STATISTICAL ANALYSIS PLAN

A randomized, double-blind, placebo-controlled, parallel-group, 12-week Proof-of-Concept (PoC) study to assess the efficacy, safety, and tolerability of SAR440340/REGN3500, and the coadministration of SAR440340/REGN3500 and dupilumab in patients with moderate-to-severe asthma who are not well controlled on inhaled corticosteroid (ICS) plus long-acting β2 adrenergic agonist (LABA) therapy

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ACQ-5:	Asthma Control Questionnaire 5-question version
ADA:	Anti-drug antibody
AE:	Adverse event
ANA:	Anti-nuclear antibody
AQLQ(S):	Asthma Quality of Life Questionnaire with Standardized Activities
ATC:	Anatomic therapeutic class
ATS:	American Thoracic Society
BD:	Bronchodilator
BID:	Twice daily
BMI:	Body mass index
CI:	Confidence interval
DMC:	Data Monitoring Committee
DPI:	Dry powder inhaler
ECG:	Electrocardiogram
eCRF:	Electronic case report form
EOT:	End of Treatment
ERS:	European Respiratory Society
FEF:	Forced expiratory flow
FeNO:	Fractional exhaled nitric oxide
FEV1:	Forced expiratory volume in one second
FVC:	Forced vital capacity
HBc Ab:	Hepatitis B core antibody
HBs Ab:	Hepatitis B surface antibody
HBs Ag:	Hepatitis B surface antigen
HCV Ab:	Hepatitis C virus antibody
HIV:	Human immunodeficiency virus
HLGT:	High-level group term
HLT:	High-level term
ICS:	Inhaled corticosteroid
Ig:	Immunoglobulin
IL33:	Interleukin-33
IMP:	Investigational medicinal product
IRT:	Interactive response technology
K-M:	Kaplan-Meier
LABA:	Long-acting β2 adrenergic agonist
LLOQ:	Lower limit of quantification
LLT:	Lower-level term
LOAC:	Loss of asthma control
MCID:	Minimal Clinically Important Difference
MDI:	Metered dose inhaler
MedDRA:	Medical Dictionary for Regulatory Activities

mITT:	Modified intent-to-treat
MMRM:	Mixed-effect model with repeated measures
NRS:	Numerical Rating Scale
NSAID:	Nonsteroidal anti-inflammatory drug
PARC:	Pulmonary and activation-regulated chemokine
PCSA:	Potentially clinically significant abnormality
PD:	Pharmacodynamic
PEF:	Peak expiratory flow
PK:	Pharmacokinetic
PoC:	Proof-of-Concept
post-BD:	post-bronchodilator
pre-BD:	pre-bronchodilator
PT:	Preferred term
q2w:	Every two weeks
RQLQ(S):	Rhinoconjunctivitis Quality of Life Questionnaire
SC:	Subcutaneous
SD:	Standard deviation
SMQs:	Standardised MedDRA Queries
SOC:	System organ class
sST2:	Soluble IL33 receptor
TEAE:	Treatment-emergent adverse event
ULN:	Upper limit of normal
WBC:	White blood cell
WHO-DD:	World Health Organization - Drug Dictionary

1 OVERVIEW AND INVESTIGATIONAL PLAN

1.1 STUDY DESIGN AND RANDOMIZATION

This is a multinational, randomized, double-blind, placebo-controlled, parallel-group, 12-week Proof-of-Concept (PoC) study accessing the efficacy, safety and tolerability of SAR440340 (also referred to as REGN3500), and the coadministration of both SAR440340 and dupilumab, in patients with moderate-to-severe asthma who are not well controlled on ICS/LABA therapy. The study utilizes an add-on therapy approach to a background therapy of ICS/LABA and consists of 3 periods:

- Screening period (4 weeks ± 3 days)
- Randomized investigational medicinal product (IMP) treatment period (12 weeks ± 3 days)
  - Background therapy stabilization phase (4 weeks)
  - Background therapy withdrawal phase (4-5 weeks)
  - No background therapy phase (3-4 weeks)
- Post IMP treatment safety follow-up period (20 weeks ± 5 days)

At the screening visit, patients must be using medium or high dose ICS therapy (≥250 mcg of fluticasone propionate twice daily [BID] or equipotent ICS daily dosage to a maximum of 2000 mcg/day of fluticasone propionate or clinically comparable) in combination with a LABA as second controller for at least 3 months with a stable dose ≥1 month prior to screening visit.

It is intended that approximately half of the patients included in the study will be on medium ICS dose at enrolment.

After completion of screening procedures, all eligible patients will be switched to clinically comparable doses of the study-specific ICS/LABA combination therapy with fluticasone/salmeterol, as approved for region:

- Fluticasone/salmeterol – dry powder inhaler (DPI):
  1 puff of 250/50 mcg BID or
  1 puff of 500/50 mcg BID

OR

- Fluticasone/salmeterol – metered dose inhaler (MDI):
  2 puffs of 115/21 mcg (230/42 mcg) BID or
  2 puffs of 230/21 mcg (460/42 mcg) BID

OR

- Fluticasone/salmeterol – MDI:
  2 puffs of 125/25 mcg (250/50 mcg) BID or
  2 puffs of 250/25 mcg (500/50 mcg) BID

Patients should use the same inhaler type (either DPI or MDI) during the study. Patients who satisfy the inclusion and exclusion criteria will be randomized (1:1:1:1 ratio) to one of the following treatment groups:

- SAR440340 (300 mg) administered as 2 subcutaneous (SC) injections q2w for 12 weeks and coadministration of dupilumab placebo as 1 SC injection q2w for 12 weeks.
- Dupilumab (300 mg) administered as 1 SC injection q2w for 12 weeks and coadministration of SAR440340 placebo as 2 SC injections q2w for 12 weeks.
- SAR440340 (300 mg) administered as 2 SC injections q2w for 12 weeks and coadministration of dupilumab (300 mg) administered as 1 SC injection q2w for 12 weeks.
- Coadministration of matching placebos for SAR440340 and dupilumab administered as 2 and 1 SC injections, respectively, q2w for 12 weeks.

Approximately 240 patients will be randomized. Randomization will be stratified by blood eosinophil count at screening visit (<150 /mm^3, 150 - <300 /mm^3, ≥300 /mm^3) and by country. Alerts will be built into the interactive response technology (IRT) system to limit enrolling patients in the following 2 strata:

- Eosinophil <150/mm^3: no more than approximately 25% (60) patients
- Eosinophil ≥300/mm^3: at least approximately 45% (108) patients

During the background therapy stable phase patients will remain on their current dose of fluticasone/salmeterol combination therapy along with the randomized IMP. The LABA component (salmeterol) will be withdrawn at Week 4 (Visit 6). Patients will be switched to a clinically comparable ICS monotherapy, as approved for region:

- Fluticasone (DPI formulation):
  1 puff of 250 mcg BID or
  2 puffs of 250 mcg (500 mcg) BID,

OR

- Fluticasone (MDI formulation):
  2 puffs of 110 mcg (220 mcg) BID or
  2 puffs of 220 mcg (440 mcg) BID

OR

- Fluticasone (MDI formulation):
  2 puffs of 125 mcg (250 mcg) BID or
  2 puffs of 250 mcg (500 mcg) BID

Starting at Week 6, ICS will be withdrawn by a step-wise dose reduction outlined in Table 1 below:

Table 1 - Withdrawal of fluticasone - downward titration doses (administered twice a day)

	Week 4/ Visit 6	Week 6/ Visit 8	Week 7/ Visit 9	Week 8/ Visit 10	Week 9/ Visit 11
Fluticasone DPI Dose (mcg) administered BID	250	100	50	0	0
	500	250	100	50	0
Fluticasone MDI Dose (mcg) administered BID	220	110	44	0	0
	440	220	110	44	0
	250	125	50	0	0
	500	250	125	50	0

BID = Twice daily; DPI = Dry powder inhaler; MDI = Metered dose inhaler.

If a patient meets the criteria for the primary endpoint, loss of asthma control (LOAC) at any time during the randomized treatment period, he/she will be withdrawn from the IMP. Patients who discontinue IMP prior to 12 weeks of treatment will be asked and encouraged to return to the clinic, as soon as possible, for End of Treatment (EOT) assessments. Upon completing 12 weeks of treatment with the IMP (or following early discontinuation of IMP), patients will resume their original ICS/LABA (ie, prior to screening) background therapy and enter the 20-week safety follow-up period. If a patient's asthma cannot be consistently controlled on his/her original ICS/LABA therapy, and there is a safety concern, additional controller therapies may be prescribed based on the Investigator's clinical judgement.

1.2 OBJECTIVES

1.2.1 Primary objectives

The primary objective of this study is to evaluate the effects of SAR440340 with or without dupilumab, compared to placebo, on reducing the incidence of LOAC events.

1.2.2 Secondary objectives

- Evaluate the effects of SAR440340 and coadministration of SAR440340 and dupilumab, compared with placebo, on forced expiratory volume in one second (FEV1).
- Estimate the effects of coadministration of SAR440340 and dupilumab, compared with SAR440340 and compared with dupilumab, on FEV1.
- Safety and tolerability of SAR440340 alone and in coadministration with dupilumab.

1.3 DETERMINATION OF SAMPLE SIZE

Data from a previous 12-week study of dupilumab with similar design, population, and background treatment (ACT11457) showed an 87% relative reduction in the rate of LOAC (44% in placebo group versus 6% in dupilumab group).

The sample size calculations are based on the primary endpoint, incidence of LOAC with the following assumptions:

- Incidence rate of 40% in the placebo group
- A 26% absolute rate reduction (to 14%) in the SAR440340 group
- A 2-sided $\chi 2$ test at 5% significance level with 80% power

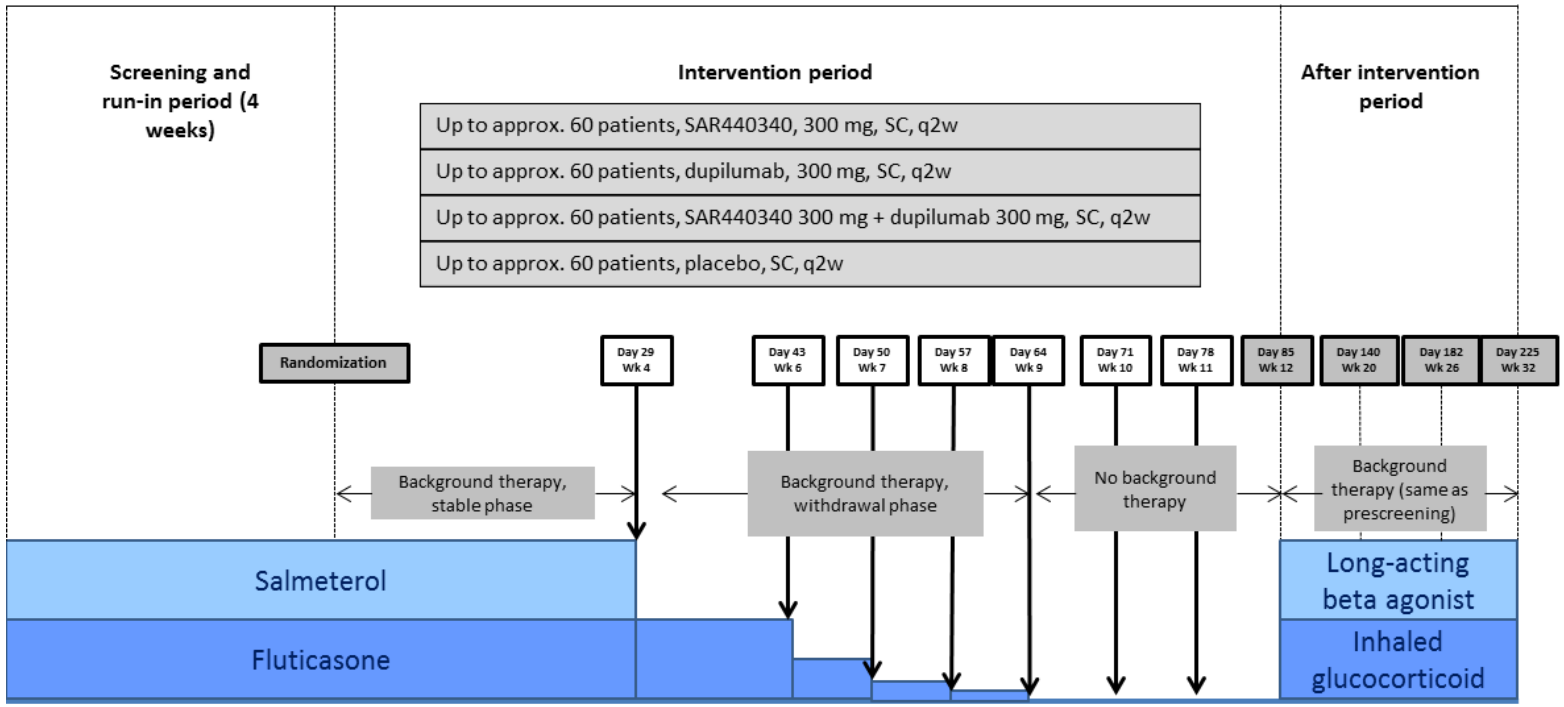
Based on the above assumptions, and allowing for approximately 15% dropout rate, 60 patients per treatment group are needed.

Calculations were made using nQuery Advisor 7.0.

1.4 STUDY PLAN

Please refer to Section 1.2 of the study protocol for study flow chart. The graphical study design is provided in Figure 1

Figure 1 – Graphical Study Design



Fluticasone-Salmeterol	Fluticasone				
Up to Wk 4, V6	Wk 4, V6	Wk 6, V8	Wk 7, V9	Wk 8, V10	Wk 9, V 11
DPI: 250/50 µg BID	250 µg BID	100 µg BID	50 µg BID	0 µg BID	
500/50 µg BID	500 µg BID	250 µg BID	100 µg BID	50 µg BID	0 µg BID
MDI*: 230/42 µg BID	220 µg BID	110 µg BID	44 µg BID	0 µg BID	
460/42 µg BID	440 µg BID	220 µg BID	110 µg BID	44 µg BID	0 µg BID
MDI*: 250/50 µg BID	250 µg BID	125 µg BID	50 µg BID	0 µg BID	
500/50 µg BID	500 µg BID	250 µg BID	125 µg BID	50 µg BID	0 µg BID

depending on regional availability

1.5 MODIFICATIONS TO THE STATISTICAL SECTION OF THE PROTOCOL

This section summarizes major changes to the protocol statistical section with emphasis on changes after study start (after the first patient was enrolled).

The protocol history table below gives the timing, rationale, and key details of major changes to the protocol statistical section.

Table 2 - Protocol amendment statistical changes

Amendment Number	Date Approved	Rationale	Description of statistical changes
1	06-Sep-2018	To clarify that the safety population will be analyzed based on the actual treatment received and non-randomized but treated patients will be included.	The following text: Analyses of safety endpoints will be performed as randomized using the mITT population. was replaced with: The safety population is defined as all patients who have received at least one dose of the IMP, analyzed according to the treatment actually received.
1	06-Sep-2018	To provide a more specific description of the ADA population.	The following text: The ADA population will consist of all patients in the mITT population with at least one qualified result in the anti-SAR440340 or anti-dupilumab assay following the first dose of study medication. was replaced with: The ADA population will consist of all patients who received any study drug and who had at least one nonmissing ADA result in the anti-SAR440340 or anti-dupilumab assay, after first dose of the study drug. Patients will be analyzed according to the treatment actually received.
1	06-Sep-2018	Reason of discontinuation will longer be used to assign LOAC event or not. The process of determination of LOAC event or not for patients discontinuing treatment for a reason other than LOAC will be based on documented medical review.	The following sentence was deleted: Patients discontinued due to lack of efficacy or an AE related to asthma worsening will be considered as having the primary endpoint. Patients discontinued for other reasons will be considered as not having the primary endpoint.
1	06-Sep-2018	To add variables identified as	Baseline background ICS dose level and

Amendment Number	Date Approved	Rationale	Description of statistical changes
		important covariates in previous dupilumab studies.	number of exacerbation events within 1 year prior to screening added as covariates in the logistic regression model in primary analysis of LOAC.
1	06-Sep-2018	The sentence was ambiguous with regards to the inclusion or not of the end of treatment value in the analysis for patients with LOAC/discontinuation for other reason. Furthermore, including data collected at EOT for these patients could confound the treatment effect due to medications administered after an LOAC event or discontinuation for another reason. Thus, this sentence is removed and details regarding the inclusion of values for analysis depending on concurrent events/treatments that could be confounded with efficacy are detailed in the SAP.	The following sentence was deleted: For patients with an LOAC event or permanently discontinued treatment, data collected up to EOT visit will be included.
1	06-Sep-2018	Time to LOAC post-randomization is being considered as supportive to the primary analysis of LOAC rather than as other efficacy endpoint.	Description on analysis of time to LOAC post-randomization moved from Sec 11.4.2.2 to Sec 11.4.2.1

1.6 STATISTICAL MODIFICATIONS MADE IN THE STATISTICAL ANALYSIS PLAN

Not applicable.

2 STATISTICAL AND ANALYTICAL PROCEDURES

2.1 ANALYSIS ENDPOINTS

2.1.1 Demographic and baseline characteristics

The baseline value is defined as the last available value prior to the first dose of IMP. For patients randomized but not treated, the baseline value is the last available value up to randomization.

All baseline safety and efficacy parameters (apart from those listed below) are presented along with the on-treatment summary statistics in the safety and efficacy sections (Section 2.4.5 and Section 2.4.4).

Demographic characteristics

The following demographic characteristics will be summarized separately by treatment:

- Gender (Male, Female),
- Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Island, White, Multiple, Unknown, Not Reported)
- Age (years)
- Age group 1 (<45, ≥45 years)
- Age group 2 (<65, ≥65 years)
- Ethnicity (Hispanic or Latino, non-Hispanic or Latino, Unknown, Not Reported)
- Region (East Europe: Poland, Russia, Turkey and Ukraine; Latin America: Argentina, Chile and Mexico; North America: USA)
- Body weight (kg)
- Body weight group (<60, ≥60 - <100, ≥100 kg)
- Body mass index (BMI, kg/m^2)
- BMI group (<25, ≥25 - <30, ≥30 kg/m^2)

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 using the version of Medical Dictionary for Regulatory Activities (MedDRA) currently in effect at Sanofi at the time of database lock.

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 and/or rhinitis history (Yes, Ongoing condition)
- Chronic rhinosinusitis history (Yes, Ongoing condition)
- Nasal polyposis history (Yes, Ongoing condition)
- Eosinophilic esophagitis history (Yes, Ongoing condition)
- Food allergy history (Yes, Ongoing condition)
- Hives history (Yes, Ongoing condition)
- Ongoing atopic medical condition*

  **A patient is considered to have atopic medical condition if he/she has any of the following ongoing condition: atopic dermatitis, allergic conjunctivitis or rhinitis, eosinophilic esophagitis, food allergy, hives; or has baseline total immunoglobulin E (*IgE*) ≥100 IU/mL.*

Disease characteristics at baseline

The following baseline disease characteristics will be summarized by treatment group separately:

- Background ICS dose level at randomization (medium, high*)

  ** Medium: total daily dose of fluticasone = 500 or 460 mcg; high: total daily dose of fluticasone = 1000 or 920 mcg*

- Age at asthma onset
- Time since first diagnosis of asthma (years) at randomization
- Smoking history (Never, Former*), time since cessation of smoking (years) and smoking quantity in pack-years for former smokers

  ** Current smokers are excluded from this study.*

- 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)
- Number of asthma exacerbation* experienced within 1 year before screening visit (quantitative variable and qualitative variable: 1, 2, 3, ≥4)

  ** Asthma exacerbation prior to the study is defined as any treatment with 1 systemic (oral or parenteral) steroid bursts or more for worsening asthma or hospitalization or an emergency/urgent medical care visit for worsening asthma.*

- Time since last asthma exacerbation (months) at randomization
- Baseline blood eosinophil level (<150 /mm^3, 150 - <300 /mm^3, ≥300 /mm^3)

- Baseline spirometry data including pre-bronchodilator (pre-BD) FEV1 (L), percent predicted FEV1, post-bronchodilator (post-BD) FEV1 (L) and FEV1 reversibility (%)
- AM and PM peak expiratory flow (PEF, L/min)
- AM and PM asthma symptom scores
- Number of nocturnal awakenings/day
- Asthma Control Questionnaire 5-question version (ACQ-5) score
- Asthma Quality of Life Questionnaire with Standardized Activities (AQLQ[S]) global score
- Number of inhalations of salbutamol/albuterol and levosalbutamol/levabuterol per day
- Hypersensitivity to aspirin (Yes, Ongoing condition)
- Hypersensitivity to nonsteroidal anti-inflammatory drug (NSAID) (Yes, Ongoing condition)

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

2.1.2 Prior or concomitant medications

All medications taken within 30 days before screening and until the end of the study, including pre-screening background therapy, study-specific background therapy, and systemic corticosteroids are to be reported in the electronic case report form (eCRF) pages.

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

- Prior medications are those the patient used prior to first IMP injection. Prior medications can be discontinued before first administration or can be ongoing during treatment phase.
- Concomitant medications are any treatments received by the patient concomitantly to the IMP, from the first administration of IMP to the last administration of IMP + 154 days.
- Post-treatment medications are those the patient took in the period from the last administration of IMP + 155 days to the end of the study.

A given medication can be classified into more than one category. Any technical details related to computation, dates, imputation for missing dates are described in Section 2.5.

2.1.2.1 Background therapy

Requirements on background therapy prior to screening as well as design of ICS/LABA withdrawal during the study are described in Section 1.1.

On a daily basis throughout the study (except in the post IMP treatment period), patients will use an electronic diary to record the number of inhalations/day of ICS/LABA or ICS background therapy.

2.1.2.2 Reliever medication

Patients may administer albuterol/salbutamol or levalbuterol/levosalbutamol MDI as reliever medication as needed during the study. Nebulizer solutions may be used as an alternative delivery method. Usage of reliever medication will be recorded in the electronic diary.

Salbutamol/albuterol nebulizer and levosalbutamol/levalbuterol nebulizer use recorded in the electronic diary will be converted to number of puffs as shown on the following tables:

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 daily dose = 7.5 mg or 12 puffs.

Levosalbutamol/Levalbuterol Nebulizer Solution Total Daily Dose (mg)	Number of Puffs*
0.63	2
1.25/1.26	4
1.89	6
2.5/2.52	8
3.15	10
3.75/3.78	12
5/5.04	16

*Conversion factor: levosalbutamol/levalbuterol nebulizer solution (1.25 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 daily dose = 3.75 mg or 12 puffs.

2.1.3 Efficacy endpoints

2.1.3.1 Primary efficacy endpoint(s)

The primary endpoint is the proportion of patients with LOAC during the treatment period.

LOAC event during the treatment period is a deterioration of asthma defined as any of the following:

- A 30% or greater reduction from baseline in morning PEF on 2 consecutive days
- ≥6 additional reliever puffs of salbutamol/albuterol or levosalbutamol/levalbuterol in a 24 hour period (compared to baseline) on 2 consecutive days
- Increase in ICS ≥4 times the last prescribed ICS dose (or ≥50% of the prescribed ICS dose at baseline if background therapy withdrawal completed)
- Requiring use of systemic (oral and/or parenteral) steroid treatment
- Requiring hospitalization or emergency room visit.

Standard medical review process (with documentation for LOAC assessment) will be used to confirm an LOAC event or not for patients with early treatment discontinuation, including those having the event as determined by the investigators, in a blinded fashion prior to the database lock.

2.1.3.2 Secondary and other efficacy endpoints

2.1.3.2.1 Secondary endpoints

The secondary endpoints for this study are:

- Change from baseline in pre-BD FEV1 at Week 12
- Change from baseline in post-BD FEV1 at Week 12

2.1.3.2.2 Other efficacy endpoints

- Change from baseline in other lung function measurement (PEF, forced vital capacity [FVC], forced expiratory flow [FEF] 25-75%) at Week 12 and at each assessment time point.
- ACQ-5 score change from baseline at Week 12 and at each assessment time point.
- AQLQ(S) change from baseline at Week 12 and at each assessment time point.
- Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ[S])* score change from baseline at Week 12 in patients with a secondary diagnosis of allergic rhinitis.

  ** Assessed only in patients with history of allergic rhinitis*
- Change from baseline at Week 12 and change from baseline at each week for asthma symptom scores in the morning and evening, and nocturnal awakenings.

- Change from baseline at Week 12 and change from baseline at each week in number of inhalations/day of albuterol or levalbuterol for symptom relief.

2.1.3.2.3 Disease-specific efficacy measures

Spirometry

Spirometry should be performed in accordance with the American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines (1) and prior to administration of investigational product.

For pre-bronchodilator parameters, including FEV1, PEF, FVC and FEF 25%-75%, spirometry will be performed after a wash out 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.

At all visits, spirometry will be performed preferably in the AM; PM is allowable in the exceptional circumstance when AM spirometry cannot be performed; spirometry should be done at approximately the same time at each visit throughout the study. The same spirometer and standard spirometric techniques, including calibration, will be used to perform spirometry at all visits and, whenever possible, the same person should perform the measurements.

Three measurements fulfilling the ATS acceptability and repeatability criteria should be obtained at every visit, if possible.

After spirometry for measuring pre-BD FEV1, patients will receive 2-4 puffs of albuterol/salbutamol or levalbuterol/levosalbutamol from a primed MDI. Alternatively, and only if it is consistent with usual office practice (to be documented), reversibility may be performed using inhalation of nebulized albuterol/salbutamol or levalbuterol/levosalbutamol. The post-BD spirometry may be repeated several times within 30 minutes after administration of bronchodilator. FEV1 reversibility is calculated as Post-BD FEV1 - Pre-BD FEV1 and percent FEV1 reversibility is calculated as (Post-BD FEV1 - Pre-BD FEV1) / Pre-BD FEV1 * 100.

2.1.3.2.4 Disease-specific, daily efficacy assessment

On a daily basis throughout the study (except in the post IMP treatment period), the patient uses an electronic diary/PEF meter to:

- Measure morning and evening PEF
- Respond to the morning and evening asthma symptom score Numerical Rating Scale (NRS) questions
- Record the number of nocturnal awakenings due to asthma symptoms
- Indicate the number of inhalations/day of salbutamol/albuterol or levosalbutamol/levalbuterol for symptom relief

For each of these efficacy assessments, post-baseline analysis values will be calculated based on periodical average. The time periods used to calculate the periodical average at designated analysis time points are specified in Section 2.5.2.

Morning (AM) and evening (PM) PEF

At screening (Visit 1), patients will be issued an electronic diary and PEF meter. Patients will be instructed on the use of the devices, and written instructions on the use of the electronic PEF meter will be provided to the patients. In addition, the Investigator will instruct 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 12 PM)
- PM PEF performed in the evening (between 5:30 PM and 12 AM)
- Patients should try to withhold albuterol or levalbuterol for at least 6 hours prior to measuring their PEF
- Three PEF efforts will be performed by the patient; all 3 values will be recorded by the electronic PEF meter, and the highest value will be used for evaluation

Baseline AM/PM PEF will be the mean of the AM/PM measurements recorded during the 7 days prior to the first dose of IMP. There should be at least 4 days' measurement out of the 7 days for setting up the baseline value. In case less than 4 days' measurement is available then the window period is increased from 7 to up to 14 days. The first dosing visit may be rescheduled until data for 4 days are available.

Asthma Symptom Score Numerical Rating Scale

Patients will record overall symptom scores in an electronic diary 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) and asthma symptoms experienced during the night will be recorded in the morning (AM symptom score) (see Appendix B). The baseline AM/PM symptom score will be computed following the same algorithm used for baseline AM/PM PEF. Scores range between 0-4 with 0 indicating more mild symptoms and 4 indicating more severe symptoms.

Number of nocturnal awakenings due to asthma symptoms

The baseline number of nocturnal awakenings due to asthma symptoms will be computed following the algorithm used for baseline PEF.

Reliever medication for symptom relief

The number of salbutamol/albuterol or levosalbutamol/levalbuterol inhalations will be recorded daily by the patients in the electronic diary. In the case that nebulizer solutions are used as an alternative delivery method, the nebulizer dose will be converted to number of puffs according to Section 2.1.2.2.

The reliever medication baseline value will be the average number of puffs taken in the most recent 7 diary days prior to Visit 2. A diary day is defined as the period beginning with an Evening diary, and ending with the following day's Morning Diary. A diary day cannot be included in the calculation if it is not complete, meaning if an evening or morning diary is missing. There must be at least 4 complete diary days to establish the baseline value.

2.1.3.2.5 Patient-reported outcomes

The questionnaires listed below will be administered at on-site visits. Responses will be recorded in the electronic diary. Based on the device design, no partial missing data is expected.

ACQ-5

The ACQ 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: 1. Frequency in past week awoken by asthma during the night, 2. Severity of asthma symptoms in the morning, 3. Limitation of daily activities due to asthma, 4. Shortness of breath due to asthma and 5. 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 C).

A global score is calculated: the questions are equally weighted and the ACQ-5 score is the mean of the 5 questions and, therefore, between 0 (totally controlled) and 6 (severely uncontrolled).

Higher score indicates lower asthma control. Patients with a score below 1.0 reflect adequately controlled asthma and patients with scores above 1.0 reflect inadequately controlled asthma. On the 7-point scale of the ACQ-5, a change or difference in score of 0.5 at patient level is the smallest change that can be considered clinically important, corresponding to the Minimal Clinically Important Difference (MCID) defined by the developer.

AQLQ(S)

The AQLQ(S) was designed as a self-administered patient reported outcome to measure the functional impairments that are most troublesome as a result of their asthma.

The instrument is comprised of 32 items (see Appendix D), each rated on a 7-point Likert scales from 1 to 7. Patients are asked to recall how their asthma has been during the previous 2 weeks. The AQLQ(S) has 4 domains. The domains and the number of items in each domain are as follows:

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

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 of the questions in that domain. The overall score and domain scores ranges from 1 to 7. Higher scores indicate better quality of life. A change or difference in AQLQ(S) score of 0.5 is the smallest change that can be considered clinically important, corresponding to the MCID defined by the developer (2).

RQLQ(S) in patients with comorbid allergic rhinitis

RQLQ(S) is a self-administered questionnaire (Appendix E) with standardized activities developed to measure health-related quality of life signs and symptoms that are most problematic in those 18 to 75 years of age, as a result of perennial or seasonal allergic rhinitis.

There are 28 items on the RQLQ(S) in 7 domains:

- Activities (3 items)
- Sleep (3 items)
- Non-Hay Fever Symptoms (7 items)
- Practical Problems (3 items)
- Nasal Symptoms (4 items)
- Eye Symptoms (4 items)
- Emotional (4 items)

The RQLQ(S) responses are based on 7-point Likert scale with responses ranging from 0 (not troubled) to 6 (extremely troubled). Individual items within the RQLQ(S) are equally weighted. The overall score is calculated as the mean score of all items. Both the domain and overall scores range from 0 to 6. Higher scores indicated more severe health-related quality of life impairment. An MCID of 0.5 has been established as the minimal important difference indicative of a clinically meaningful change (3).

2.1.3.3 Exploratory endpoint(s)

CompEx

CompEx is a composite endpoint combining severe exacerbation and deterioration of asthma captured by diary variables. It was developed to allow trials with shorter duration and smaller sample size while preserving similar treatment effect compared to severe exacerbation (4).

Six diary variables are included in defining deterioration of asthma in CompEx. For each variable, a threshold deterioration criterion and a slope criterion are defined as follows:

	Threshold criterion	Slope criterion*
AM/PM PEF	A 15% or greater reduction from baseline for 2 consecutive days	An average of 3% or greater reduction per day
AM/PM Reliever medication use	≥1.5 times increase from baseline for 2 consecutive days	An average of ≥0.3 times increase per day
AM/PM asthma symptom score	≥1 increase in score from baseline or absolute maximum score for 2 consecutive days	An average of ≥0.2 increase in score per day

*Slope will be calculated via linear regression over a 5-day period. At least two days of data are needed.

Deterioration of asthma occurs when

A) The threshold criterion is met for at least one of the PEF variables at the same time when the criterion is met for at least one of the remaining four variables

OR

B) The threshold criterion is met for one of the six variables and at the same time, the slope criterion is met for all six variables.

The start date of the deterioration is the first of the two consecutive days (days 0 and 1) when a threshold criterion is met. The slope criterion has to be met on days -4 to 0 to be considered as concurrent with the threshold criterion.

A CompEx event is defined as the first occurrence of either a diary event (deterioration of asthma) or a severe exacerbation. Thus, the event date is onset date of severe exacerbation or start date of deterioration. The time to event is defined as (event date – randomization date +1). Patient without an event will be censored at date of EOT/Week 12 or date of last electronic diary entry, whichever occurs later.

2.1.4 Safety endpoints

The safety analysis will be based on the reported adverse events (AEs) and other safety information, such as clinical laboratory data, vital signs, electrocardiogram (ECG), etc.

Observation period

The observation period will be divided into 4 epochs:

- The **screening** epoch is defined as the time from the signed informed consent date up to the first administration of the IMP.
- The **treatment** epoch is defined as the time from the first administration of the IMP to the last administration of the IMP + 14 days.
- The **residual treatment** epoch is defined as the time from the last administration of the IMP + 15 days to the last administration of the IMP + 154 days.

The treatment-emergent adverse event (TEAE) period will include both **treatment** and **residual treatment** epochs.

- The **post-treatment** epoch is defined as the period of time starting the day after the end of the treatment-emergent adverse event period up to the patient's end of study (defined as last protocol-planned visit or the resolution/stabilization of all serious adverse events and adverse events with pre-specified monitoring).

The on-study observation period is defined as the time from start of treatment until the end of the study.

2.1.4.1 Adverse events variables

Adverse event observation period

- Pre-treatment adverse events are adverse events that developed or worsened or became serious during the screening epoch.
- Treatment-emergent adverse events are adverse events that developed or worsened or became serious during the treatment-emergent adverse event epoch.
- Post-treatment adverse events are adverse events that developed or worsened or became serious during the post-treatment epoch.

All adverse events (including serious adverse events and adverse events with pre-specified monitoring) 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 MedDRA currently in effect at Sanofi at the time of database lock.

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

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

AE Grouping	Criteria
AESI	
Anaphylactic reaction (medically reviewed)	Anaphylactic reaction algorithmic approach (*Introductory Guide for Standardised MedDRA Queries (SMQs) Version 20.0*): includes anaphylactic reaction narrow SMQ (20000021) terms and programmatic identification of cases based on occurrence of at least two preferred terms meeting the algorithm criteria occurring within 24 hours of each other. The latter cases identified using the algorithm will undergo blinded medical review taking into account the timing of events relative to each other and to IMP administration for final determination of an anaphylactic reaction or not.
Hypersensitivity (medically reviewed)	SMQ hypersensitivity (20000214) narrow search and [AE corrective treatment/therapy='Y' or Action taken with IMP='Drug withdrawn' or Action taken with IMP='Drug interrupted'] followed by blinded medical review (documented process) for selection of relevant systemic events
Injection site reaction (serious or severe and lasting 24 hours or longer)	HLT = 'Injection site reaction' and either with serious status, or non-serious events with (AE end date/time - AE start date/time) ≥ 24 hours or ongoing and at least one of the following checked on the Injection Site Reaction Complementary Form: – Diameter of at least 10cm – Prevents daily activities – Presence of ulceration or necrosis – Operative intervention required
Infection	Primary SOC = 'Infections and infestations' and meeting at least one of the following criteria – Serious status – 'Have any parenteral treatment (IV, Intramuscular, SC) been given for this event?' is answered Yes on eCRF Infection Event Form – 'Did this event require Prolonged Medication (greater than 14 Days)' is answered Yes on eCRF Infection Event Form
Parasitic infection	Infection Type 'Parasitic' selected on eCRF Infection Event Form
Opportunistic infection	'Has the AE been assessed as opportunistic infection?' is answered Yes on eCRF Infection Event Form
Potential drug-related hepatic disorder	Drug-related hepatic disorders-Comprehensive search narrow SMQ (20000006)
Malignancy	Sub-SMQ (20000091)– Malignant or unspecified tumors
Pregnancy	'Pregnancy' or 'Partner Pregnancy' ticked on the Pregnancy eCRF.
Symptomatic overdose with IMP	'Overdose of IMP' and 'Symptomatic Overdose' are both ticked Yes on the Overdose eCRF
Symptomatic overdose with NIMP	'Overdose of NIMP' and 'Symptomatic Overdose' are both ticked Yes on the Overdose eCRF

AE Grouping	Criteria
Other selected AE grouping	
Injection site reaction	HLT = 'Injection site reaction'
Eosinophilia	HLT = 'Eosinophilic disorders' or PT = 'Eosinophil count increased'

2.1.4.2 Deaths

The death observation periods are per the observation periods defined above.

- Death on-study: deaths occurring during the on-study observation period
- Death on-treatment: deaths occurring during the treatment-emergent adverse event period
- Death post-study: deaths occurring after the end of the study and recorded in the clinical database

2.1.4.3 Laboratory safety variables

Clinical laboratory data consists of blood analysis, including hematology, clinical chemistry, and urinalysis. Clinical laboratory values after conversion will be analyzed in standard international units and international units will be used in all listings and tables.

Blood samples for clinical laboratories will be taken at Visits 1, 2, 6, 10, 14, 15 and 17 and early termination unless otherwise specified. The laboratory parameters will be classified as follows:

- Hematology
  - **Red blood cells and platelets and coagulation**: hemoglobin, hematocrit, total red blood cell count, platelet count
  - **White blood cells:** total white blood cell (WBC) count, neutrophils, lymphocytes, monocytes, basophils, eosinophils
- Clinical chemistry
  - **Metabolism**: glucose, total cholesterol, total protein, creatine phosphokinase, albumin
  - **Electrolytes**: sodium, potassium, chloride, bicarbonate
  - **Renal function**: creatinine, estimated creatinine clearance (Cockcroft's formula Section 2.5.1), blood urea nitrogen, uric acid
  - **Liver function**: alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, total bilirubin (in case of values above the normal range, differentiation in conjugated and non-conjugated bilirubin)
  - **Pregnancy test**: serum beta-human chorionic gonadotropin (β-hCG) will be performed at Visit 1 in women of childbearing potential

- **Hepatitis screen:** clinical laboratory testing at Visit 1 will include hepatitis screen covering hepatitis B surface antigen (HBs Ag), hepatitis B surface antibody (HBs Ab), hepatitis B core antibody (HBc Ab), and hepatitis C virus antibody (HCV Ab).
- **QuantiFERON-TB Gold** will be tested at Visit 1
- **Human immunodeficiency virus (HIV) screen**: anti-HIV-1 and HIV-2 antibodies will be tested at Visit 1
- **Anti-nuclear antibody (ANA)** will be tested at Visit 1

  Note: Anti-ds DNA antibody will be tested if ANA is positive (≥1:160 titer).

Urine samples will be collected at Visits 1, 2, 6, 10, 14, 15 and 17 and early termination.

- **Urinalysis:** dipstick for specific gravity, pH, glucose, ketones, blood, protein, nitrate, leukocyte esterase, urobilinogen, and bilirubin. If any parameter on the dipstick is abnormal, a urine sample should be sent to the central laboratory for quantitative measurement. If positive for protein and/or red blood cells, microscopic analysis will be performed by the central laboratory.
- **Urine dipstick pregnancy test** will be performed at Visits 2 (prior to randomization), 6, 10, 14 and 17.

Technical formulas are described in Section 2.5.1.

2.1.4.4 Vital signs variables

Systolic and diastolic blood pressure (mmHg), pulse rate (beats per minute), respiratory rate (breaths per minute), and body temperature (°C) will be measured at all visits from Visit 1 to 17 except for Visit 16. Vital signs will be measured in the sitting position using the same arm (preferably). Body weight (kg) will be measured at Visits 1, 2 and 14. Height (cm) will be measured at Visit 1 only.

2.1.4.5 Electrocardiogram variables

Recording of a standard 12-lead ECG will be performed at the clinical site at Visits 1, 6, 14 and 17. At the post-randomization visits, ECGs will be performed prior to investigational product administration. A minimum of 3 complexes in an appropriate lead (lead II) will be averaged to determine the PR-interval, QT/QTc-interval, QRS-complex and heart rate will be measured for each ECG. All ECG recordings will be centrally read by independent experts.

2.1.4.6 Physical Examination

Physical examinations will be performed at Visits 1, 2. 6, 10, 14, 15 and 17 including an assessment of skin, nasal cavities, eyes, ears, respiratory, cardiovascular, gastrointestinal, neurological, lymphatic, and musculoskeletal systems. All deviations from normal will be recorded in the eCRF, including those attributable to the patient's disease.

2.1.5 Pharmacokinetic (PK) variables

Pre-dose serum SAR440340 and dupilumab concentrations at Week 0 (baseline), and trough levels at Weeks 2, 4, 8, and 12 will be collected. Follow-up concentrations will be collected at Weeks 20 and 32.

2.1.6 Anti-drug antibody (ADA) variables

The ADA variables are ADA status and titer over time.

Serum samples for anti-SAR440340 and anti-dupilumab antibody bioanalysis will be collected at Weeks 0 (baseline), 12 and 32. If ADA assessment at week 12 (or the first post-treatment time point analyzed) is positive, additional measurements may be performed from PK samples collected at Week 4. ADA for each drug will be summarized separately.

Patients who discontinue early from treatment may be asked to return to the clinic to have additional PK/ADA samples collected for up to 20 weeks after treatment discontinuation.

2.1.7 Pharmacodynamic (PD)/genomics endpoints

PD endpoints include:

- **Whole blood biomarkers:** blood eosinophil and neutrophil count will be measured at Visits 1, 2, 4, 6, 8, 10, 14, 15 and 17 as part of the standard 5-part WBC differential cell count on a hematology autoanalyzer.
- **Plasma biomarkers:** eotaxin-3 will be measured at Visits 1, 2, 6, 10, and 14.
- **Serum biomarkers:** pulmonary and activation-regulated chemokine (PARC) will be measured at Visits 1, 2, 6, 10 and 14. Total interleukin-33 (IL33), soluble IL33 receptor (sST2) and calcitonin will be assayed at Visits 1, 2, 6, 10, 14, 15 and 17. Total IgE and periostin will be measured at Visits 1, 2, 6 and 14.
- **Fractional exhaled nitric oxide (FeNO)** will be assessed prior to spirometry and following a fast of at least 1 hour at Visits 1, 2, 4, 6, 10, 14, 15 and 17.

Pharmacogenetic testing is optional and voluntary. A separate written informed consent form must be signed before sampling. For those patients who provided written consent to the collection of the optional pharmacogenetics samples, blood samples for exploratory genetic analysis of DNA will be collected at the study visit as specified in the study flow chart, and these samples will be stored for future analysis.

2.2 DISPOSITION OF PATIENTS

This section describes patient disposition for both patient study status and the patient analysis populations.

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

Randomized patients are any patient who has signed informed consent and has been allocated to a randomized treatment regardless of whether the treatment kit was used.

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

- Screened patients
- Screen failure patients and reasons for screen failure
- Non-randomized but treated patients
- Randomized patients
- Randomized but not treated patients
- Randomized and treated patients
- Patients who did not complete the treatment as per protocol
- Patients who discontinued treatment by main reason for permanent treatment discontinuation
- Patients who withdraw from study
- Patients who withdraw from study by main reason for study discontinuation
- Status at last study contact

For all categories of patients (except for the screened and non-randomized categories) percentages will be calculated using the number of randomized patients as the denominator. Reasons for treatment discontinuation will be supplied in tables giving numbers and percentages by treatment group.

All critical or major deviations potentially impacting efficacy analyses, randomization, and drug-dispensing irregularities, and other major or critical deviations will be summarized in tables giving numbers and percentages of deviations by treatment group.

Additionally, the analysis populations for safety, efficacy, PK and ADA will be summarized in a table by number of patients on the randomized population.

2.2.1 Randomization and drug dispensing irregularities

Randomization and drug-dispensing irregularities occur whenever:

1. A randomization is not in accordance with the protocol-defined randomization method, such as a) an ineligible patient is randomized, b) a patient is randomized based on an incorrect stratum, or c) a patient is randomized twice.

   OR

2. A patient is dispensed an IMP kit not allocated by the protocol-defined randomization, such as a) a patient at any time in the study is dispensed a different treatment kit than as

randomized (which may or may not contain the correct-as-randomized IMP), or b) a non-randomized patient is treated with IMP reserved for randomized patients.

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

All randomization and 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 randomized patients (number and percentages).

Randomization and drug-dispensing irregularities to be prospectively identified include but are not limited to:

Randomization and drug allocation irregularities
Kit dispensation without IRT transaction
Erroneous kit dispensation
Kit not available
Randomization by error
Patient randomized twice
Stratification error
Patient switched to another site

2.3 ANALYSIS POPULATIONS

The randomized population includes any patient who has signed informed consent and has been allocated to a randomized treatment regardless of whether the treatment kit was used.

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

2.3.1 Efficacy populations

The primary efficacy analysis population will be the mITT population.

2.3.1.1 Modified intent-to-treat (mITT) population

The mITT population includes all randomized patients who have received at least one dose of investigational product analyzed according to the treatment group allocated by randomization.

Randomized patients for whom it is unclear whether they took the study medication will be included in the mITT population.

2.3.2 Safety population

The safety population is defined as all patients exposed to IMP, regardless of the amount of exposure, analyzed according to the treatment actually received.

In addition:

- Randomized patients for whom it is unclear whether they took the IMP will be included in the safety population as randomized
- The actual treatment group will be the one for which the patient received the majority of doses.

2.3.3 Pharmacokinetic analysis population

The PK population will consist of all patients in the safety population with at least one post-dose, non-missing serum SAR440340 or serum dupilumab concentration. Patients will be analyzed according to the treatment actually received.

2.3.4 Anti-drug antibody population

The ADA population will consist of all patients who received any study drug and who had at least one non-missing ADA result in the anti-SAR440340 or anti-dupilumab assay after first dose of the study drug. Patients will be analyzed according to the treatment actually received.

2.4 STATISTICAL METHODS

2.4.1 Demographics and baseline characteristics

Continuous data will be summarized using the number of available data, mean, standard deviation (SD), median, Q1, Q3, minimum and maximum for each treatment group. Categorical and ordinal data will be summarized using the number and percentage of patients in each treatment group.

Parameters will be summarized on the randomized population analyzed in the treatment group to which they were randomized. Parameters described in Section 2.1.1 will be summarized by treatment group and overall treatment groups using descriptive statistics.

Medical and surgical history will be summarized by treatment group and by primary 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 incidence across treatment groups. Atopic medical history will be summarized separately.

No statistical testing on demographic and baseline characteristic data will be performed.

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

2.4.2 Prior or concomitant medications

The prior and concomitant medications will be presented for the mITT population.

Medications will be summarized by treatment group according to the WHO-DD dictionary, considering the first digit of the Anatomic Therapeutic Class (ATC) (anatomic category) and the first 3 digits of the ATC class (therapeutic category). All ATC codes corresponding to a medication will be summarized, and patients will be counted once in each ATC category (anatomic or therapeutic) linked to the medication. Therefore patients may be counted several times for the same medication.

The table for prior medications will be sorted by decreasing frequency of anatomic class followed by decreasing frequency of therapeutic classes within anatomic class based on the overall incidence across treatment groups. In case of equal frequency regarding ATCs (anatomic or therapeutic categories), alphabetical order will be used.

Concomitant medications will be summarized for the treatment epoch and treatment emergent period separately. The tables for concomitant medications will be sorted by decreasing frequency of anatomic class followed by decreasing frequency of therapeutic classes within anatomic class based on the incidence in the SAR440340 and dupilumab coadministration group. In case of equal frequency regarding ATCs (anatomic or therapeutic categories), alphabetical order will be used.

2.4.2.1 Background therapy

Pre-screening ICS/LABA background therapy will be summarized by treatment group sorted by decreasing frequency of standard medication name on the incidence in the overall treatment group.

During the screening and randomized IMP treatment periods, the daily intake of the study-specific background therapy will be recorded in the electronic diary. Compliance rate for the study-specific background therapy will be calculated for each patient. For each day, a patient is considered as compliant if the actual dose taken is the same as or greater than the prescribed dose recorded on the eCRF. Compliance rate is defined as the number of days when the patient is compliant divided by the number of days the patient stays in the background therapy stabilization phase and the background therapy withdrawal phase.

2.4.3 Extent of investigational medicinal product exposure and compliance

The overall extent of IMP exposure and compliance will be assessed and summarized by actual treatment within 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.

Duration of IMP exposure is defined as last dose date – first dose date + 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, Q1, Q3, minimum, and maximum). In addition, duration of treatment exposure will also be summarized categorically by numbers and percentages of patients in each of the following categories and cumulatively according to these categories:

>0 and ≤2 weeks

>2 and ≤4 weeks

>4 and ≤8 weeks

>8 weeks and < 12 weeks – 3 days

≥12 weeks – 3 days

Additionally, the cumulative duration of treatment exposure will be provided, defined as the sum of the duration of treatment exposure for all patients, and will be expressed in patient years.

2.4.3.2 Compliance

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

Percentage of compliance for a patient will be defined as the number of administrations 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 will be summarized descriptively as quantitative variables (number, mean, SD, median, Q1, Q3, minimum, and maximum). The percentage of patients whose compliance is <80% will be summarized. In addition, numbers and percentages of patients with an overdose will be summarized.

Cases of overdose (defined as at least twice the intended dose during an interval of less than 8 days) will be listed as such. More generally, dosing irregularities are listed in Section 2.2.1.

2.4.4 Analyses of efficacy endpoints

All efficacy endpoints will be analyzed using the mITT population. Table 4 summarizes the pairwise comparisons to be conducted in accordance with study objectives. Each comparison on each endpoint will be tested at a two-sided 5% significance level.

Table 4 - Pairwise comparisons and study objectives

	Primary endpoint	Secondary endpoints	Other efficacy endpoints
SAR440340 vs. placebo	P	S	O
Coadministration of SAR440340 and dupilumab vs. placebo	P	S	O
Coadministration of SAR440340 and dupilumab vs. SAR440340	O	S	O
Coadministration of SAR440340 and dupilumab vs. dupilumab	O	S	O
Dupilumab vs. placebo (as calibrator only)	O	O	O

P: Primary objective; S: Secondary objective; O: Other objective

2.4.4.1 Analysis of primary efficacy endpoint(s)

Main statistical model and adjustment of covariates

The primary endpoint of incidence of LOAC will be analyzed using a logistic regression model. The model will include terms for treatment, baseline eosinophil strata, region (pooled countries), background ICS dose level at randomization and number of exacerbation events within 1 year prior to screening.

For each pairwise treatment comparison, the odds ratio, and corresponding 95% confidence interval (CI) and two-sided p-value will be derived from this model. Sample SAS code is provided below:

```
proc genmod data=loacdata descending;
  class trt01pn eosbgp1n cntygr1 icsgrp;
  model resp = trt01pn eosbgp1n cntygr1 icsgrp asmanum /dist=bin
link=logit type3;
  estimate "SAR440340 vs Placebo"          trt01pn -1 1 0 0 / exp;
  estimate "Coadministration vs Placebo"   trt01pn -1 0 1 0 / exp;
  estimate "Coadministration vs SAR440340" trt01pn 0 -1 1 0 / exp;
  estimate "Coadministration vs Dupilumab" trt01pn 0 0 1 -1 / exp;
  estimate "Dupilumab vs Placebo"          trt01pn -1 0 0 1 / exp;
  ods output Estimates = Estimates;
run;
```

All reported LOAC events will undergo the standard medical review process to ensure the events are in-line with the protocol definition. For patients discontinued due to a reason other than LOAC, but for which LOAC could be suspected, the case will be medically reviewed, with appropriate queries sent to the respective site, for final determination of LOAC status to be recorded in the clinical database prior to database lock. As such, there should not be missing data for the primary LOAC endpoint.

Supportive analysis

- *Supportive analysis 1:* Relative risk and corresponding 95% CI for each pairwise treatment comparison will be estimated from a log-binomial regression model. The covariates to be included will be the same as those in the main model.
- *Supportive analysis 2*: Time to LOAC post-randomization, defined as (onset date of LOAC – randomization date + 1), will be analyzed using a Cox regression model. The model will include treatment, baseline eosinophil strata, region, background ICS dose level at randomization and number of exacerbation events within 1 year prior to screening as covariates. A patient without experiencing the event of interest will be considered as censored at date of EOT/Week 12 or the last contact date, whichever occurs earlier. Hazard ratio and corresponding 95% CI and p-value will be estimated for each pairwise treatment comparison. The Kaplan-Meier (K-M) method will be used to estimate the probabilities of the event at Weeks 4, 8 and 12 for each treatment group. K-M curves will be generated; quartiles and point probabilities will be calculated. Interval estimates will be calculated using 95% point wise CIs. P-value from log-rank test stratified by baseline eosinophil strata and region will also be provided for each pairwise treatment comparison.

  Below is sample SAS code for the Cox regression model:

```
proc phreg data=ttevent;
class trt01pn eosbgp1n cntygr1 icsgrp / param = glm;
model aval*cnsr(1) = trt01pn eosbgp1n cntygr1 icsgrp asmanum;
estimate "SAR440340 vs Placebo"          trt01pn -1 1 0 0 / exp;
estimate "Coadministration vs Placebo"   trt01pn -1 0 1 0 / exp;
estimate "Coadministration vs SAR440340" trt01pn 0 -1 1 0 / exp;
estimate "Coadministration vs Dupilumab" trt01pn 0 0 1 -1 / exp;
estimate "Dupilumab vs Placebo"          trt01pn -1 0 0 1 / exp;
ods output Estimates = Estimates;
run;
```

Subgroup analysis

To assess the consistency of treatment effects across the subgroup levels, subgroup analyses will be performed by:

- Age group 1 (<45, ≥45 years)
- Age group 2 (<65, ≥65 years)
- Gender (Male, Female)
- Region (East Europe: Poland, Russia, Turkey and Ukraine; Latin America: Argentina, Chile and Mexico; North America: USA)
- Race (White, the others)
- Baseline blood eosinophil strata (<150/mm^3, ≥150 – <300/mm^3, ≥300/mm^3)
- Background ICS dose level at randomization (medium, high)
- Baseline FEV1 (< median, ≥ median)

- ACQ-5 (≤ 2, >2)
- Number of asthma exacerbation prior to the study as defined in Section 2.1.1 (≤1,>1)
- Baseline weight (<60, ≥60 - <100, ≥100 kg)
- BMI (<25, ≥25 - <30, ≥30 kg/m^2)
- Smoking history (Former, Never)
- Atopic medical condition (Yes, No)
- Age at onset of asthma (<12, ≥12 - <18, ≥18 - 40, ≥40 years)
- Baseline predicted FEV1% (< median, ≥median)
- Baseline periostin (NG/ML) (< median, ≥ median)
- Baseline FeNO (< 25, ≥25- < 50, ≥50 ppb)

Within each subgroup, descriptive statistics including number of patients and incidence of LOAC will be provided by treatment group. Odds ratio and the corresponding 95% CI for each pairwise comparison will be derived.

Treatment-by-subgroup interaction and its p-value will be derived by a logistic regression model. The model will include treatment, baseline eosinophil strata, region, baseline background ICS dose level, number of exacerbation events within 1 year prior to screening, subgroup (if different from the aforementioned covariates), and subgroup-by-treatment interaction.

2.4.4.2 Analyses of secondary efficacy endpoints

Main statistical model and adjustment of covariates

Change from baseline in pre- and post-BD FEV1 at Week 12 will be analyzed using a mixed-effect model with repeated measures (MMRM) approach. The analysis model will include change from baseline values up to week 12 as response variable and treatment, gender, baseline height, baseline eosinophil strata, region (pooled countries), background ICS dose level at randomization, visit, treatment-by-visit interaction, baseline value and baseline-by-visit interaction as covariates.

Given the potential effects on FEV1 and the goal to obtain as precise a treatment effect estimate as possible, FEV1 values after a LOAC event or initiation of rescue medication will not be included for primary assessment of the secondary endpoints. Inclusion of change from baseline in FEV1 values in the model will follow the rules in Table 5. Data not included in the analysis according to these rules will be set to missing. No imputation will be made for other missing FEV1 measurements.

Table 5 – Data inclusion rules for analyses of secondary and other efficacy endpoints

If the patient has	Use data up to
LOAC with rescue medication[a]	last value before start of LOAC
LOAC without rescue medication[b]	value collected at EOT
OCS use without LOAC	last value before start of OCS
neither LOAC or OCS	value collected at Week 12/EOT

a If the patient meets at least one of the following three criteria:
- ≥6 additional reliever puffs of salbutamol/albuterol or levosalbutamol/levalbuterol in a 24 hour period (compared to baseline) on 2 consecutive days
- Increase in ICS ≥4 times the last prescribed ICS dose (or ≥50% of the prescribed ICS dose at V2 if background therapy withdrawal completed)
- Requiring use of systemic (oral and/or parenteral) steroid treatment

b If the patient meets none of the three criteria listed above and meets one or both of the following:
- A 30% or greater reduction from baseline in morning PEF on 2 consecutive days
- Requiring Hospitalization or emergency room visit

The repeated measures analysis will be based on the restricted maximum likelihood method assuming an unstructured covariance to model the within-subject errors. A Kenward-Roger approximation will be used for the denominator degree of freedom. Descriptive statistics including number of patients, mean, standard error, and least squares (LS) means will be provided for each treatment group. Difference in LS means and the corresponding two-sided 95% CI and p-value will be provided for each pairwise treatment comparison. Sample SAS code can be found below:

```
proc mixed data=fev1data method=reml;
  class usubjid trt01pn sex cntygr1 eosbgp1n icsgrp avisitn;
  model chg = trt01pn sex hgtbl cntygr1 eosbgp1n icsgrp avisitn
              trt01pn*avisitn base base*avisitn /ddfm=kr residual;
  repeated avisitn / subject=usubjid type=un;
  lsmeans trt01pn*avisitn / pdiff cl;
  ods output LSMeans=LSMeans Diffs=Diffs;
run;
```

If the above model fails to converge, the specification may be changed as follows: 1) use maximum likelihood estimation instead of restricted maximum likelihood method; 2) specify a different covariance structure to reduce the number of unknown parameters to be estimated, the path will be UN→TOEPH→TOEP→AR(1).

Sensitivity analysis

The following sensitivity analyses will be conducted to assess the robustness of the main model:

Analyses using the same MMRM model and estimation methods as specified above:

- *Sensitivity analysis 1:* Inclusion of all FEV1 measurements collected up to EOT for all patients. Missing data will not be imputed.

- *Sensitivity analysis 2: Per protocol analysis*

Exclusion of post-baseline FEV1 measurements in patients (and within time windows) where the patient had a protocol deviation considered to have a potential impact on efficacy, ie, (1) intake of a prohibited medication(s); (2) IMP and/or required background therapy non-compliance; (3) entry criteria violation. Deviations will be medically/clinically reviewed during the study, with final classification made and recorded prior to database lock. Missing data will not be imputed.

Analyses with imputation for missing FEV1:

- *Sensitivity analysis 3:Multiple imputation*

  Missing pre-BD/post-BD FEV1 values will be imputed multiple times using a regression model. Imputation will be conducted sequentially as the imputation for each visit will incorporate information from prior visits. Specifically, the covariates to be included are treatment group, gender, baseline height, baseline eosinophil strata, region, background ICS dose level at randomization, baseline value, and change from baseline in FEV1 at all prior visits. Forty imputations will be performed. For each imputation, the change from baseline in pre-BD/post-BD FEV1 at Week 12 will be analyzed by an ANCOVA model with treatment, gender, height, baseline value, baseline eosinophil strata, region, and background ICS dose level at randomization as covariates. Valid statistical inference will be generated by combining results from these 40 analyses using Rubin's rule.

- *Sensitivity analysis 4: Control-based multiple imputation*

  This approach assumes that after treatment discontinuation, patients from the active treatment groups will exhibit the same future evolution as those in the placebo group. The implementation is similar to that of the standard multiple imputation approach above (sensitivity analysis 3), except when fitting the imputation model, only data from the placebo group will be used and treatment will not be included as a covariate.

Technical details are provided in Appendix H.

Subgroup analysis

Subgroup analyses of change from baseline in pre-BD and post-BD FEV1 will be conducted in the same subgroups as defined for the primary endpoint based on the primary analysis method for the secondary endpoints. Within each subgroup, descriptive statistics including number of patients, mean, standard error, and LS means will be provided for each treatment group. Difference in LS means and the corresponding two-sided 95% CI will be provided for each pairwise treatment comparison.

Treatment-by-subgroup interaction at Week 12 and its p-value will be derived from a MMRM model. The model will include change from baseline in FEV1 values up to week 12 following the rules in Table 5. Treatment, gender, baseline height, baseline eosinophil strata, region, background ICS dose level at randomization, visit, treatment by-visit interaction, baseline value, baseline-by-visit interaction, subgroup (if different from the aforementioned covariates), subgroup-by-treatment interaction and subgroup-by-treatment-by-visit interaction will be the covariates.

2.4.4.3 Multiplicity issues

No adjustments for multiplicity are planned for this Phase 2a study. More specifically, no adjustments will be made in comparing the multiple treatment groups based on the primary and secondary efficacy endpoints and no adjustments will be made for the subgroup analyses.

2.4.4.4 Additional efficacy analysis(es)

2.4.4.4.1. Change from baseline analysis in other continuous endpoints

Change from baseline in AM/PM PEF, FVC, FEF 25%-75%, ACQ-5 score, AQLQ(S) domain scores, AQLQ(S) overall score, RQLQ(S) domain scores, RQLQ(S) overall score, AM/PM asthma symptom score, number of nocturnal awakenings, and number of inhalations/day of albuterol or levalbuterol for symptom relief will be analyzed using the MMRM approach described above. Inclusion of data will follow the rules listed in Table 5. The covariates will be treatment, baseline eosinophil strata, region, background ICS dose level at randomization, visit, treatment-by-visit interaction, baseline value and baseline-by-visit interaction. Gender and height will also be included in the model for spirometry endpoints. No imputation will be performed on missing values.

Descriptive statistics including number of patients, mean, standard error, and LS means will be provided for each treatment group. Difference in LS means and the corresponding 95% CI and p-value will be provided for each pairwise treatment comparison.

A responder analysis will also be performed for ACQ-5 and AQLQ(S) endpoints, where responder status is determined based only on data included according to the rules in Table 5. A logistic regression model will be used to compare the percentage of patients reaching the MCID (responders) at Weeks 4, 8, and 12 for ACQ-5 and AQLQ(S) overall scores. For ACQ-5, a patient is considered as a responder if change from baseline in ACQ-5 is ≤ -0.5, or as a non-responder if change from baseline is > 0.5 or missing. For AQLQ(S), a patient is considered as a responder if change from baseline in AQLQ(S) global score is ≥ 0.5, or as a non-responder if change from baseline is < 0.5 or missing.

At each time point, the model will include treatment, baseline score, baseline eosinophil strata, region and background ICS dose level at randomization. Odds ratio, the corresponding 95% CI and p-value will be derived for each pairwise treatment comparison. Descriptive statistics including number and percentage of responders will also be provided.

2.4.4.4.2. CompEx

Time to CompEx will be analyzed in an exploratory fashion using the same Cox model described in Section 2.4.4.1.

2.4.5 Analyses of safety data

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

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:

- Safety data in patients who do not belong to the safety population will be listed separately
- The baseline value is defined as the last available value prior to the first dose of the IMP
- The potentially clinically significant abnormality (PCSA) values are defined as abnormal values considered medically important by the Sponsor according to predefined criteria/thresholds based on literature review and defined by the Sponsor for clinical laboratory tests, vital signs, and ECG (PCSA version dated May 2014, see Appendix A)
- PCSA criteria will determine which patients had at least 1 PCSA during the treatment-emergent adverse event period, taking into account all evaluations performed during the treatment-emergent adverse event period, including nonscheduled or repeated evaluations. The number of all such patients will be the numerator for the on-treatment PCSA percentage
- The treatment-emergent PCSA denominator by group for a given parameter will be based on the number of patients assessed for that given parameter in the TEAE period by treatment group 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 group. Summaries will include the endpoint value. The endpoint value is defined as the value collected at or just prior to the last dose date + 14 days, or at end of treatment visit, whichever comes later. If this value is missing, this endpoint value will be the closest value prior to the last dose intake. The worst value is defined as the nadir and/or the peak post-baseline (up to last administration of IMP) according to the direction (minimum or maximum) of the abnormality as defined in the PCSA list
- The analysis of the safety variables will be essentially descriptive and no systematic testing is planned.

All safety values including unscheduled measurements will be assigned to the appropriate safety analysis visit window defined in Section 2.5.4.

2.4.5.1 Analyses of adverse events

Generalities

The primary focus of adverse event reporting will be on TEAEs. Pre-treatment and post-treatment 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, treatment-emergent, or post-treatment. 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 or post-treatment. Details on classification of adverse events with missing or partial onset dates are provided in Section 2.5.3.

Adverse event incidence tables will present the number (n) and percentage (%) of patients experiencing an event by treatment group. Multiple occurrences of the same event in the same patient will be counted only once in the tables within a treatment phase. The denominator for computation of percentages is the safety population within each treatment group. Sorting will be based on results for the SAR440340 and dupilumab coadministration group by the following orders:

- Tables presented by SOC: sorted by internationally agreed SOC order
- Tables presented by PT: sorted by decreasing frequency of PT
- Tables presented by SOC and PT: sorted by internationally agreed SOC order and decreasing frequency of PT within SOC
- Tables presented by SOC, HLGT, HLT, and PT: sorted by internationally agreed SOC order and then alphabetical order of HLGT, HLT, and PT

Analysis of all TEAEs

The following TEAE summaries will be generated for the safety population.

- Overview of TEAE, summarizing number (%) of patients with any
  - TEAE
  - Severe TEAE
  - Serious TEAE
  - TEAE leading to death
  - TEAE leading to permanent treatment discontinuation
- All TEAEs by primary SOC
- All TEAEs by primary SOC, HLGT, HLT, and PT
- All TEAEs by primary SOC and PT
- All TEAEs by PT
- All TEAEs related to SAR440340 or matching placebo by primary SOC, HLGT, HLT and PT
- All TEAEs related to dupilumab or matching placebo by primary SOC, HLGT, HLT and PT
- All TEAEs by maximal severity, presented by primary SOC and PT
- Listing of all TEAEs

Analysis of all treatment emergent SAEs

- All treatment-emergent SAEs by primary SOC, HLGT, HLT, and PT
- All treatment-emergent SAEs by primary SOC and PT
- All treatment-emergent SAEs by PT

- All treatment-emergent SAEs related to SAR440340 or matching placebo by primary SOC, HLGT, HLT and PT
- All treatment-emergent SAEs related to dupilumab or matching placebo by primary SOC, HLGT, HLT and PT
- Listing of all treatment-emergent SAEs

Analysis of all TEAEs leading to permanent treatment discontinuation

- All TEAEs leading to permanent treatment discontinuation by primary SOC, HLGT, HLT, and PT
- All TEAEs leading to permanent treatment discontinuation by primary SOC and PT
- All TEAEs leading to permanent treatment discontinuation by PT
- Listing of all TEAEs leading to permanent treatment discontinuation

Analysis of AESI

A summary of number of patients with any TEAE by AESI category (defined by the search criteria in Section 2.1.4.1) will be generated. In addition, for each AESI category the following will be provided:

- All TEAEs by PT
- Overview summary including
  - 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 study drug discontinuation
  - Number (%) of patients with any TEAE related to IMP reported by investigator
  - Number (%) of patients with any TEAE by maximum intensity, corrective treatment, and final outcome
  - Number of TEAE adjusted by the exposure duration

For categories with at least 5 events in at least one treatment group, K-M plots of time to first event will be provided to depict the course of onset over time.

Analysis of pre-treatment and post-treatment adverse events

Listings will be provided for all pre- and post-treatment AEs. The following summaries may be generated if the number of events is large enough:

- All pre-treatment AEs by primary SOC and PT

- All pre-treatment SAEs by primary SOC and PT
- All pre-treatment AEs leading to treatment discontinuation by primary SOC and PT
- All pre-treatment AEs leading to death by primary SOC and PT
- All post-treatment AEs by primary SOC and PT
- All post-treatment SAEs by primary SOC and PT
- All post-treatment AEs leading to death by primary SOC and PT

2.4.5.2 Deaths

The following summaries of deaths will be generated for the safety population depending on the overall incidence.

- Number (%) of patients who died by study period (on-study, on-treatment, post-study)
- TEAEs leading to death (death as an outcome on the adverse event case report form page as reported by the Investigator) by primary SOC, HLGT, HLT, and PT
- Listing of all AEs leading to death

In addition, summary of deaths in non-randomized patients or randomized but not treated patients may be generated.

2.4.5.3 Analyses of laboratory variables

The summary statistics (including number, mean, median, Q1, Q3, SD, 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 last on-treatment) by treatment group. For each continuous parameter listed in Section 2.1.4.3, mean changes from baseline with the corresponding standard error will be plotted over time in each treatment group. This section will be organized by biological function as specified in Section 2.1.4.3.

The incidence of PCSAs (list provided in Appendix A) at any time during the TEAE period will be summarized by biological function and treatment group whatever the baseline level and/or according to the following baseline status categories:

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

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

Laboratory measurements obtained at either scheduled or unscheduled visits will be used in analyses of PCSA. In addition, both centralized and local test results will be used. Centralized data will be used preferentially to the local measures in the analysis when several measurements are performed on the same date and at the same time for a given laboratory test.

Listings will be provided with flags indicating the out of range values as well as the PCSA values.

Potential drug-induced liver injury

If there is any imbalance in the incidence of liver-related adverse events across the treatment groups, the following analysis of liver-related adverse events will be performed.

The liver function tests, namely AST, ALT, alkaline phosphatase, and total bilirubin will be used to assess possible drug-induced liver toxicity. The proportion of patients with PCSA values at any post-baseline visit will also be displayed by duration of exposure for each treatment group.

Time to onset of the initial ALT and AST elevation (>3 x ULN) and total bilirubin elevation (>2 x ULN) will be analyzed using Kaplan-Meier estimates presented by treatment group. A graph of distribution of peak values of ALT versus peak values of total bilirubin will also be presented on a logarithmic scale. The graph will be divided into 4 quadrants with a vertical line corresponding to 3 x ULN for ALT and a horizontal line corresponding to 2 x ULN for total bilirubin.

Listings of selected laboratory parameters for possible Hy's law cases identified by treatment group (eg, patients with any elevated ALT>3 x ULN, and associated with an increase in bilirubin ≥2 x ULN) will be provided.

The normalization (to ≤1 x ULN) or return to baseline (if baseline is >ULN) of elevated liver function tests will be summarized by categories of elevation (>3 x ULN, >5 x ULN, >10 x ULN, >20 x ULN for ALT and AST, >1.5 x ULN for alkaline phosphatase, and >1.5 x ULN and >2 x ULN for total bilirubin) with the following categories of normalization: never normalized, normalized despite treatment continuation of IMP, or normalized after IMP discontinuation. A patient will be counted only under the maximum elevation category.

Change in blood eosinophil

Mean changes from baseline in eosinophil count will be summarized and plotted (with corresponding standard error) over time in each treatment group for patients with baseline blood eosinophil < 0.5 Giga/L and patients with baseline blood eosinophil ≥0.5 Giga/L. Number (%) of patients with post-baseline peak blood eosinophil ≥1 Giga/L and < 3 Giga/L, ≥3 Giga/L and < 5 Giga/L, and ≥5 Giga/L will also be summarized in each treatment group and by baseline blood eosinophil status (All, <0.5 Giga/L, ≥0.5 Giga/L).

2.4.5.4 Analyses of vital sign variables

The summary statistics (including number, mean, median, Q1, Q3, SD, minimum and maximum) of all vital signs variables (values and changes from baseline) will be calculated for each visit or study assessment (baseline, each post-baseline time point, and last on-treatment) by treatment group. For all parameters, mean changes from baseline with corresponding standard error will be plotted over time in each treatment group.

The incidence of PCSAs at any time during the TEAE period will be summarized by treatment group irrespective of the baseline level and/or according to the following baseline status categories:

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

Listings will be provided with flags indicating the PCSA values.

2.4.5.5 Analyses of electrocardiogram variables

The summary statistics (including number, mean, median, Q1, Q3, SD, minimum and maximum) of all ECG variables (central laboratory values and changes from baseline) will be calculated for each visit or study assessment (baseline, each post-baseline time point, and last on-treatment) by treatment group. For all parameters, mean changes from baseline with corresponding standard error will be plotted over time in each treatment group.

The incidence of PCSAs at any time during the TEAE period will be summarized by treatment group irrespective of the baseline level and/or according to the following baseline status categories:

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

Listings will be provided with flags indicating the PCSA values.

2.4.6 Analyses of pharmacokinetic and pharmacodynamic variables

2.4.6.1 Analyses of serum concentrations

Serum concentrations will be analyzed in the PK population. Concentrations of SAR440340 will be summarized in SAR440340-treated patients. Concentrations of dupilumab will be summarized in dupilumab-treated patients.

Arithmetic and geometric means, SD, standard error of the mean (SEM), coefficient of variation (CV), minimum, median and maximum per sampling time will be provided. If date and/or time of the drug injection and/or sampling is missing then the concentration will not be taken into account. Concentrations below the lower limit of quantification (LLOQ) will be set to zero for pre-dose samples (Week 0). Other concentrations below LLOQ will be replaced by LLOQ/2. Values will be expressed in the tables with no more than three significant figures.

2.4.6.2 Pharmacodynamics/genomics analyses

PD biomarkers will be analyzed in the safety population. Baseline values will be the last value collected prior to the first IMP.

For all parameters, absolute change from baseline and percent change from baseline will be summarized descriptively (number, arithmetic and geometric means, SD, SEM, CV, median, minimum, and maximum) by treatment group and time point. Values reported as below the LLOQ will be imputed as LLOQ/2.

Summary plots (mean +/- standard error of the mean) of levels, absolute changes from baseline and percent changes from baseline by visit and plot of median percent change (with interquartile range) from baseline by visit will be provided for each biomarker by treatment group.

Exploratory analysis of DNA/RNA will be addressed in a separate document.

2.4.7 Analyses of immunogenicity data

2.4.7.1 Analysis of ADA bioanalytical data

Analyses described in this section will be performed separately for ADA against SAR440340 and ADA against dupilumab in all treatment groups unless otherwise specified.

ADA response categories and titer categories are defined as follows:

- **Pre-existing immunoreactivity:** defined as either an ADA positive response in the assay at baseline with all post first dose ADA results negative, OR a positive response at baseline with all post first dose ADA responses less than 4-fold (for anti-dupilumab) or 9-fold (for anti-SAR440340), over baseline titer levels.
- **Treatment-emergent response:** defined as a positive response in the ADA assay post first dose when baseline results are negative or missing.
- **Treatment-boosted response**: defined as a positive response in the ADA assay post first dose that is greater than or equal to 4-fold (for anti-dupilumab) or 9-fold (for anti-SAR440340) over baseline titer levels, when baseline results are positive.

A treatment-emergent response is further classified as persistent, indeterminate or transient:

  - **Persistent response**: treatment-emergent ADA response detected at 2 or more consecutive ADA positive sampling time points, separated by at least 16-week period (based on nominal sampling time), for both anti-dupilumab and anti-SAR440340, with no ADA negative samples in between.
  - **Indeterminate response**: treatment-emergent response when only the last collected sample is positive.
  - **Transient response**: a treatment-emergent response that is not persistent or indeterminate.

- **ADA positive patients:** patients with treatment-emergent or treatment-boosted response.
- **ADA negative patients:** patients with pre-existing immunoreactivity or negative in the ADA assay at all time points.

Titer values (Titer value category)

- Low (Titer < 1000)
- Moderate (1,000 ≤ Titer ≤ 10,000)
- High (Titer > 10,000)

The following summaries will be provided based on ADA population:

Baseline summary:

- Number (%) of patients with a positive response in the ADA assay at baseline
  - Summary statistics (including number, median, Q1, Q3, minimum, and maximum) of titer for patients with a positive response
- Number (%) of patients with a negative response in the ADA assay at baseline

Post-baseline summary:

- Number (%) of patients with treatment-emergent ADA response
  - Number (%) with persistent response
  - Number (%) with indeterminate response
  - Number (%) with transient response
- Number (%) of patient with treatment-boosted ADA response
- Number (%) of ADA positive patients
- Number (%) of ADA negative patients
- Number (%) of patients with pre-existing immunoreactivity

Listing of all ADA peak titer levels will be provided for treatment emergent and treatment-boosted ADA response patients.

2.4.7.2 Association of immunogenicity with exposure, safety and efficacy

The potential association between key ADA variables (ADA positive, persistent ADA and titer) and exposure, safety and efficacy will be explored.

Possible associations between ADA and PK (exposure)

Associations between key ADA variables and systemic exposure to study drug will be explored by treatment group. The following summaries will be provided:

- Descriptive summary of functional SAR440340 concentrations by anti-SAR440340 antibody patient classification in SAR440340-treated patients at each visit
- Descriptive summary of functional dupilumab concentrations by anti-dupilumab antibody patient classification in dupilumab-treated patients at each visit

In addition, plots of drug concentration may be provided for analyzing the potential impact of ADA on PK.

Possible association between ADA and clinical efficacy

Associations between the key ADA variables and key efficacy endpoints will be explored by treatment group. Plots of efficacy variables may be provided for potential impact of ADA on efficacy.

Possible association between ADA and clinical safety

Association of safety versus key ADA variables will be explored by treatment group. The safety assessment may focus on the following events:

- Injection site reaction (serious or severe and lasting 24 hours or longer)
- Hypersensitivity reactions
- Anaphylactic reactions

2.5 DATA HANDLING CONVENTIONS

2.5.1 General conventions

Demographic formulas

- Age at onset of asthma (years) is calculated as:

  Year of diagnosis of asthma – Year of birth

- Time since first diagnosis of asthma (years) is calculated as:

  (Year of randomization –Year of first diagnosis of asthma) + (month of randomization – month of first diagnosis of asthma)/12

- Time since cessation of smoking (years) is calculated as:

  (Year of randomization – Year of cessation) + (month of randomization – month of cessation) /12

- Time since last asthma exacerbation (months) is calculated as:

  (Year of randomization – Year of last asthma exacerbation)×12 + (month of randomization – month of last asthma exacerbation)

- BMI is calculated as:

  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 (CrCl) value will be derived using the equation of Cockroft and Gault:

$$\text{CLcr (ml/min)} = (140 - \text{age}) \times \text{weight (kg)} \times (1 - 0.15 \times \text{sex (0-M, 1-F)})/$$

$$(0.814 \times \text{creatinine } (\mu\text{mol/l}))$$

CLcr will be calculated using the last weight measurement on or before the visit of the creatinine measurement and age at the lab sampling date. Here age is calculated as following:

Integer part of (Lab sampling date – Date of screening visit)/365.25

+ Age at screening visit

2.5.2 Data handling conventions for other efficacy variables

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

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 6. First IMP administration is used as the reference day (Day 1).

Table 6 - Periodical average of daily efficacy assessment

Time point	Morning PEF, asthma symptom score, number of awakenings	Evening PEF, asthma symptom score	Number of inhalations/day of salbutamol/albuterol or levosalbutamol/levalbuterol
Day 8	2-8	1-7	Diary Day 1-7
Day 15	9-15	8-14	Diary Day 8-14
Day 22	16-22	15-21	Diary Day 15-21
Day 29	23-29	22-28	Diary Day 22-28
Day 36	30-36	29-35	Diary Day 29-35
Day 43	37-43	36-42	Diary Day 36-42
Day 50	44-50	43-49	Diary Day 43-49
Day 57	51-57	50-56	Diary Day 50-56
Day 64	58-64	57-63	Diary Day 57-63
Day 71	65-71	64-70	Diary Day 64-70
Day 78	72-78	71-77	Diary Day 71-77
Day 85	79 - (Day of EOT)	78 - (Day before EOT)	Diary Day 78 - (Day before EOT)

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 of adverse events

If the severity is missing for one 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

Visit windows based on days relative to the first IMP administration will be used to map the efficacy parameters (Table 7), selected safety variables (Table 8) and PK/PD variables (Table 9) to each scheduled visit. Date of randomization will be used as the reference date for patients not treated. The following rules will be applied:

1. For efficacy parameters, only scheduled measurements will be considered. If a patient has more than one measurement for the same parameter at different dates within the same visit window, the one that is closest to the target date will be used (or the latest in case of tie).
2. Only values from the central laboratory will be considered for laboratory variables.
3. For the same laboratory/vital sign/ECG/PK/PD parameter, if a patient has more than one measurement at different dates within the same visit window, the scheduled measurement that is closest to the target date will be used (or the latest in case of tie). If there is no scheduled measurement within the visit window, the unscheduled measurement that is closest to the target date will be used (or the latest in case of tie).
4. When a patient has more than one measurement on the same laboratory/vital sign/ECG/PK/PD parameter on the same date, then the one with the later/largest sample ID will be used.
5. For procedures planned on Visit 2, if it is done on the same date as the first IMP but the performance time is missing, it will be assigned to the Visit 2 time window.

Table 7 – Time window for efficacy endpoints

Visit Label	Target Day	Pre-BD spirometry	Post-BD spirometry	ACQ-5	AQLQ(S), RQLQ(S)
Baseline	≤1	≤1	≤1	≤1	≤1
Week 1	8	2-11			
Week 2	15	12-18		2-21	2-21
Week 3	22	19-25			
Week 4	29	26-32	2-35	22-35	22-35
Week 5	36	33-39			
Week 6	43	40-46	36-49	36-49	36-49
Week 7	50	47-53			
Week 8	57	54-60	50-63	50-63	50-63
Week 9	64	61-67			
Week 10	71	68-74	64-77	64-77	64-77
Week 11	78	75-81			
Week 12	85	82-112	78-112	78-112	78-112
Week 20	141	113-182	113-182	113-182	113-182
Week 32	225	≥183	≥183	≥183	≥183

Table 8 – Time window for safety endpoints

Visit Label	Target Day	Vital signs[a]	Weight	Height	ECG	Hamatology, biochemistry, urinalysis	Heptitis and HIV serology tests, quantiferon gold testing, serum pregnancy test	Urine pregnancy test
Baseline	1	≤1	≤1	≤1	≤1	≤1	≤1	≤1
Week 1	8	2-11						
Week 2	15	12-18						
Week 3	22	19-25						
Week 4	29	26-32			2-56	2-42		2-42
Week 5	36	33-39						
Week 6	43	40-46						
Week 7	50	47-53						
Week 8	57	54-60				43-70		43-70
Week 9	64	61-67						
Week 10	71	68-74						
Week 11	78	75-81						
Week 12	85	82-112	≥2		57-154	71-112		71-154
Week 20	141	113-182				113-182		
Week 32	225	≥183			≥155	≥183		≥155

a Except for weight and height

Table 9 – Time window for PK/PD endpoints

Visit Label	Target Day	Serum SAR440340/ dupilumab concentration	Anti-drug anti-body	Blood eosinophil /neutrophil	FeNO	Total IL33, sST2, calcitonin	PARC, eotaxin-3	Total IgE, periostin
Baseline	1	≤1	≤1	≤1	≤1	≤1	≤1	≤1
Week 1	8							
Week 2	15	2-21		2-21	2-21			
Week 3	22							
Week 4	29	22-42		22-35	22-42	2-42	2-42	2-56
Week 5	36							
Week 6	43			36-49				
Week 7	50							
Week 8	57	43-70		50-70	43-70	43-70	43-70	
Week 9	64							
Week 10	71							
Week 11	78							
Week 12	85	71-112	2-154	71-112	71-112	71-112	≥71	≥57
Week 20	141	113-182		113-182	113-182	113-182		
Week 32	225	≥183	≥155	≥183	≥183	≥183		

2.5.5 Unscheduled visits

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

2.5.6 Pooling of centers for statistical analyses

Due to small sample size in some countries, the countries will be pooled into regions as defined below for the analyses:

- East Europe: Poland, Russia, Turkey and Ukraine
- Latin America: Argentina, Chile and Mexico
- North America: USA

2.5.7 Statistical technical issues

Not applicable.

3 INTERIM ANALYSIS

No formal interim analysis is planned. Analyses will be performed for safety/efficacy monitoring and internal decision making. The analyses will be conducted by individuals independent of the study and the development program and reviewed by an independent Data Monitoring Committee (DMC). No formal stopping rules or adjustment for multiplicity will be applied. Full details on DMC procedures and data to be reviewed are described in the DMC charter.

4 DATABASE LOCK

A core database lock is planned to occur approximately 4 weeks after all patients have completed End of Treatment visit. The final database is planned to be locked 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. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardization of spirometry. Eur Resir J. 2005 Aug;26(2):319-38.

2. 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 Jan;47(1):81-7.

3. Juniper EF, Guyatt GH, O'Byrne PM, Viveiros M. Aqueous beclomethasone dipropionate nasal spray "regular" versus "as required" use in the treatment of seasonal allergic rhinitis. J Allergy Clin Immunol. 1990 Sep; 86(3 Pt 1):380-6.

4. Fuhlbrigge AL, Bengtsson T, Peterson S, Jauhiainen A, Eriksson G, Da Silva CA, et al. A novel endpoint for exacerbations in asthma to accelerate clinical development: a post-hoc analysis of randomised controlled trials. Lancet Respir Med. 2017 Jul;5(7):577-90.

7 LIST OF APPENDICES

Appendix A: Potentially clinically significant abnormalities (PCSA) criteria

Appendix B: Asthma Symptom Score Numerical Rating Scale (NRS)

Appendix C Asthma Control Questionnaire (ACQ) 5-Question version

Appendix D: Asthma Quality of Life Questionnaire

Appendix E: Standardized Rhinoconjunctivitis Quality of Life Questionnaire RQLS(S)

Appendix F: List of opportunistic infections

Appendix G Definition of Anaphylaxis

Appendix H Technical details of sensitivity analysis

Appendix A Potentially clinically significant abnormalities criteria

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES
for phase 2/3 studies (oncology excepted)
(From BTD-009536 "Analysis and reporting of safety data from clinical trials through the Clinical Study Report" Version 3, 21-MAY-2014)

Parameter	PCSA	Comments
Clinical Chemistry		
ALT	By distribution analysis : >3 ULN >5 ULN >10 ULN >20 ULN	Enzymes activities must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007. Internal DILI WG Oct 2008. Categories are cumulative. First row is mandatory. Rows following one mentioning zero can be deleted.
AST	By distribution analysis : >3 ULN >5 ULN >10 ULN >20 ULN	Enzymes activities must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007. Internal DILI WG Oct 2008. Categories are cumulative. First row is mandatory. Rows following one mentioning zero can be deleted.
Alkaline Phosphatase	>1.5 ULN	Enzymes activities must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007. Internal DILI WG Oct 2008.
Total Bilirubin	>1.5 ULN >2 ULN	Must be expressed in ULN, not in µmol/L or mg/L. Categories are cumulative. Concept paper on DILI – FDA draft Guidance Oct 2007. Internal DILI WG Oct 2008.
Conjugated Bilirubin	>35% Total Bilirubin and TBILI>1.5 ULN	Conjugated bilirubin dosed on a case-by-case basis.
ALT and Total Bilirubin	ALT>3 ULN and TBILI>2 ULN	Concept paper on DILI – FDA draft Guidance Oct 2007. Internal DILI WG Oct 2008. To be counted within a same treatment phase, whatever the interval between measurement.

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES

for phase 2/3 studies (oncology excepted)

(From BTD-009536 "Analysis and reporting of safety data from clinical trials through the Clinical Study Report" Version 3, 21-MAY-2014)

Parameter	PCSA	Comments
CPK	>3 ULN >10 ULN	FDA Feb 2005. Am J Cardiol April 2006. Categories are cumulative. First row is mandatory. Rows following one mentioning zero can be deleted.
CLcr (mL/min) (Estimated creatinine clearance based on the Cokcroft-Gault equation)	<15 (end stage renal disease) ≥15 - <30 (severe decrease in GFR) ≥30 - < 60 (moderate decrease in GFR) ≥60 - <90 (mild decrease in GFR) ≥ 90 (normal GFR)	FDA draft Guidance 2010 Pharmacokinetics in patients with impaired renal function-study design, data analysis, and impact on dosing and labeling
eGFR (mL/min/1.73m2) (Estimate of GFR based on an MDRD equation)	<15 (end stage renal disease) ≥15 - <30 (severe decrease in GFR) ≥30 - < 60 (moderate decrease in GFR) ≥60 - <90 (mild decrease in GFR) ≥ 90 (normal GFR)	FDA draft Guidance 2010 Pharmacokinetics in patients with impaired renal function-study design, data analysis, and impact on dosing and labeling
Creatinine	≥150 µmol/L (Adults) ≥30% change from baseline ≥100% change from baseline	Benichou C., 1994.
Uric Acid Hyperuricemia Hypouricemia	 >408 µmol/L <120 µmol/L	Harrison- Principles of internal Medicine 17th Ed., 2008.
Blood Urea Nitrogen	≥17 mmol/L	
Chloride	<80 mmol/L >115 mmol/L	
Sodium	≤129 mmol/L ≥160 mmol/L	
Potassium	<3 mmol/L ≥5.5 mmol/L	FDA Feb 2005.
Total Cholesterol	≥7.74 mmol/L	Threshold for therapeutic intervention.
Triglycerides	≥4.6 mmol/L	Threshold for therapeutic intervention.
Lipasemia	≥3 ULN	
Amylasemia	≥3 ULN	

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES

for phase 2/3 studies (oncology excepted)

(From BTD-009536 "Analysis and reporting of safety data from clinical trials through the Clinical Study Report" Version 3, 21-MAY-2014)

Parameter	PCSA	Comments
Glucose		
Hypoglycaemia	≤3.9 mmol/L and <LLN	ADA May 2005.
Hyperglycaemia	≥11.1 mmol/L (unfasted); ≥7 mmol/L (fasted)	ADA Jan 2008.
HbA1c	>8%	
Albumin	≤25 g/L	
CRP	>2 ULN or >10 mg/L (if ULN not provided)	FDA Sept 2005.
Hematology		
WBC	<3.0 Giga/L (Non-Black); <2.0 Giga/L (Black) ≥16.0 Giga/L	Increase in WBC: not relevant. To be interpreted only if no differential count available.
Lymphocytes	>4.0 Giga/L	
Neutrophils	<1.5 Giga/L (Non-Black);<1.0 Giga/L (Black)	International Consensus meeting on drug-induced blood cytopenias, 1991. FDA criteria.
Monocytes	>0.7 Giga/L	
Basophils	>0.1 Giga/L	
Eosinophils	>0.5 Giga/L or >ULN (if ULN≥0.5 Giga/L)	Harrison- Principles of internal Medicine 17th Ed., 2008.
Hemoglobin	≤115 g/L (Male); ≤95 g/L (Female) ≥185 g/L (Male); ≥165 g/L (Female) Decrease from Baseline ≥20 g/L	Criteria based upon decrease from baseline are more relevant than based on absolute value. Other categories for decrease from baseline can be used (≥30 g/L, ≥40 g/L, ≥50 g/L).
Hematocrit	≤0.37 v/v (Male) ; ≤0.32 v/v (Female) ≥0.55 v/v (Male) ; ≥0.5 v/v (Female)	
RBC	≥6 Tera/L	Unless specifically required for particular drug development, the analysis is redundant with that of Hb. Otherwise, consider FDA criteria.
Platelets	<100 Giga/L ≥700 Giga/L	International Consensus meeting on drug-induced blood cytopenias, 1991.

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES

for phase 2/3 studies (oncology excepted)

(From BTD-009536 "Analysis and reporting of safety data from clinical trials through the Clinical Study Report" Version 3, 21-MAY-2014)

Parameter	PCSA	Comments
Urinalysis		
pH	≤4.6 ≥8	
Vital signs		
HR	≤50 bpm and decrease from baseline ≥20 bpm ≥120 bpm and increase from baseline≥20 bpm	To be applied for all positions (including missing) except STANDING.
SBP	≤95 mmHg and decrease from baseline ≥20mmHg ≥160 mmHg and increase from baseline ≥20 mmHg	To be applied for all positions (including missing) except STANDING.
DBP	≤45 mmHg and decrease from baseline ≥10 mmHg ≥110 mmHg and increase from baseline ≥10 mmHg	To be applied for all positions (including missing) except STANDING.
Orthostatic Hypotension		
Orthostatic SDB	≤-20 mmHg	
Orthostatic DBP	≤-10 mmHg	
Weight	≥5% increase from baseline ≥5% decrease from baseline	FDA Feb 2007.

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES

for phase 2/3 studies (oncology excepted)

(From BTD-009536 "Analysis and reporting of safety data from clinical trials through the Clinical Study Report" Version 3, 21-MAY-2014)

Parameter	PCSA	Comments
ECG		Ref.: ICH E14 guidance (2005) and E14 Q&A (2012), and Cardiac Safety Research Consortium White Paper on PR and QRS (Nada et al. Am Heart J. 2013; 165(4) : 489-500)
HR	<50 bpm <50 bpm and decrease from baseline ≥20 bpm <40 bpm <40 bpm and decrease from baseline ≥20 bpm <30 bpm <30 bpm and decrease from baseline ≥20 bpm	Categories are cumulative
	>90 bpm >90 bpm and increase from baseline ≥20bpm >100 bpm >100 bpm and increase from baseline ≥20bpm >120 bpm >120 bpm and increase from baseline ≥20 bpm	Categories are cumulative
PR	>200 ms >200 ms and increase from baseline ≥25% > 220 ms >220 ms and increase from baseline ≥25% > 240 ms > 240 ms and increase from baseline ≥25%	Categories are cumulative
QRS	>110 ms >110 msec and increase from baseline ≥25% >120 ms >120 ms and increase from baseline ≥25%	Categories are cumulative
QT	>500 ms	

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES

for phase 2/3 studies (oncology excepted)

(From BTD-009536 "Analysis and reporting of safety data from clinical trials through the Clinical Study Report" Version 3, 21-MAY-2014)

Parameter	PCSA	Comments
QTc	Absolute values (ms)	To be applied to any kind of QT correction formula. Absolute values categories are cumulative
	>450 ms	
	>480 ms	QTc >480 ms and ΔQTc>60 ms are the 2 PCSA categories to be identified in individual subjects/patients listings.
	>500 ms	
	Increase from baseline	
	Increase from baseline]30-60] ms	
	Increase from baseline >60 ms	

Appendix B Asthma Symptom Score Numerical Rating Scale (NRS)

Morning Diary:

Please rate your asthma symptoms since last night

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

Evening Diary:

Please rate your asthma symptoms since this morning

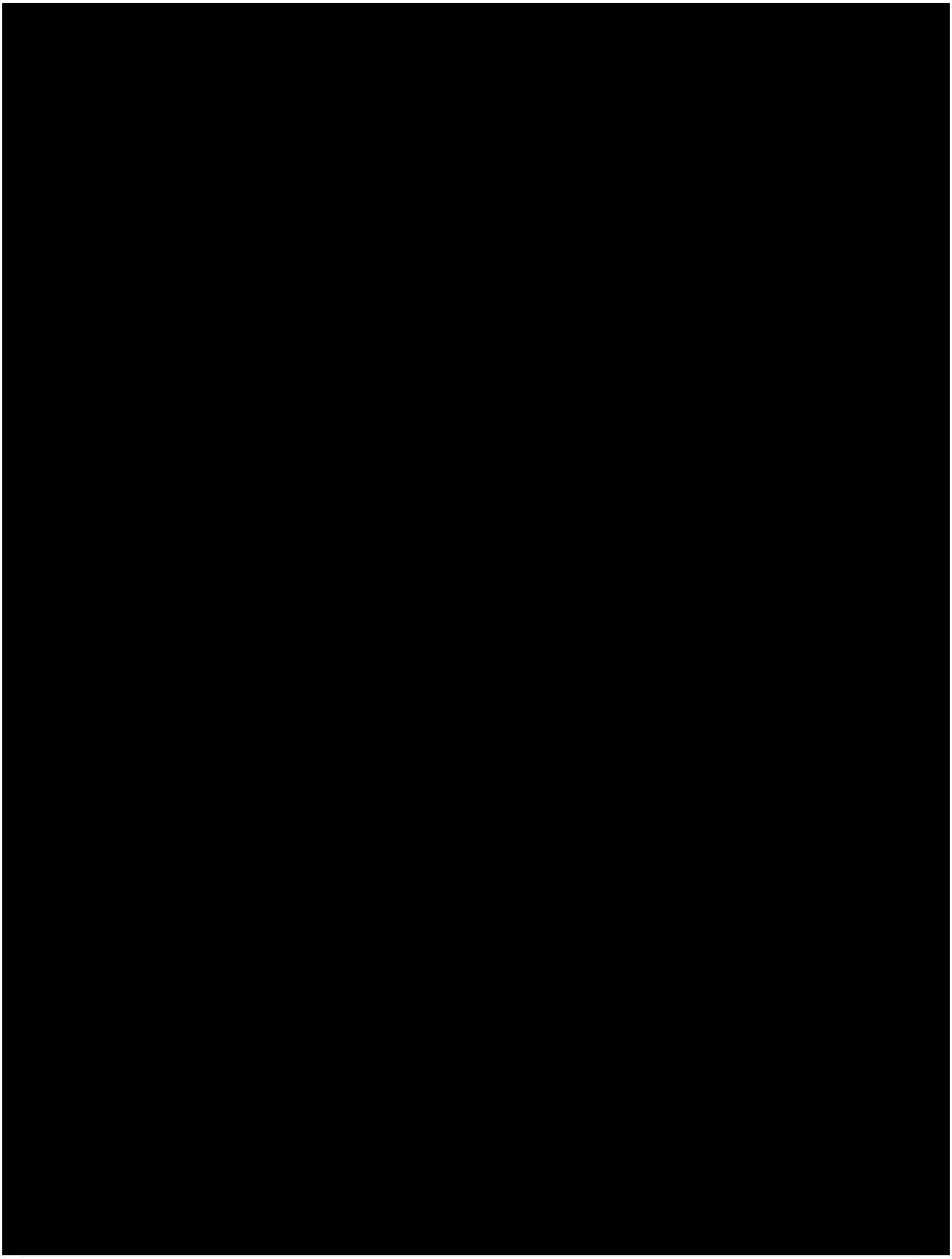
- Very well, no asthma symptoms
- One episode of wheezing, cough, or breathlessness
- More than one episode of wheezing, cough, or breathlessness without interference with normal activities
- Wheezing, cough, or breathlessness most of the day, which interfered to some extent with normal activities
-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

Appendix C Asthma Control Questionnaire 5-Question Version

December 2002

SYMPTOMS ONLY MODIFIED 30 JAN 04

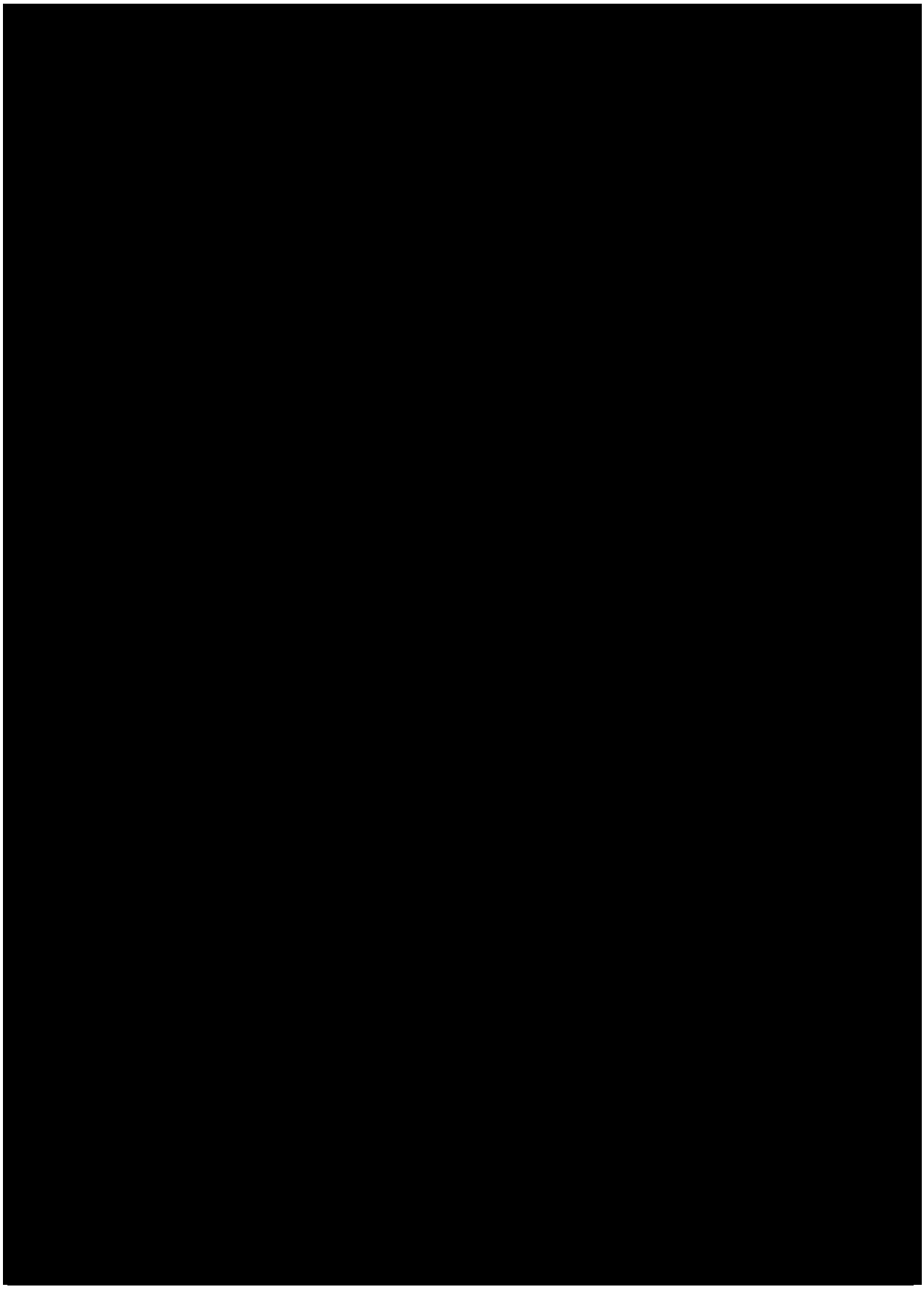
NORTH AMERICAN ENGLISH

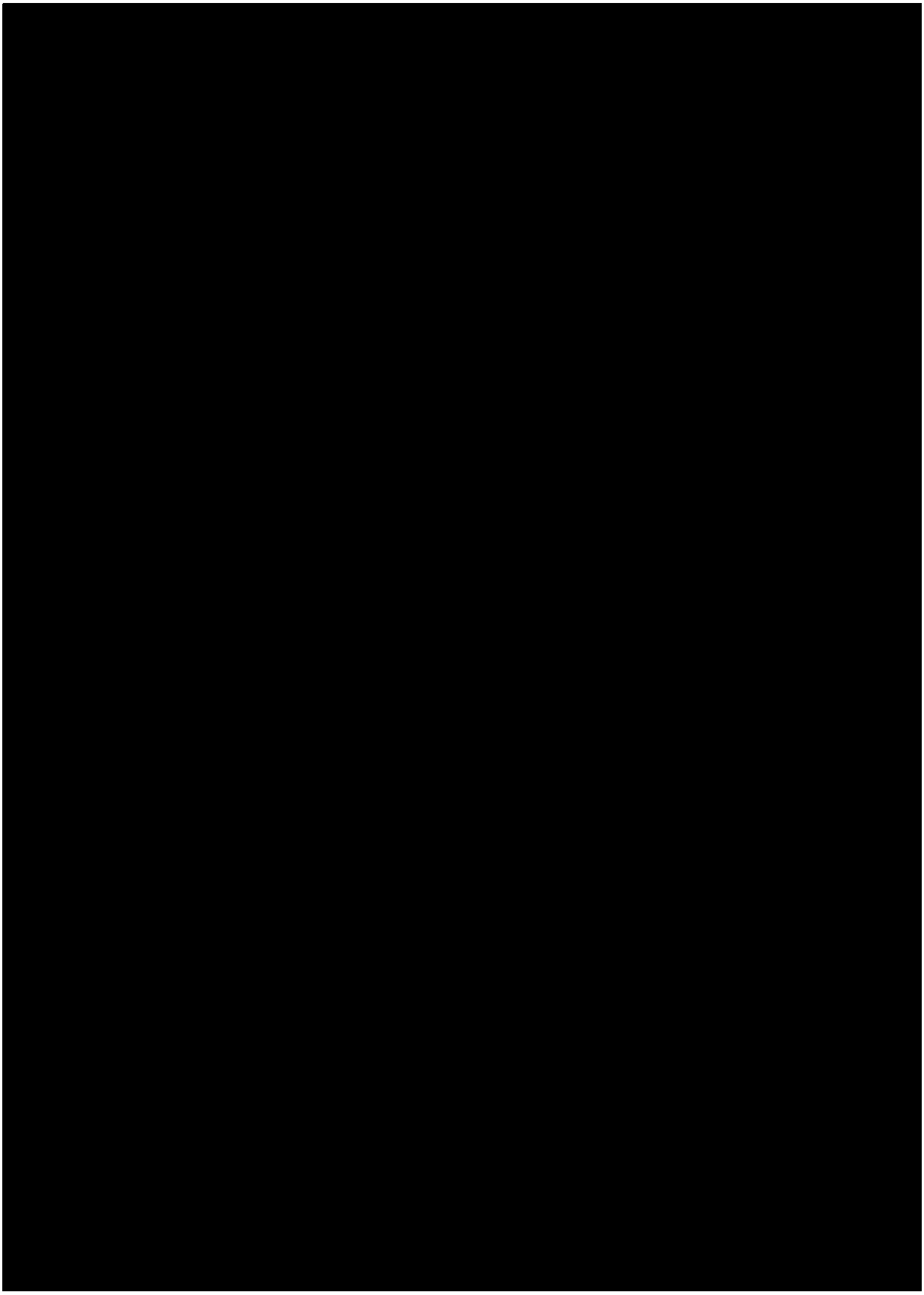


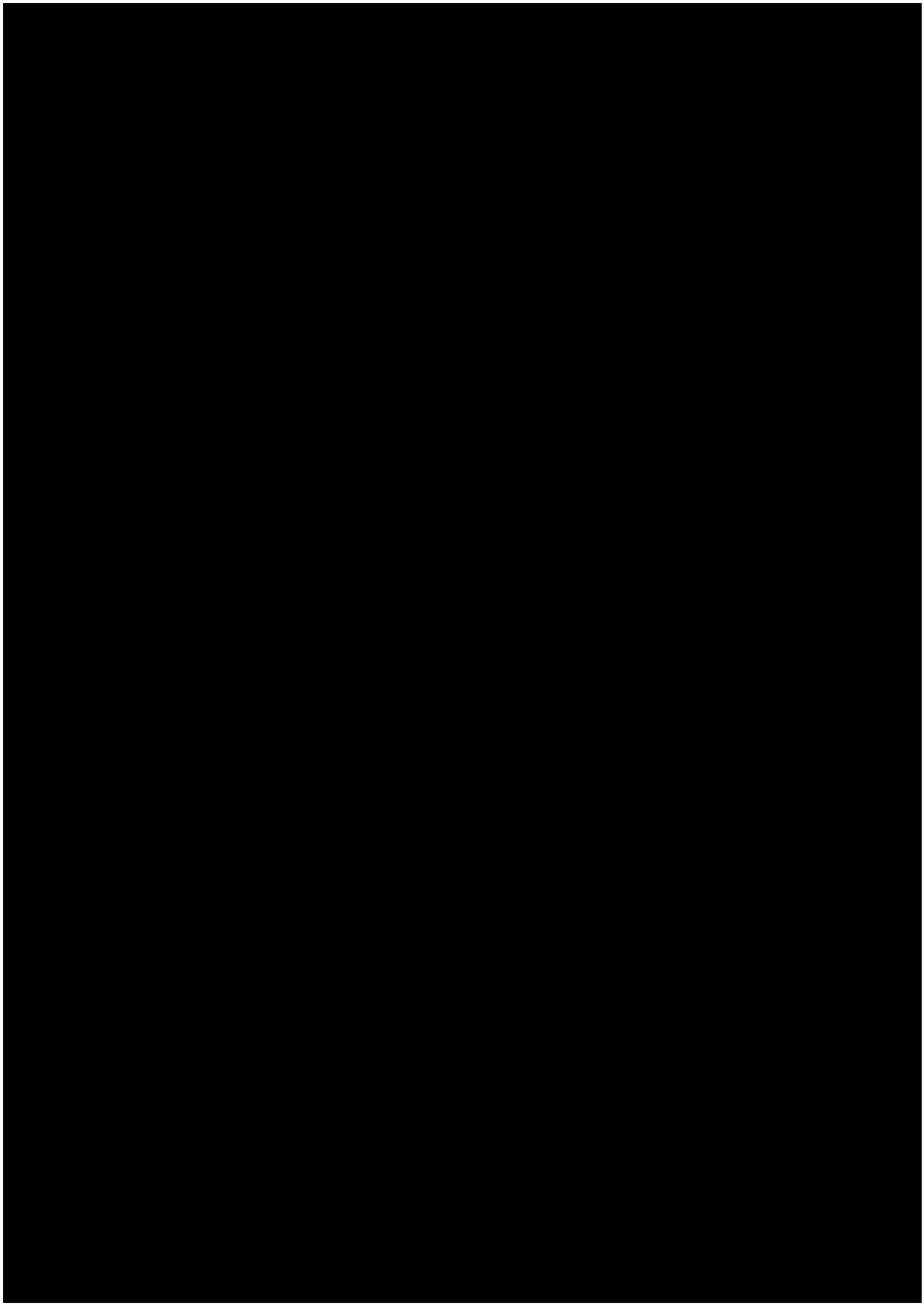
Appendix D Asthma Quality of Life Questionnaire

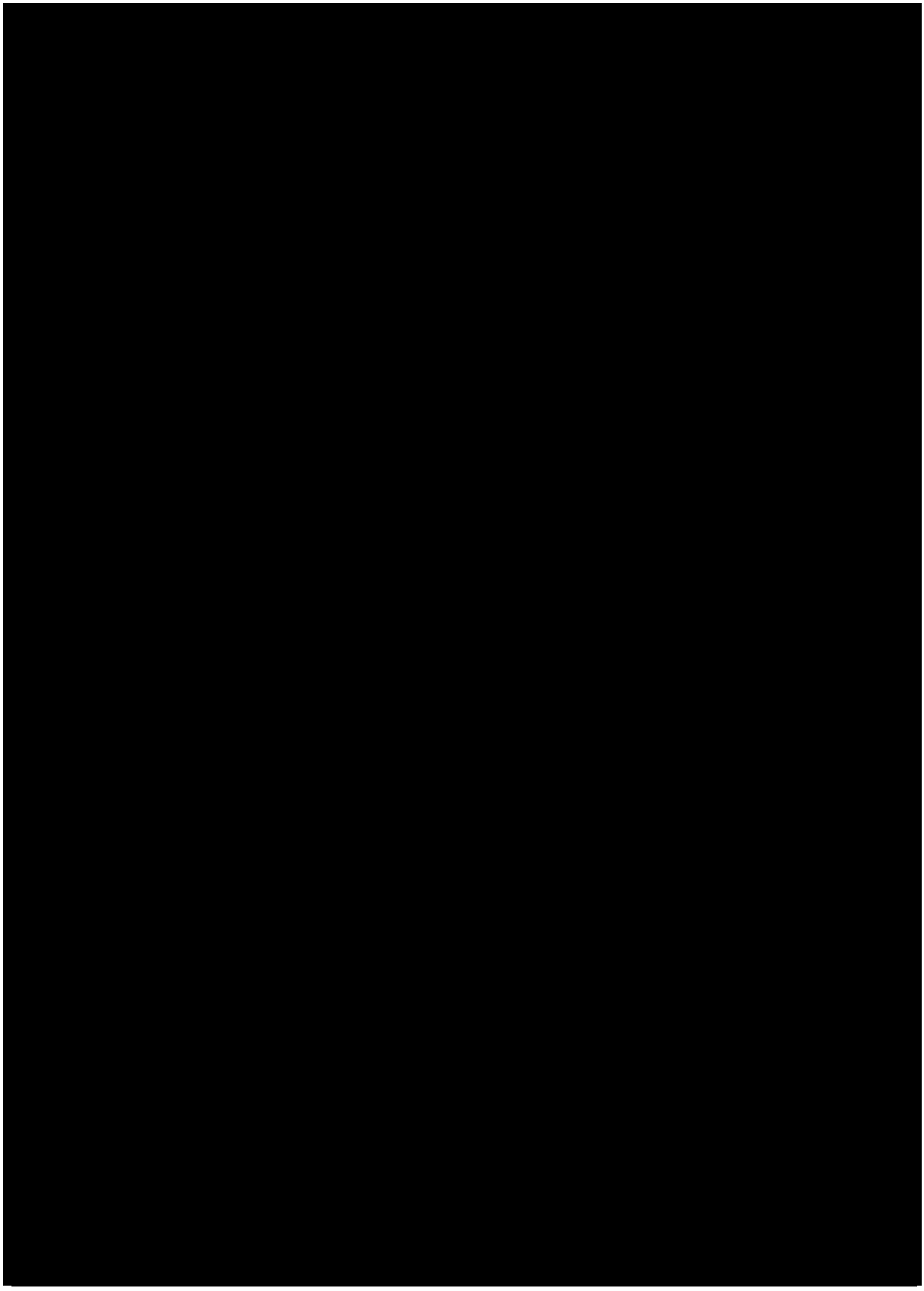
APRIL 2008

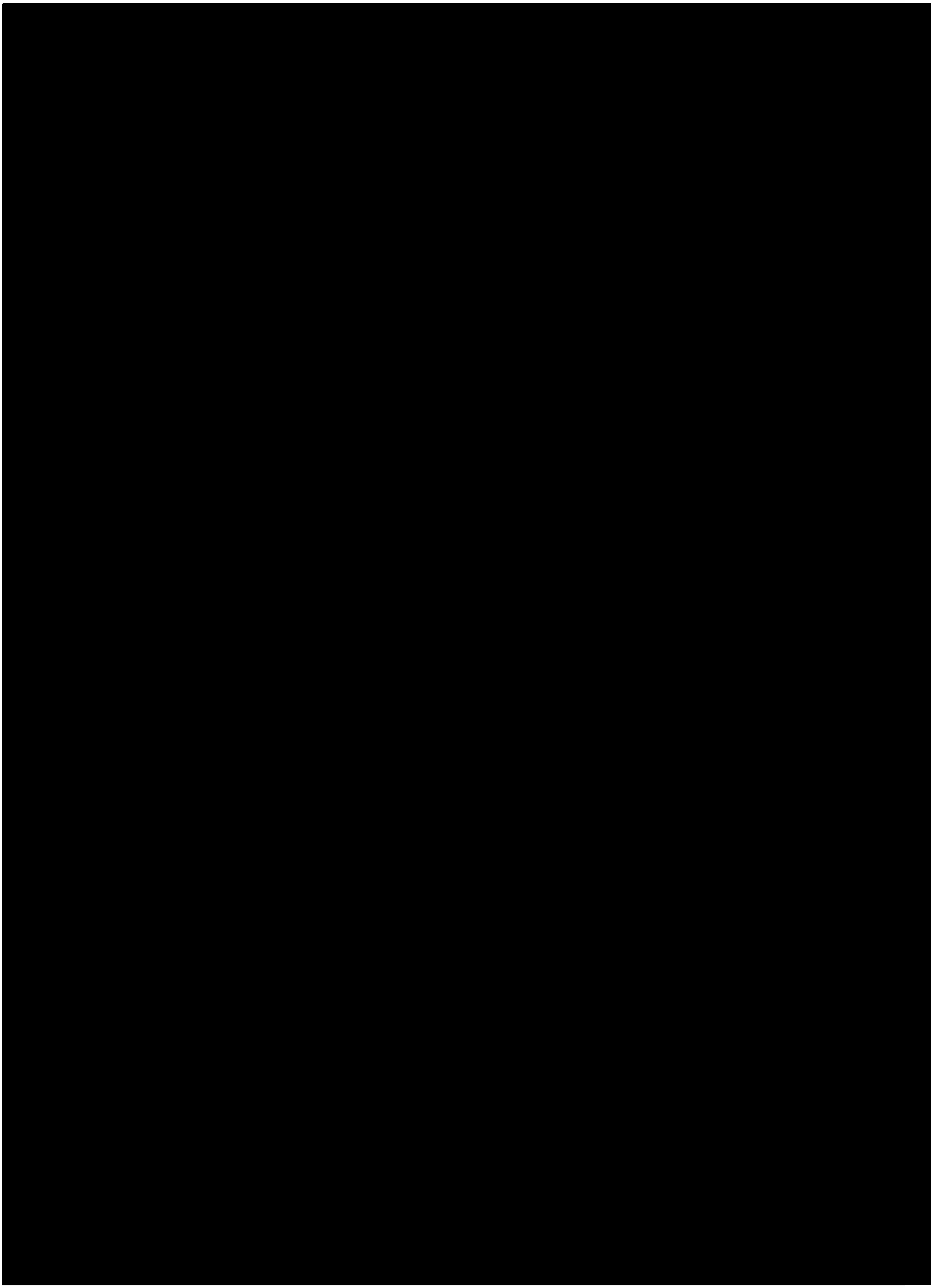
Modified September 2010
AQLQ(S)-SA North American English Version



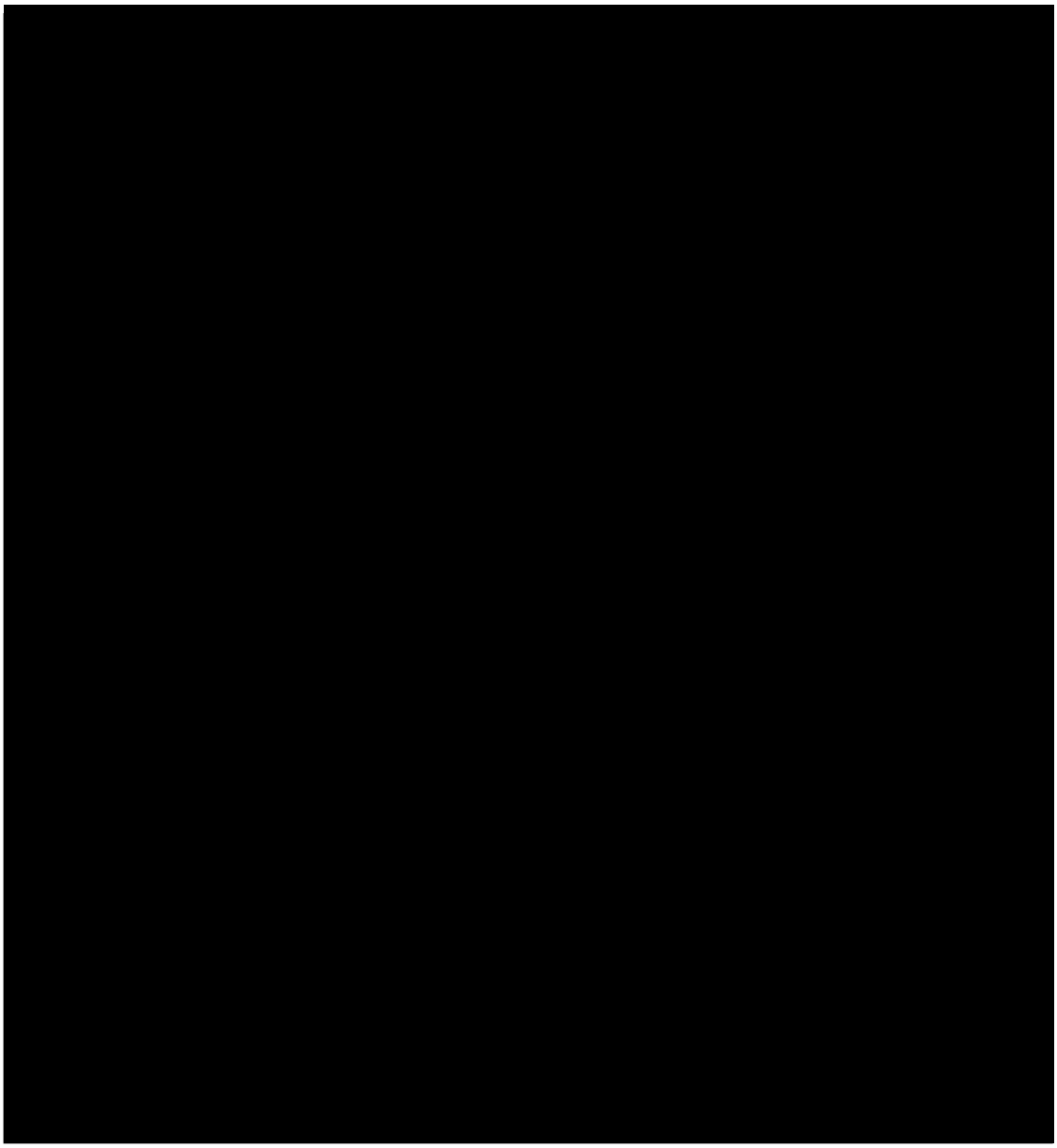








Appendix E Standardized Rhinoconjunctivitis Quality of Life Questionnaire RQLQ(S)



NOVEMBER 2001

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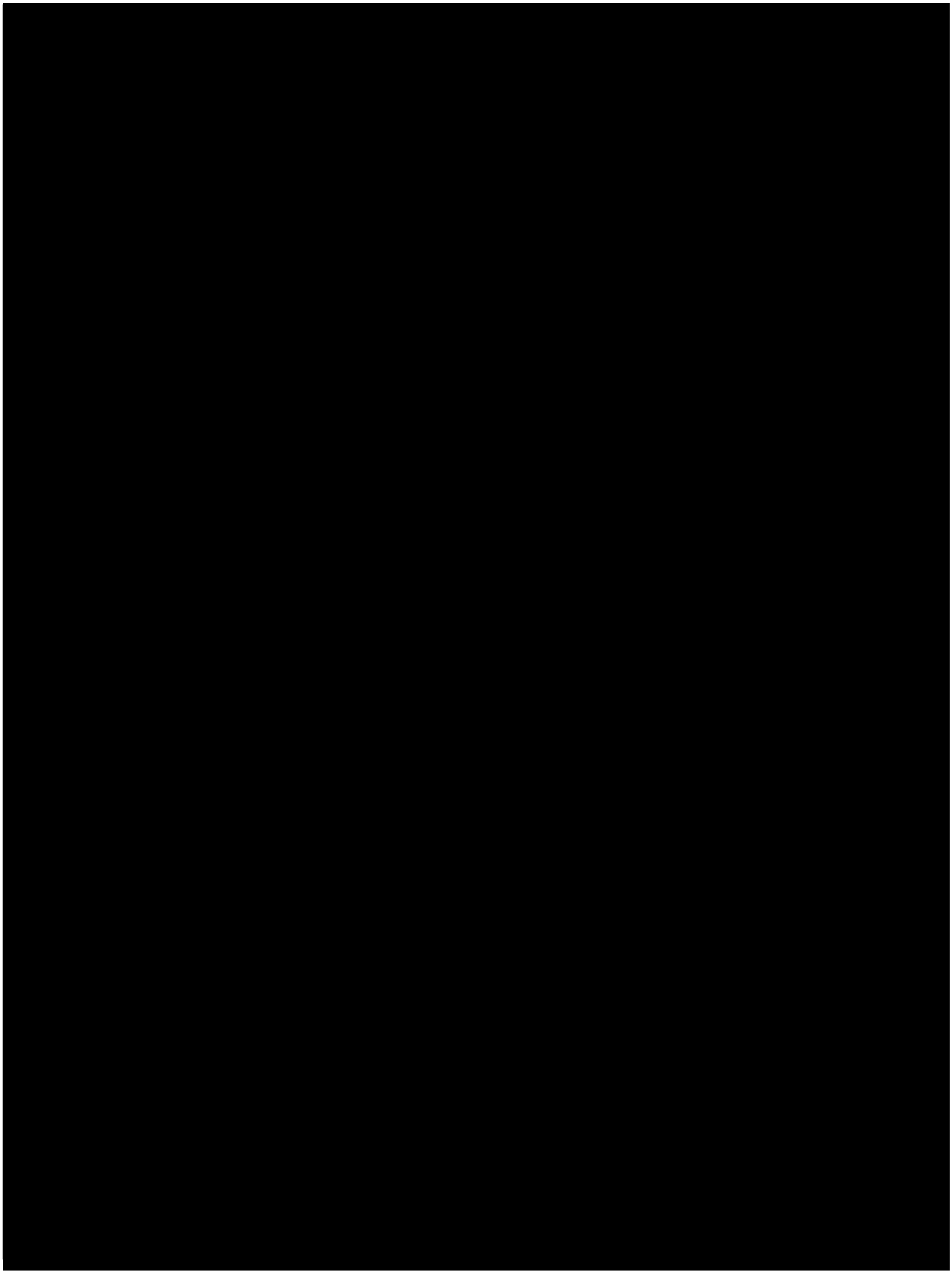

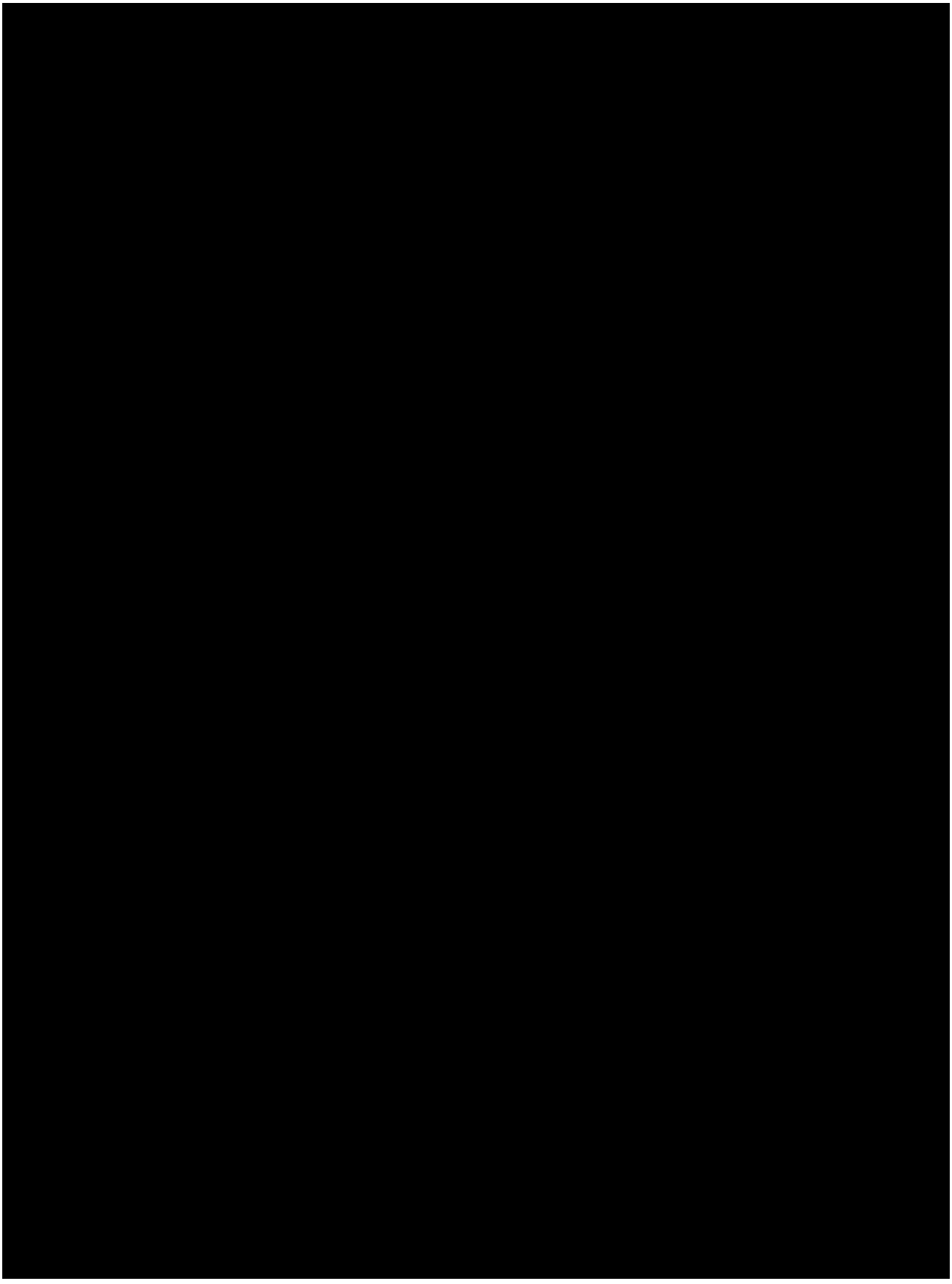

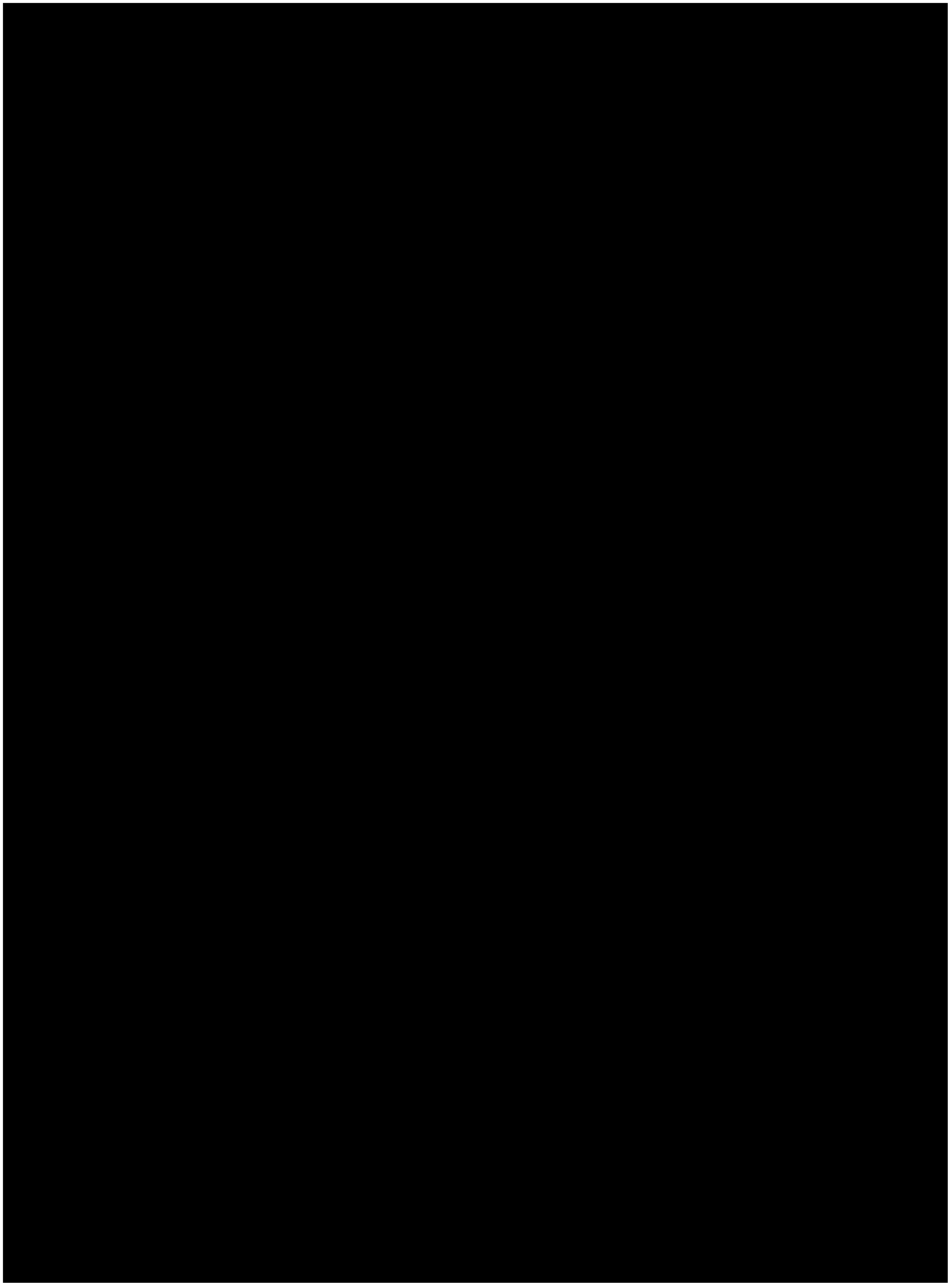

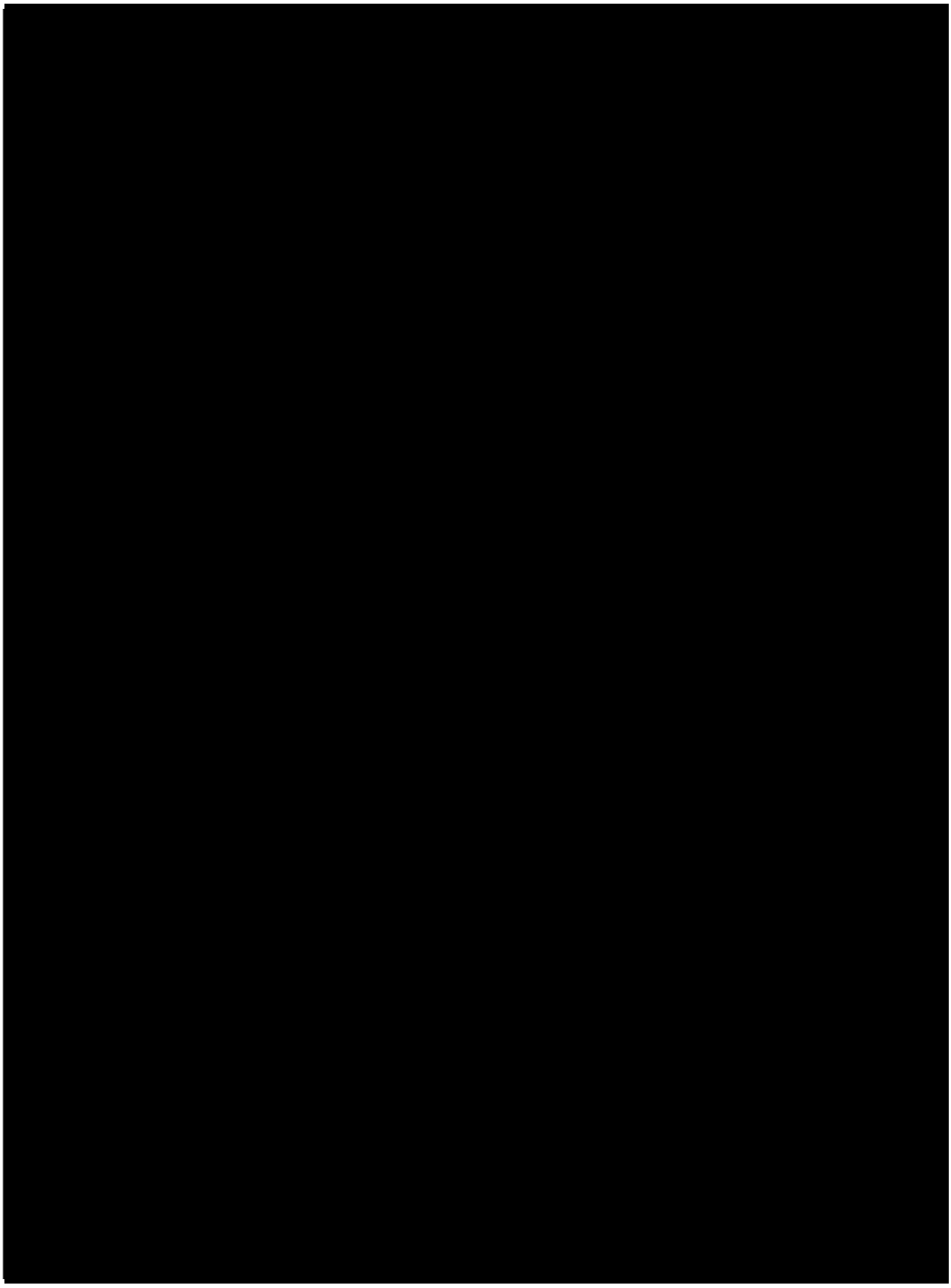

Appendix F List of opportunistic infections

- 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 (severe/disseminated)
- Herpes Zoster
- Histoplasmosis (pulmonary or disseminated; most common tropical areas Tennessee-Ohio-Mississippi river basins)
- Listeriosis
- Mycobacterium avium
- Nontuberculosis mycobacteria
- Pneumocystis pneumonia (PCP)
- Tuberculosis (TB)

This list is indicative and not exhaustive.

Appendix G 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;117:391-7)*

Clinical criteria for diagnosing anaphylaxis

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

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

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

Appendix H Technical details of sensitivity analysis

Change from baseline in FEV1

Multiple imputation

1. Partially impute data using Markov Chain Monte Carlo method to obtain 40 datasets with monotone missing pattern:

```
proc mi data=&DSTIN seed=&seed nimpute=40 out=monotone;
  mcmc impute=monotone;
  var base &chg_all;
run;
```

   where `&chg_all` includes change from baseline in FEV1 at all visits.

2. For each of the imputed dataset with monotone missing pattern, the remaining missing data will be imputed by a regression model

```
proc mi data=monotone seed=&seed nimpute=1 out=data_imp;
  by _imputation_;
  class trt01pn sex eosbgp1n cntygr1 icsgrp;
  var sex hgtbl eosbgp1n cntygr1 trt01pn icsgrp base
&chg_all;
  monotone reg;
run;
```

3. Analyze the 40 imputed datasets by the ANCOVA model described in Section 2.4.4.2:

```
proc glm data=data_imp;
  by _imputation_;
  class trt01pn sex eosbgp1n cntygr1 icsgrp;
  model chg_12 = trt01pn sex hgtbl eosbgp1n cntygr1 icsgrp
base;
  lsmeans trt01pn / stderr;
  estimate "SAR440340 vs Placebo"          trt01pn -1 1 0 0;
  estimate "Coadministration vs Placebo"   trt01pn -1 0 1 0;
  estimate "Coadministration vs SAR440340" trt01pn 0 -1 1 0;
  estimate "Coadministration vs Dupilumab" trt01pn 0 0 1 -1;
  estimate "Dupilumab vs Placebo"          trt01pn -1 0 0 1;
  ods output LSMeans = LSMeans_imp Estimates = Diff_imp;
run;
```

4. Apply Rubin's rule to combine analysis results:

```
proc sort data=LSMeans_imp;
  by trt01pn _imputation_;
```

```
run;

proc mianalyze data=LSMeans_imp;
  by trt01pn;
  modeleffects lsmean;
  stderr stderr;
  ods output ParameterEstimates=LSMeans;
run;

proc mianalyze data= Diff_imp;
  modeleffects estimate;
  stderr stderr;
  ods output ParameterEstimates=LSDiff;
run;
```

Control-based multiple imputation

This approach is similar to the standard method described above, except for Step 2. After obtaining datasets with monotone missing patterns in Step 1, the following steps will be repeated to sequentially impute missing data at each time point:

1) For time point *t*, separate the imputed datasets into two parts: `imp_&t`, containing all placebo patients and those from the active treatment groups that have missing change from baseline in FEV1 at time *t*; and `rest_&t`, containing the rest of the patients from the active treatment groups.
2) Impute missing values at *t* based on the model estimated from placebo group patients:

```
proc mi data=imp_&t seed=&seed.&t nimpute=1
out=imputed_&t;
  by _imputation_;
  class sex eosbgp1n cntygr1 icsgrp;
  var sex hgtbl eosbgp1n cntygr1 icsgrp base
      &chg_prior chg_&t;
  monotone reg (chg_&t);
run;
```

   where `chg_&t` is change from baseline in FEV1 at `t` and `&chg_prior` includes change from baseline in FEV1 at all visits prior to *t*. No prior value will be included when imputing the first post-randomization time point.

3) Combine the imputed data `imputed_&t` with `rest_&t`.

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ELECTRONIC SIGNATURES

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