OF, Brusasco V, Burgos F. Standardization of the measurement of lung volumes. Series "ATS/ERS TASK FORCE: Standardization of lung function testing" Edited by Brusasco V, Crapo R, and Viegi G. Eur Respir J. 2005;26(3):511-522.

2. Cohen J. Statistical power analysis for the behavioral sciences (2nd edition). Lawrence Erlbaum Associates; Hillsdale, NJ. 1988.

3. Juniper EF, Svensson K, Mork AC, Stahl E. Measurement properties and interpretation of three shortened versions of the asthma control questionnaire. Respir med. 2005;99(5):553-8.

4. Juniper E. Asthma control questionnaire - background, administration and analysis. 2012; QOL Technologies, West Sussex, UK.

5. Juniper EF, Guyatt GH, Willan A, Griffith LE. Determining a minimal important change in a disease-specific quality of life questionnaire. J Clin Epidemiol. 1994;47(1):81-7.

6. EuroQol Group. EuroQol - a new facility for the measurement of health-related quality of life. Health Policy. 1990;16:199-208.

7. Dolan P. Modeling valuations for EuroQol health states. Medical Care. 1997;35(11):1095-1108.

8. Norman GR, Sloan JA, Wyrwich KW. Point/Counterpoint, Interpretation of Changes in Health-related Quality of life: the remarkable university of half a standard deviation. Medical Care. 2003;41(5):582-592.

9. Global Initiative for Asthma (GINA). Global strategy for asthma management and prevention. 2014; available at www.ginasthma.org.

7 LIST OF APPENDICES

Appendix A: Potentially clinically significant abnormalities (PCSA) criteria

Appendix B: Summary of statistical analyses

Appendix C: Low, medium and high dose inhaled corticosteroids- Adults and adolescents (≥12 years)

Appendix D: Definition of Anaphylaxis

Appendix E: List of opportunistic infections

Appendix F: Asthma Control Questionnaire, 5-question Version

Appendix G: Asthma Quality of Life Questionnaire

Appendix H: EuroQol Questionnaire (EQ-5D-3L)

Appendix I: SAS code for EQ-5D index utility scoring

Appendix A Potentially clinically significant abnormality criteria for included laboratory parameters: Combined Adult (≥ 18) and Adolescent (≥ 12 to < 18) criteria abstracted from BTD-009536 V3.0 with approved modifications

Where adolescent criteria (age ≥12 to <18) are different than adult criteria (≥18), the adolescent criteria are provided in parentheses in the combined column.

Parameter	Adults (≥ 18)	Adolescents (≥12 to <18)	Combined
Vitals			
SBP (mmHg)	≤95 mmHg and decrease from baseline ≥20mmHg ≥160 mmHg and increase from baseline ≥20 mmHg	≤90 mmHg and decrease from baseline ≥20 mmHg ≥119mmHg and increase from baseline ≥20 mmHg	≤95 (≤90) mmHg and decrease from baseline ≥20 mmHg ≥160 (≥119) mmHg and increase from baseline ≥20 mmHg
DBP (mmHg)	≤45 mmHg and decrease from baseline ≥10 mmHg ≥110 mmHg and increase from baseline ≥10 mmHg	≤54 mmHg and decrease from baseline ≥10 mmHg ≥78mHg and increase from baseline ≥10 mmHg	≤45 (≤54) mmHg and decrease from baseline ≥10 mmHg ≥110 (≥78) mmHg and increase from baseline ≥10 mmHg
HR (bpm)	≤50 bpm and decrease from baseline ≥20 bpm ≥120 bpm and increase from baseline≥20 bpm	NONE	≤50 bpm and decrease from baseline ≥20 bpm ≥120 bpm and increase from baseline ≥20 bpm
Respiratory rate (breaths/min)	NONE	<12 breaths/min >20 breaths/min	<12 breaths/min >20 breaths/min
Temperature (◦C)	NONE	Rectal, ear or temporal artery: ≥100.4°F/38.0 °C Oral or pacifier: ≥99.5 °F/37.5 °C Axillary or skin infrared: ≥99°F/37.2 °C	≥38.0 °C rectal/ear/temporal ≥37.5 °C oral ≥37.2 °C axillary
Weight (kg)	≥5% increase from baseline	≥5% weight loss from baseline	≥5% increase from baseline (adults only)

Parameter	Adults (≥ 18)	Adolescents (≥12 to <18)	Combined
	≥5% decrease from baseline		≥5% decrease from baseline
ECG			
Heart rate (bpm)	<50 bpm	≤50 bpm and decrease from baseline ≥20 bpm	<50 bpm
	<50 bpm and decrease from baseline ≥20 bpm	≥120 bpm and increase from baseline ≥20 bpm	<50 bpm and decrease from baseline ≥20 bpm
	<40 bpm		<40 bpm
	<40 bpm and decrease from baseline ≥20 bpm		<40 bpm and decrease from baseline ≥20 bpm
	<30 bpm		<30 bpm
	<30 bpm and decrease from baseline ≥20 bpm		<30 bpm and decrease from baseline ≥20 bpm
	>90 bpm		>90 bpm
	>90 bpm and increase from baseline ≥20bpm		>90 bpm and increase from baseline ≥20 bpm
	>100 bpm		>100 bpm
	>100 bpm and increase from baseline ≥20bpm		>100 bpm and increase from baseline ≥20 bpm
	>120 bpm		>120 bpm
	>120 bpm and increase from baseline ≥20 bpm		>120 bpm and increase from baseline ≥20 bpm
PR interval (ms)	>200 ms	≥180 ms	>200 (≥180) ms
	>200 ms and increase from baseline ≥25%		>200 (≥180) ms and increase from baseline ≥25%
	> 220 ms		>220 ms
	>220 ms and increase from baseline ≥25%		>220 ms and increase from baseline ≥25%
	> 240 ms		>240 ms
	> 240 ms and increase from		>240 ms and increase from

Parameter	Adults (≥ 18)	Adolescents (≥12 to <18)	Combined
	baseline ≥25%		baseline ≥25%
QRS interval (ms)	>110 ms >110 msec and increase from baseline ≥25% >120 ms >120 ms and increase from baseline ≥25%	≥110 ms	>110 ms >110 ms and increase from baseline ≥25% >120 ms >120 ms and increase from baseline ≥25%
QT interval (ms)	>500 ms	NONE	>500 ms
QTc (ms)	>450 ms >480 ms >500 ms AND Increase from baseline]30-60] ms Increase from baseline >60 ms	Borderline: 431-450 ms (Boys); 451-470 ms (Girls) Prolonged*: >450 ms (Boys); >470 ms (Girls) Additional: ≥500 ms AND Borderline: Increase from baseline 30-60 ms Prolonged*: Increase from baseline >60 ms	Borderline: 451- 480 ms (431- 450 ms boys; 451- 470 ms girls) Prolonged: >480 ms (>450 ms boys; >470 ms girls) Additional: > 500 ms AND >30 to ≤60 ms increase from baseline >60 ms increase from baseline
Hematology			
Hemoglobin (g/L)	≤115 g/L (Male); ≤95 g/L (Female) ≥185 g/L (Male); ≥165 g/L (Female) Decrease from Baseline ≥20 g/L	<6.2 mmol/L or 10 g/dL or any decrease ≥1.2 mmol/L or 2 g/dL	Decrease from baseline ≥20 g/L ≤115 g/L males; ≤95 g/L females (<100 g/L adolescents) ≥185 g/L males; ≥165 g/L females (≥185 g/L adolescents)
Hematocrit	≤0.37 v/v (Male) ; ≤0.32	<0.32 l/l or 32 %	≤0.37 v/v males; ≤0.32 v/v

Parameter	Adults (≥ 18)	Adolescents (≥12 to <18)	Combined
(v/v)	v/v (Female) ≥0.55 v/v (Male) ; ≥0.5 v/v (Female)	>0.47 l/l or 47 %	females (<0.32 v/v) ≥0.55 v/v males; ≥0.5 v/v females (>0.47 v/v)
RBC (Tera/L)	≥6 Tera/L	NONE	≥6 Tera/L
Platelets (Giga/L)	<100 Giga/L ≥700 Giga/L	<100 GIGA/L or 100,000 /mm3 >700 GIGA/L or 700,000 /mm3	<100 Giga/L ≥700 Giga/L
WBC (Giga/L)	<3.0 Giga/L (Non-Black); <2.0 Giga/L (Black) ≥16.0 Giga/L	<4,5 GIGA/L or 5,000 /mm3 >13.5 GIGA/L or 17,000 /mm3	<3.0 Giga/L non-Black; <2.0 Giga/L Black (<4.5 Giga/L) ≥16 (>13.5) Giga/L
Lymphocytes (Giga/L)	>4.0 Giga/L	<0.6 GIGA/L or 600 /mm3 >6.0 GIGA/L or 6,000 /mm3	<0.6 Giga/L (adolescents only) >4.0 (>6.0) Giga/L
Neutrophils (Giga/L)	<1.5 Giga/L (Non-Black);<1.0 Giga/L (Black)	<1.2 GIGA/L or 1,200 /mm3 > 1 ULN	<1.5 Giga/L non-Black; <1.0 Giga/L Black (<1.2 Giga/L) >1xULN (adolescents only)
Monocytes (Giga/L)	>0.7 Giga/L	NONE	>0.7 Giga/L (adults only)
Basophils (Giga/L)	>0.1 Giga/L	NONE	>0.1 Giga/L (adults only)
Eosinophils (Giga/L)	>0.5 Giga/L or >ULN (if ULN≥0.5 Giga/L)	>0.5 GIGA/L or 500 /mm3 Or >ULN if ULN >0.5 GIGA/L or 500/mm3	>0.5 Giga/L or > ULN if ULN >0.5 Giga/L
Clinical Chemistry			
Glucose (mmol/L)	≤3.9 mmol/L and <LLN ≥11.1 mmol/L (unfasted); ≥7 mmol/L (fasted)	Hypoglycaemia <2.7 mmol/L Hyperglycaemia ≥7 mmol/L (fasted after >12 hours of fast); ≥10.0 mmol/L (unfasted)	≤3.9 mmol/L and < LLN (<2.7 mmol/L) ≥11.1 (≥10) mmol/L unfasted; ≥7 mmol/L fasted
Glucose (mg/dL)	NONE	Hypoglycaemia <50 mg/dL	≤70 mg/dL and < LLN (<50 mg/dL)

Parameter	Adults (≥ 18)	Adolescents (≥12 to <18)	Combined
		Hyperglycaemia ≥120 mg/dL (fasted after >12 hours of fast); ≥180 mg/dL (unfasted)	≥200 (≥180) mg/dL unfasted; 126 (≥120) mg/dL fasted
Total cholesterol (mmol/L)	≥7.74 mmol/L	≥6.20 mmol/L	≥7.74 (≥6.20) mmol/L
Total cholesterol (mg/dL)	NONE	≥240 mg/dL	≥300 (≥240) mg/dL
Creatine phosphokinase (ULN)	>3 ULN >10 ULN	≥3 ULN	>3 ULN >10 ULN
Albumin (g/L)	≤25 g/L	NONE	≤25 g/L (adults only)
Sodium (mmol/L)	≤129 mmol/L ≥160 mmol/L	≤129 mmol/L or 129 mEq/L ≥150 mmol/L or 150 mEq/L	≤129 mmol/L ≥160 (≥150) mmol/L
Potassium (mmol/L)	<3 mmol/L ≥5.5 mmol/L	≤3.5 mmol/L or 3.5 mEq/L ≥5.5 mmol/L or 5.5 mEq/L	<3.0 (≤3.5) mmol/L ≥5.5 mmol/L
Bicarbonate (mmol/L)	NONE	≤16 mmol/L or 16 mEq/L ≥30 mmol/L or 30 mEq/L	≤16 mmol/L ≥30 mmol/L
Chloride (mmol/L)	<80 mmol/L >115 mmol/L	≤80 mmol/L or 80 mEq/L ≥115 mmol/L or 115 mEq/L	<80 mmol/L >115 mmol/L
Creatinine (µmol/L)	≥150 µmol/L (Adults) ≥30% change from baseline ≥100% change from baseline	≥132µmol/L	≥150 (≥132) µmol/L ≥30% change from baseline ≥100% change from baseline
Creatinine (mg/dL)	NONE	≥1.5mg/dL	≥1.7 (≥1.5) mg/dL ≥30% change from baseline ≥100% change from baseline
Creatinine clearance	<15 (end stage renal disease)	<15 (end stage renal disease)	<15 mL/min (end stage renal disease)

Parameter	Adults (≥ 18)	Adolescents (≥12 to <18)	Combined
(mL/min)	≥15 - <30 (severe decrease in GFR) ≥30 - < 60 (moderate decrease in GFR) ≥60 - <90 (mild decrease in GFR) ≥ 90 (normal GFR)	≥15 - <30 (severe decrease in GFR) ≥30 - < 60 (moderate decrease in GFR) ≥60 - <90 (mild decrease in GFR) ≥ 90 (normal GFR)	≥15 - <30 mL/min (severe decrease in GFR) ≥30 - <60 mL/min (moderate decrease in GFR) ≥60 - <90 mL/min (mild decrease in GFR)
BUN (mmol/L)	≥17 mmol/L	≥6.4 mmol/L	≥17 (≥6.4) mmol/L
BUN (mg/dL)	≥48 mg/dL	≥18 mg/dl	≥48 (≥18) mg/dL
Uric acid (µmol/L)	<120 µmol/L >408 µmol/L	≤119 µmol/L ≥476 µmol/L	<120 µmol/L >408 (≥476) µmol/L
Uric acid (mg/dL)	NONE	≤2.0 mg/dL ≥8.0 mg/dL	≤2 mg/dL ≥7 (≥8) mg/dL
ALT (ULN)	>3 ULN >5 ULN >10 ULN >20 ULN	≥3 ULN ≥5 ULN ≥10 ULN ≥20 ULN	>3 ULN >5 ULN >10 ULN >20 ULN
AST (ULN)	>3 ULN >5 ULN >10 ULN >20 ULN	≥3 ULN ≥5 ULN ≥10 ULN ≥20 ULN	>3 ULN >5 ULN >10 ULN >20 ULN
ALP (ULN)	>1.5 ULN	≥1.5 ULN	>1.5 ULN
Total bilirubin (ULN)	>1.5 ULN >2 ULN	≥1.3 ULN	>1.5 (≥1.3) ULN >2 ULN
ALT and total bilirubin (ULN)	ALT>3 ULN and TBILI>2 ULN	ALT ≥ 3 ULN and Total Bilirubin ≥ 2 ULN	ALT >3 ULN and TBILI >2 ULN

Parameter	Adults (≥ 18)	Adolescents (≥12 to <18)	Combined
Conjugated and total bilirubin (ULN)	Conjugated Bilirubin >35% Total Bilirubin and TBILI>1.5 ULN	>35% Total Bilirubin and TBILI≥1.3 ULN	Conjugated bilirubin > 35% total bilirubin and total bilirubin >1.5 (≥1.3) ULN

Appendix B Summary of statistical analyses

EFFICACY ANALYSIS

Endpoint	*Analysis population*	*Primary analysis*	*Statistical Method*	*Supportive analysis*	*Subgroup analysis*	*Other analyses*
FEV1, % Predicted FEV1, FVC and FEF 25-75%	*Safety*	*Measurement and change from baseline at all visits*	*Descriptive statistics*	*No*	*Yes (Baseline ICS dose and EOS count subgroups)*	*No*
Severe exacerbation: number of events/annualized event rate during the treatment period	*Safety*	*Summary of number/annualized rate of severe exacerbation events during the treatment period*	*Descriptive statistics*	*No*	*Yes (Baseline ICS dose and EOS count subgroups)*	*No*
Morning asthma symptom score	*Safety*	*Measurement and change from baseline at all visits, for patients from the DRI12544 study only*	*Descriptive statistics*	*No*	*No*	*No*
Evening asthma symptom score	*Safety*	*Measurement and change from baseline at all visits, for patients from the DRI12544 study only*	*Descriptive statistics*	*No*	*No*	*No*
ACQ-5 score	*Safety*	*Measurement, change from baseline, and responder status at all visits*	*Descriptive statistics*	*No*	*Yes (Baseline ICS dose and EOS count subgroups)*	*No*
AQLQ overall score	*Safety*	*Measurement, change from baseline, and responder status at all visits, excluding patients from the PDY14192 study*	*Descriptive statistics*	*No*	*Yes (Baseline ICS dose and EOS count subgroups)*	*No*
AM PEF	*Safety*	*Measurement and change from baseline at all visits, for patients from the DRI12544 study only*	*Descriptive statistics*	*No*	*No*	*No*
PM PEF	*Safety*	*Measurement and change from baseline at all visits, for patients from the DRI12544 study only*	*Descriptive statistics*	*No*	*No*	*No*
Number of inhalations/day of	*Safety*	*Measurement and change from baseline at all visits, for patients from the DRI12544 study only*	*Descriptive statistics*	*No*	*No*	*No*

Endpoint	Analysis population	Primary analysis	Statistical Method	Supportive analysis	Subgroup analysis	Other analyses
reliever medication						
Number of nocturnal awakenings	*Safety*	*Measurement and change from baseline at all visits, for patients from the DRI12544 study only*	*Descriptive statistics*	*No*	*No*	*No*
EQ-5D-3L single utility score and VAS	*Safety*	*Measurement and change from baseline at all visits, for patients from the DRI12544 study only*	*Descriptive statistics*	*No*	*No*	*No*
Percentage change from baseline in OCS dose	*Safety*	*Summary statistics for percentage change from baseline in oral corticosteroids (OCS) dose over visits, for patients from the EFC13691 study only*	*Descriptive statistics*	*No*	*No*	*No*
Proportion of patients achieving a reduction of 50% or greater in their OCS dose compared with baseline in the parent study	*Safety*	*Proportion of patients achieving a reduction of 50% or greater in their OCS dose compared with the baseline in the parent study over visits, for patients from the EFC13691 study only*	*Descriptive statistics*	*No*	*No*	*No*
Proportion of patients whose background OCS are completely tapered off	*Safety*	*Proportion of patients whose background OCS are completely tapered off over visits, for patients from the EFC13691 study only*	*Descriptive statistics*	*No*	*No*	*No*

SAFETY ANALYSES

Endpoint	Analysis population	Primary analysis	Statistical Method	Supportive analysis	Subgroup analysis	Other analyses
Adverse events	*Safety*	*Follow safety guidelines*	*Descriptive statistics*	*No*	*Yes (Baseline ICS dose, Age, Race, Sex and Ethnicity subgroups)*	*No*
Lab/vital signs/ECGs	*Safety*	*Follow safety guidelines; PCSA analysis; Descriptive*	*Descriptive statistics*	*No*	*No*	*No*

Appendix C Low, medium and high dose inhaled corticosteroids- Adults and adolescents (≥12 years)

INHALED CORTICOSTEROID	TOTAL DAILY DOSE (MCG)		
	LOW	MEDIUM	HIGH
BECLOMETASONE DIPROPIONATE (CFC)	200–500	>500–1000	>1000
BECLOMETASONE DIPROPIONATE (HFA)	100–200	>200–400	>400
BUDESONIDE (DPI)	200–400	>400–800	>800
CICLESONIDE (HFA)	80–160	>160–320	>320
FLUTICASONE PROPIONATE (DPI OR HFA)	100–250	>250–500	>500
MOMETASONE FUROATE	110–220	>220–440	>440
TRIAMCINOLONE ACETONIDE	400–1000	>1000–2000	>2000

(ADAPTED FROM GINA 2014 GUIDELINES)

Low, medium and high dose inhaled corticosteroids Adults (Japan)

Agent Treatment	Low daily dose (mcg)	Medium daily dose (mcg)	High daily dose (mcg)
BDP-HFA	100-200	400	800
FP-HFA	100-200	400	800
CIC-HFA	100-200	400	800
FP-DPI	100-200	400	800
BUD-DPI	200-400	800	1600
BIS	0.5 mg/day	1.0 mg/day	2.0 mg/day
MF-DPI	100-200	400	800

BDP= Beclomethasone dipropionate, FP= Fluticasone propionate, CIC= Ciclesonide, BIS= Budesonide inhalation suspension, HFA= hydrofluoroalkane, DPI= Dry Powder Inhaler

(Adapted from Japanese Guideline for Adult Asthma 2014)

Low, medium and high dose inhaled corticosteroids
Children (Japan)

Agent Treatment	Low daily dose (mcg)	Medium daily dose (mcg)	High daily dose (mcg)
Fluticasone (FP)	100	200	400
Beclomethasone (BDP)	100	200	400
Ciclesonide (CIC)	100	200	400
Budesonide(BUD-DPI)	200	400	800
Budesonide inhalation solution(BIS)	250	500	1000

(Adapted from Japanese Guideline for Childhood Asthma 2014)

The above lists are indicative and not exhaustive.

Appendix D 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

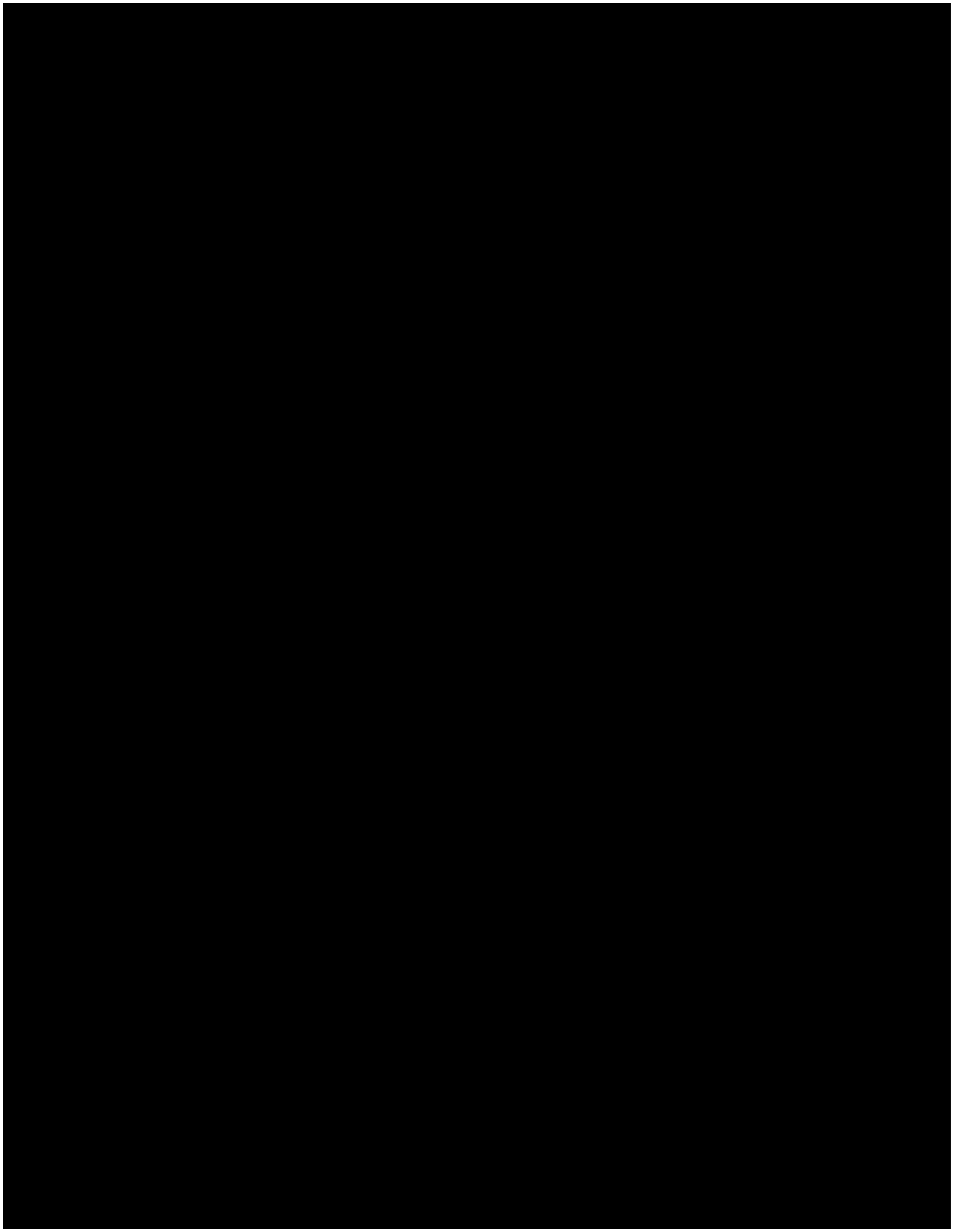
PEF, Peak expiratory flow; *BP*, blood pressure.
*Low systolic blood pressure for children is defined as less than 70 mm Hg from 1 month to 1 year, less than (70 mm Hg + [2 × age]) from 1 to 10 years, and less than 90 mm Hg from 11 to 17 years.

Appendix E List of opportunistic infections

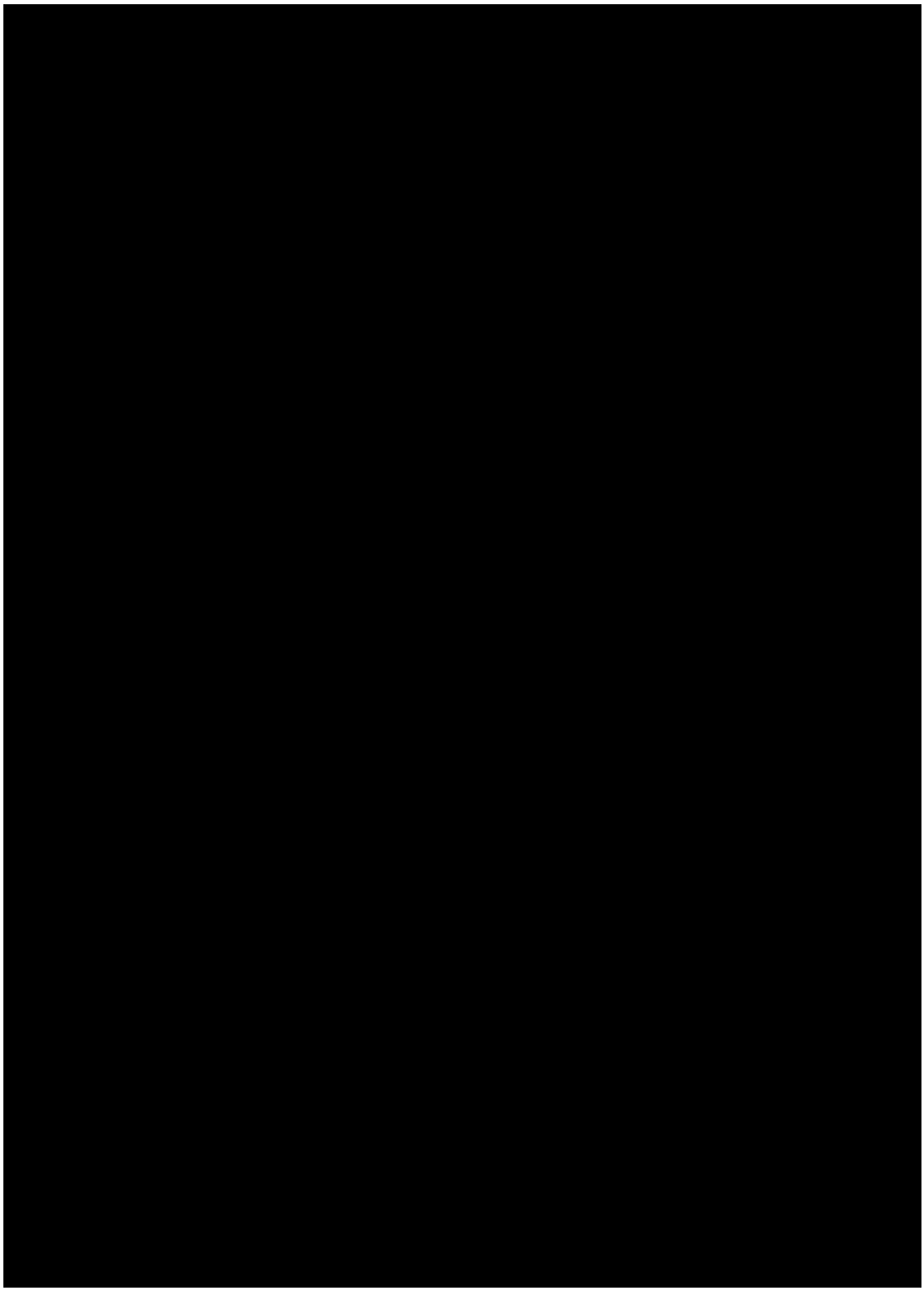
- Aspergillosis
- Blastomyces dermatitidis (endemic in the south-eastern and south-central states US, along Mississippi and Ohio Rivers)
- Candidiasis – only systemic or extensive mucosal or cutaneous candidiasis
- Coccidioides immitis (endemic south-western US and Central and South America)
- Cryptococcus
- 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)

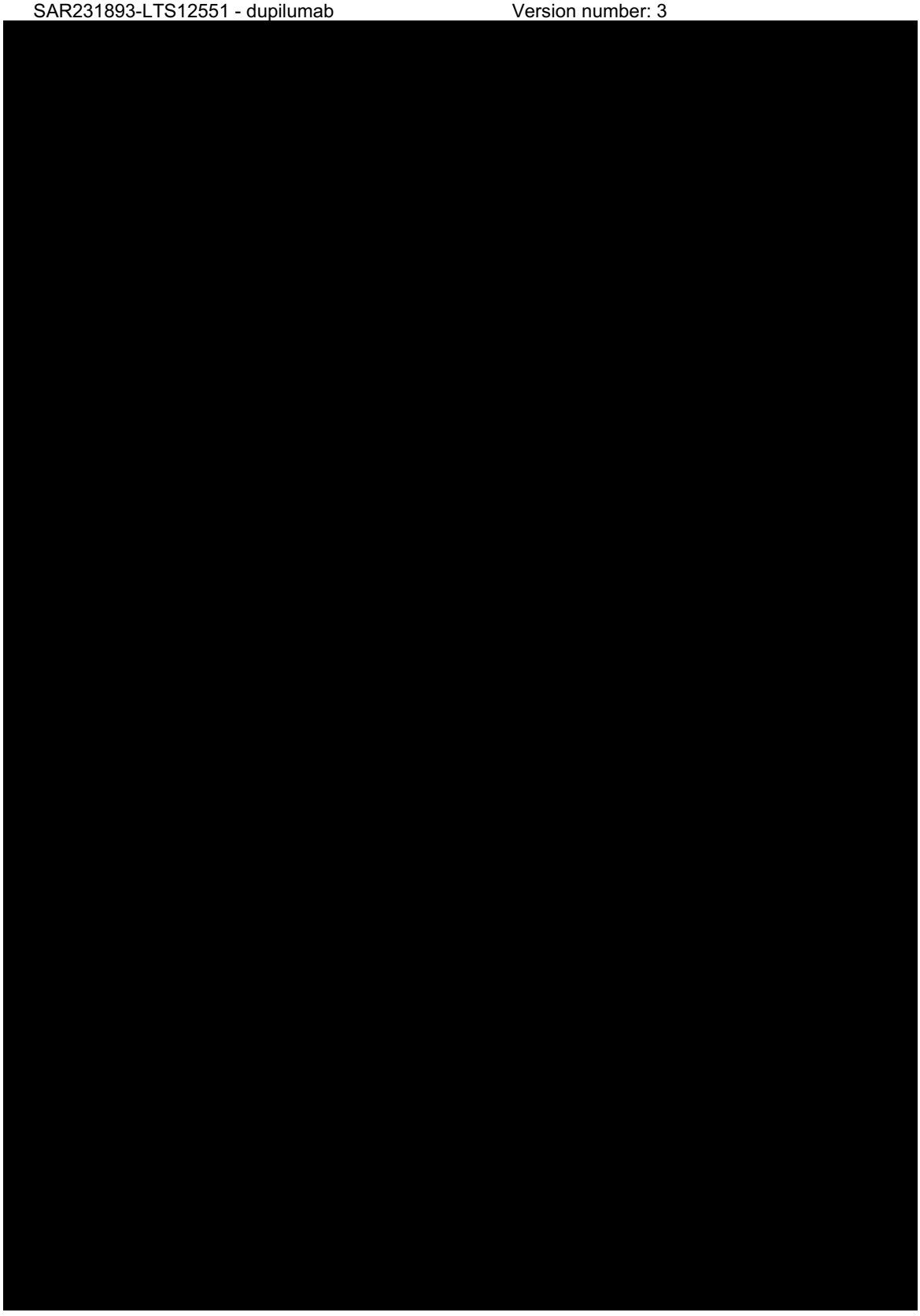
This list is indicative and not exhaustive.

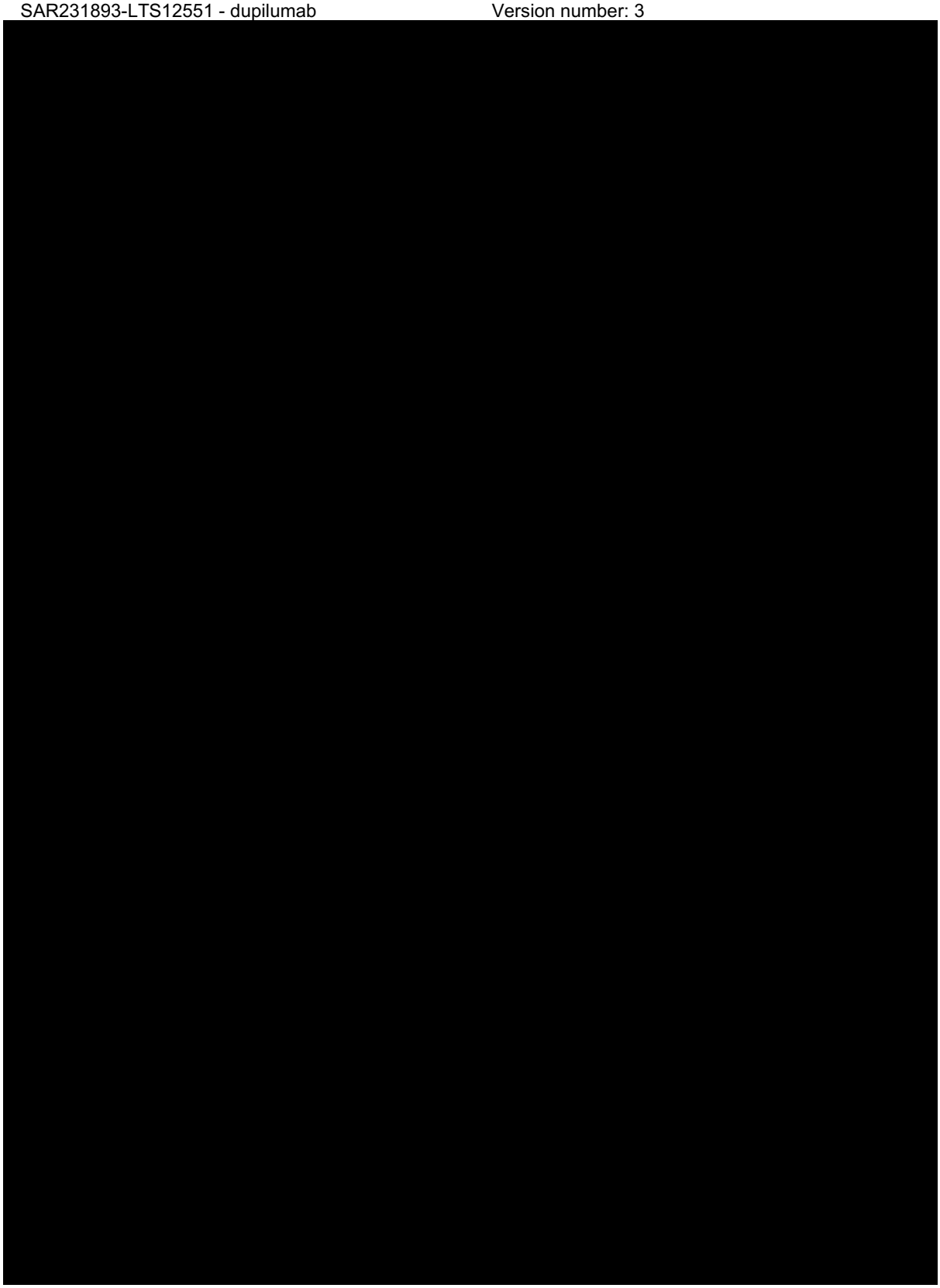
Appendix F Asthma Control Questionnaire, 5-question Version

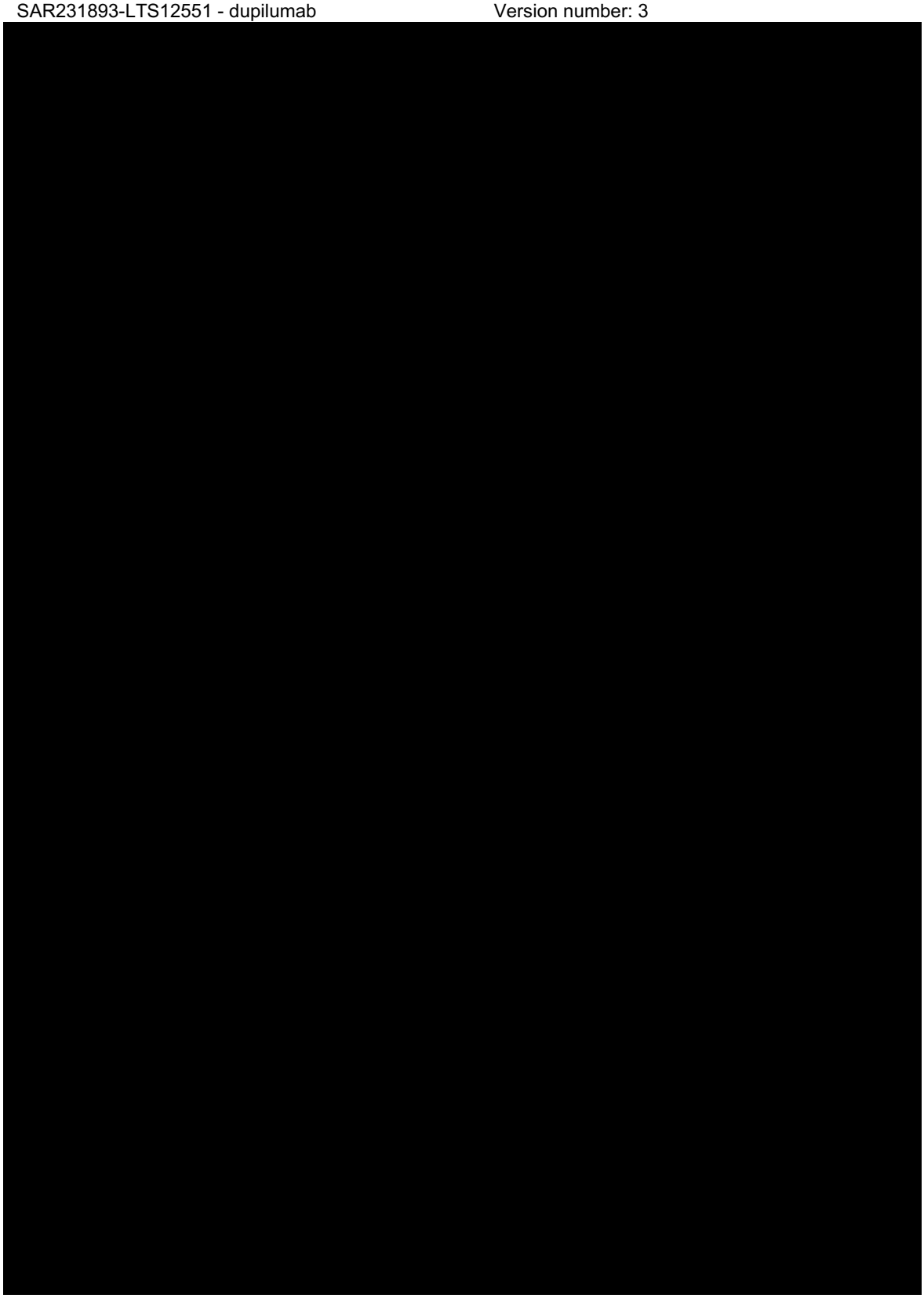


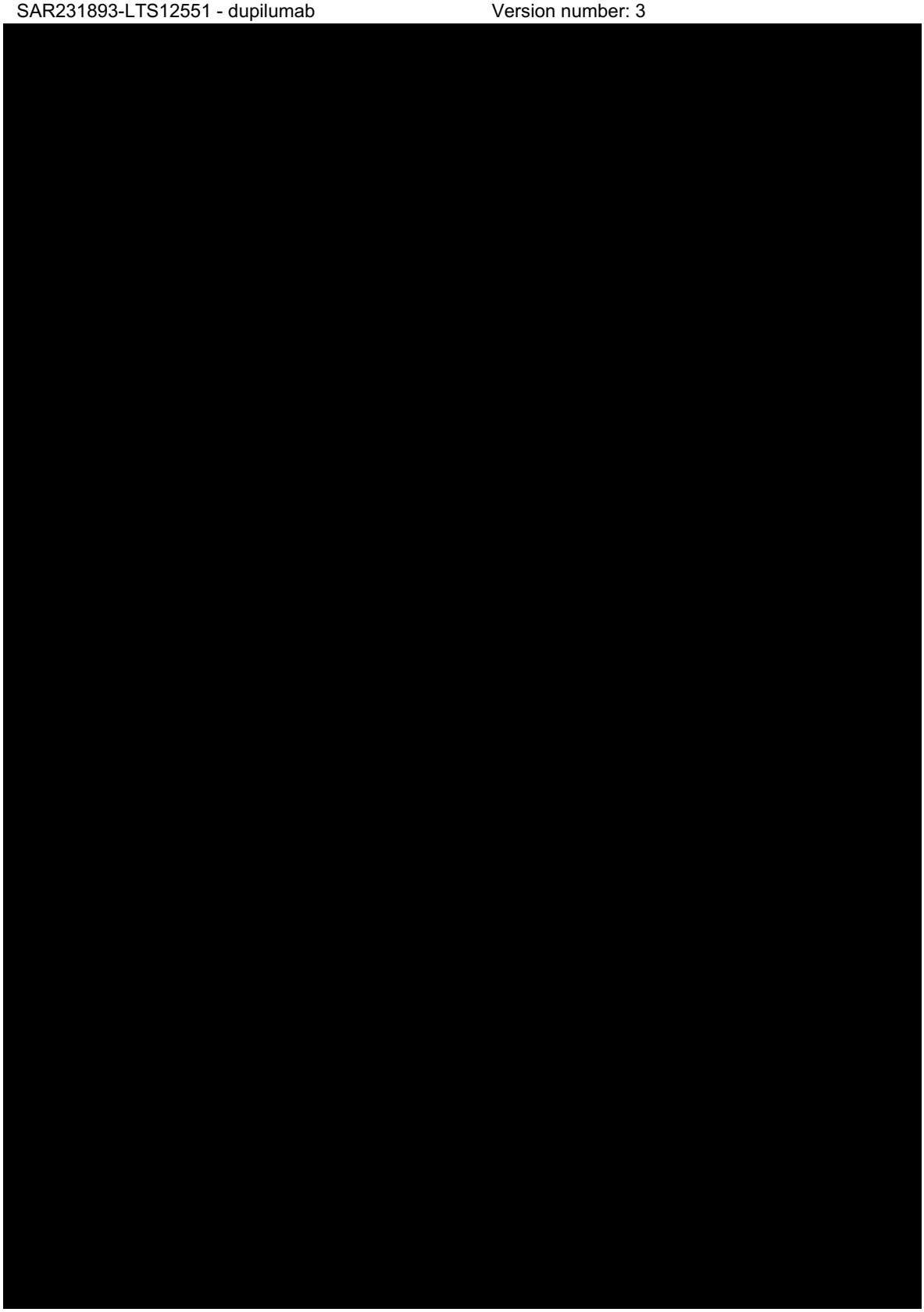
Appendix G Asthma Quality of Life Questionnaire

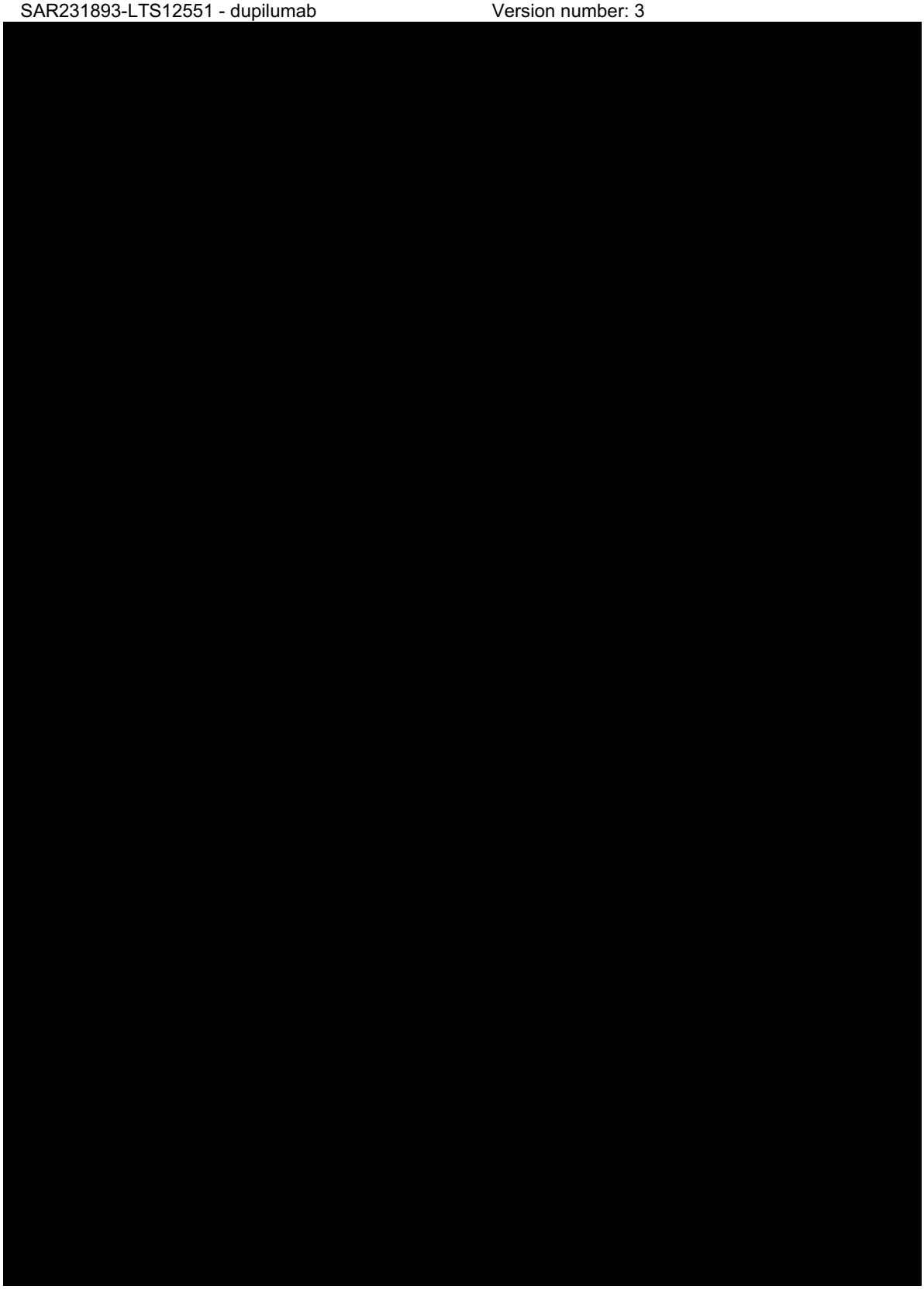




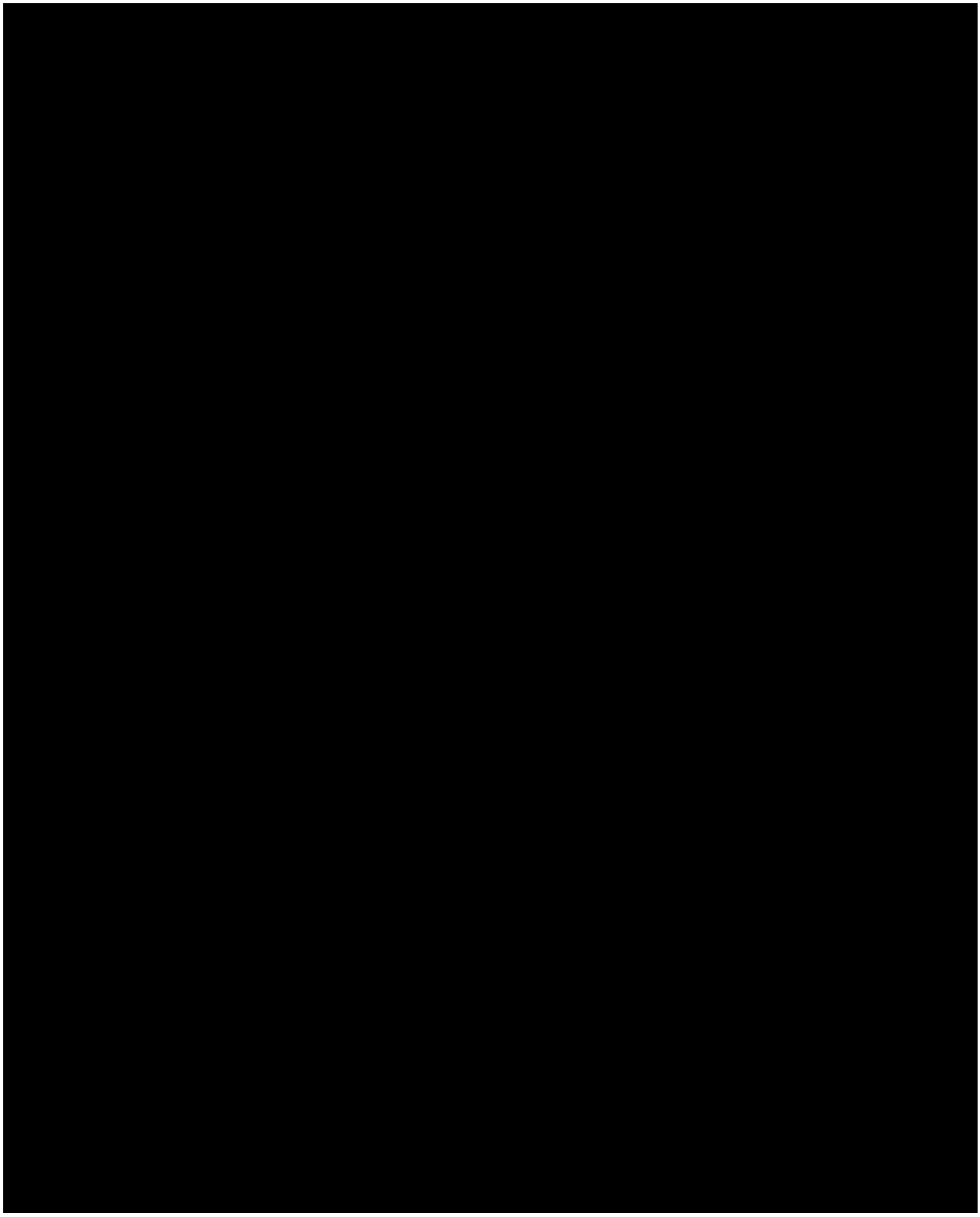


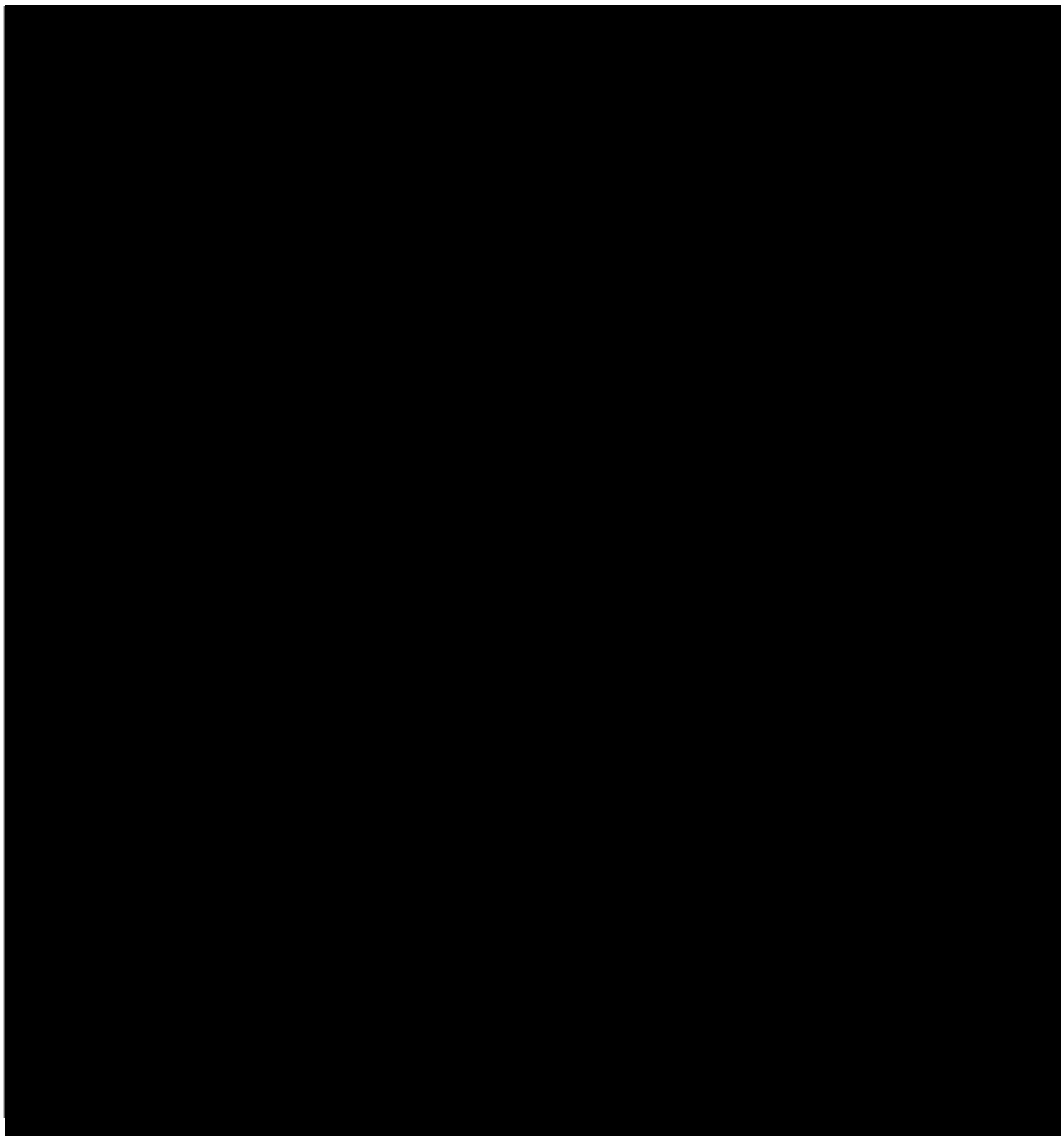






Appendix H EuroQol Questionnaire (EQ-5D-3L)





Appendix I SAS code for EQ-5D index utility scoring