AMENDED CLINICAL TRIAL PROTOCOL 01

COMPOUND: SAR440340/REGN3500

A randomized, double-blind, placebo-controlled, parallel-group, 12-week Proof-of-Concept (PoC) study to assess the efficacy, safety, and tolerability of SAR440340, and the coadministration of SAR440340 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

STUDY NUMBER: SAR440340-ACT15102

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NAMES AND ADDRESSES OF

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

PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY

Document	Country/countries impacted by amendment	Date, version
Amended Clinical Trial protocol 01	*All*	*[06 Sep 2018], version 1 (electronic 1.0)*
Original Protocol	*All*	*[30 NOV 2017], version 1 (electronic 3.0)*

Amended protocol 01 (06-Sep-2018)

This amended protocol (amendment 01) is considered to be non-substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it neither significantly impacts the safety or physical/mental integrity of participants nor the scientific value of the study.

OVERALL RATIONALE FOR THE AMENDMENT

The main reason for the amendment is to clarify that the responsibilities of the Data Monitoring Committee (DMC) are to evaluate the study safety as well as efficacy data, and to allow samples collected for pharmacokinetics at earlier timepoints to be used for anti-drug antibody (anti-SAR440340 antibody or anti dupilumab antibody) analysis, if ADA samples test positive at Week 12.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Clinical Trial Summary and 6.1 Description of the study	Text added to specify the aim to include half of the patients on a medium dose and half on a high ICS dose	While enrolment of patients on either medium or high dose ICS therapy is stipulated by the protocol, clarification is provided that an about equal proportion of patients on medium and high dose ICS is intended to have a broad representation of background therapy in the study.
Clinical Trial Summary and 7.2. Exclusion Criteria (EO3)	Exclude patients diagnosed with pulmonary or systemic disease associated with elevated peripheral eosinophil counts, for eg eosinophilic granulomatosis with polyangiitis.	Eosinophilia associated with clinical symptoms in asthma patients has been identified as important potential risk with dupilumab treatment. That´s why the intention is to exclude patients with pre-existing eosinophilic disease since a causal association between dupilumab and these underlying conditions has not been established. This is also aligned with other protocols for the same compound.

Section # and Name	Description of Change	Brief Rationale
Clinical Trial Summary and 9.2.1 Other efficacy endpoints	Time to LOAC post-randomization removed.	Time to LOAC post-randomization is being considered as supportive to the primary analysis of LOAC rather than as other efficacy endpoint.
Clinical Trial Summary and 11.3.2 Safety population	Defined the safety population as all patients who have received at least one dose of the IMP, analyzed according to the treatment actually received.	Clarify that the safety population will be analysed based on the actual treatment received and not treatment group allocated by randomization.
11.3.3.1 Antidrug antibody population	Definition of the ADA population updated.	To provide a more specific description of the population.
Clinical Trial Summary and 11.4.2.1 Analysis of primary efficacy endpoint	Baseline background ICS dose level and number of exacerbation events within 1 year prior to screening added as covariates in the logistic regression model.	Both variables were identified as important covariates in previous dupilumab studies.
	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."	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.
11.4.2.2 Analyses of secondary and other efficacy endpoints	The following sentence was deleted: "For patients with an LOAC event or permanently discontinued treatment, data collected up to EOT visit will be included."	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 will be detailed in the SAP.
1.1 Graphical Flow Design	Flowchart modified	Clarify background therapy after the intervention period
1.2 Study Flow Chart, 9.3.1.1 Sampling time	Allow samples collected for pharmacokinetics at Week 4 to be used for anti-drug antibody (anti-SAR440340 antibody or anti dupilumab antibody) analysis, if ADA samples test positive at Week 12 or at the first post-treatment time point analyzed	As per the FDA request to include additional sampling times between Week 0 and Week 12 the sponsor proposed that in the event a patient sample is positive in the SAR440340 ADA assay at Week 12 or the first post-treatment time point analyzed, the Week 4 PK sample may be analyzed in the ADA assay.
1.2 Study Flow Chart, 9.2.3.4 Clinical Laboratory Tests	HBs Ab (negative) test is removed from decision making if to perform HBV DNA testing or not	To fix inconsistency between exclusion criterion E37 and sections 1.2 and 9.2.3.4 of the protocol. The sections mention that HBV DNA testing should only be performed if HBsAg negative, HBsAb negative and HBcAb positive. HBs Ab positivity, however, should not exclude possibility to perform HBV DNA testing in

Section # and Name	Description of Change	Brief Rationale
		patients who are HBcAb positive. HBs Ab develops in patients who recovered from hepatitis B virus infection or who have been successfully vaccinated against hepatitis B.
6.1 Description of the study, 8.2 Noninvestigational medicinal products	The same inhaler type is required throughout study	Clarification: it was intended that patients use the same inhaler type throughout the study, taking into account the withdrawal design and the primary endpoint of Loss of asthma control (LOAC), but this was not specified.
6.4.1 Data Monitoring Committee	Specify the responsibities of the DMC to evaluate all study data (ie.not limited to safety data). Specify that the DMC members are independent of the project/study teams and are not involved in the study conduct	Allow the DMC to review all data (efficacy and safety), as per internal DMC charter.
7.2. Exclusion Criteria (EO9)	Patients with a history of a systemic hypersensitivity reaction to biologic drug is changed to “Patients with a history of a systemic hypersensitivity reaction to a monoclonal antibody”.	To add clarity and specifity regarding the systemic hypersensitivity to a monoclonal antibody, since class of biological drugs is very broad and unlikely to be predictive of hypersensitivity to either of IMPs. Therefore exclusion was narrowed down to past hypersensitivity to a monoclonal antibody.
7.2 Exclusion Criteria (E17)	Exclude patients who have been treated with commercially available dupilumab	Dupilumab is commercially available in some countries.
7.2 Exclusion Criteria (E27)	Exclude patients with known allergy to doxycycline or related compounds, or a known allergy to SAR440340 excipients	Clarify that in addition to patients with a known allergy to doxycycline, patients with a known allergy to any SAR440340 excipient should be excluded from the study.
8.2 Noninvestigational medicinal products, 8.8 Concomitant Medication	Specify that the third controller is not allowed for an additional 4 weeks prior to screening visit (V1).	To clarify time window required between the third controller withdrawal and the screening visit V1.
8.8 Concomitant Medication	Remove intra-articular steroids from permitted concomitant therapy	Resolve an inconsistency as relevant systemic exposure may occur with intra-articular steroids. Systemic steroids (except systemic steroids to treat asthma exacerbations) are not permitted during the screening or treatment phases.
9.2.2.5 Standardized Rhinoconjunctivitis Quality of Life Questionnaire in those patients with comorbid allergic rhinitis	Corrected from Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ[S] +12) to RQLQ[S]	To fix discrepancy between the Appendix F and section 9.2.2.5. RQLQ [S] is the questionnaire intended to be used in the study since only adult patients can participate in the study. Section 9.2.2.5 incorrectly mentions the RQLQ[S] +12 questionnaire that is intended for adults and kids of age ≥ 12.
9.3.1.1 Sampling time, 10.6.4 Elevated liver function tests	Specify that ADA sampling should only be performed for SAEs and AESIs of anaphylaxis, hypersensitivity reaction, injection site reaction	To harmonize with other SAR440340 studies. It is anticipated that formation of ADA will likely have limited effect on liver function.

Section # and Name	Description of Change	Brief Rationale
	but not in case of liver ALT increase	
9.3.2.1 Pharmacodynamic variables	Serum (not plasma) will be collected for testing Pulmonary and activation-regulated chemokine (PARC)	Serum will be used to assay for PARC
10.1 Visit Schedule	Change the order of assessments (ECG positioned prior to lung function measurements).	All ECGs should be preferably performed prior to FeNO and spirometry measurements in order to prevent potential effect of albuterol/salbutamol/levalbuterol/levosalbutamol administration on ECG tracing.
10.4.1.3 Adverse event of Special Interest	Modify the definition of overdose with NIMP to "An overdose (accidental or intentional) with any NIMP is an event suspected by the Investigator or spontaneously notified by the patient and defined as at least twice the maximum daily dose as specified in a drug label, within the intended therapeutic interval"	The definition has been modified to better reflect the fact that NIMP dose (inhaled steroids, long-acting beta agonists, short-acting beta agonists) may increase if patients experience a worsening of asthma symptoms. This should be considered as therapeutic intervention and not overdose.
Appendix A	Delete the footnote, "Hormonal contraception may be susceptible to interaction with the study treatment, which may reduce the efficacy of the contraceptive method. In this case TWO highly effective methods of contraception should be utilized during the treatment period and for at least 20 weeks after the last dose of study treatment."	This footnote is not applicable as the hormonal contraception is not expected to interact with study treatment.

CLINICAL TRIAL SUMMARY

COMPOUND: SAR440340	**STUDY No.: ACT15102**
TITLE	A randomized, double-blind, placebo-controlled, parallel-group, 12-week Proof-of-Concept (PoC) study to assess the efficacy, safety, and tolerability of SAR440340, and the coadministration of SAR440340 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
INVESTIGATOR/TRIAL LOCATION	Worldwide
PHASE OF DEVELOPMENT	2a
STUDY OBJECTIVE(S)	**Primary objective:** 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 "loss of asthma control" (LOAC*) events. **Secondary objectives:** Evaluate the effects of SAR440340 and coadministration of SAR440340 and dupilumab, compared with placebo, on forced expiratory volume in 1 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. **Other objectives:** Evaluation of the calibrator (dupilumab) arm performance. To evaluate the effects of SAR440340 and the coadministration of both compared to placebo on: - Other spirometric assessments (peak expiratory flow [PEF], forced vital capacity [FVC], forced expiratory flow [FEF] 25-75%). - Patient reported outcomes. - Immunogenicity (ie, anti-drug antibodies [ADA]). - The pharmacokinetic (PK) profile of SAR440340 and dupilumab in serum. - Selected biomarkers of the interleukin (IL)-33 and IL4/IL13 pathway. Furthermore, the effects of the coadministration of SAR440340 and dupilumab on relevant endpoints compared to each monotherapy treatment arm will be assessed as well. * **Definition of loss of asthma control (LOAC)** Loss of asthma control (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 V2 if background therapy withdrawal completed) Requiring use of systemic (oral and/or parenteral) steroid treatment Requiring Hospitalization or emergency room visit.
STUDY DESIGN	Multinational, randomized, double-blind, placebo-controlled, parallel-group (4 groups), 12-week Proof of Concept (PoC) study that is designed to assess the efficacy, safety, and tolerability of SAR440340 (an anti-IL33 monoclonal antibody), and the coadministration of SAR440340 and dupilumab (an anti-IL4-Rα monoclonal antibody that blocks the biologic activities of both IL4 and IL13), in patients with moderate-to-severe asthma who are not well controlled on inhaled ICS/LABA therapy. Study treatment includes IMP (SAR440340 and/or dupilumab and/or placebo) added-on to a background therapy of ICS/LABA (fluticasone/salmeterol [noninvestigational medicinal product], standardized at screening). Background therapy of ICS/LABA will be withdrawn during the 12-week randomized treatment period and resumed at the end of the IMP treatment period for the 20-week safety follow-up period, as outlined below: Screening period (4 weeks ± 3 days) Randomized 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 screening, 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 for at least 3 months with a stable dose ≥1 month prior to Screening Visit 1. 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 twice daily (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 who satisfy the inclusion and exclusion criteria will be randomized (1:1:1:1 ratio) to one of the following IMP treatment groups: SAR440340 (300 mg) administered as 2 subcutaneous (SC) injections every 2 weeks (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 Visits during the 12-week IMP treatment period will occur every week and will be followed by a 20-week observational follow-up period. **Background therapy (ICS/LABA) withdrawal phase:** At Week 4 (Visit 6) post-randomization, the LABA component (salmeterol) will be withdrawn, and patients will be switched from their BID fluticasone/salmeterol combination therapy to a clinically comparable ICS dose of fluticasone BID 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 The ICS component (fluticasone) will be withdrawn by a step-wise dose reduction starting at Week 6 (Visit 8) and will continue at each Weeks 7, 8, and 9 (Visits 9, 10, and 11, respectively), provided that patients do not experience a LOAC event. Patients that meet the criteria for a LOAC, at any time during the randomized IMP treatment phase, will (be): - Discontinue early from IMP treatment, - Evaluated and receive treatment by the Investigator with standard of care according to standard medical practice, - Resume their individual prescreening ICS/LABA background therapy and, - Followed for safety during a 20-week Post IMP Treatment Period. **Early treatment discontinuation (ETD) follow-up:** Patients who discontinue IMP treatment prior to completing the 12-week IMP treatment (due to LOAC or due to early treatment discontinuation), will be evaluated as soon as possible at the individual patients' End of Treatment (EOT) Visit, using procedures as planned for the EOT Visit at Week 12 (Visit 14). At their EOT visit, patients will resume their prescreening ICS/LABA background therapy and enter the 20-week safety follow-up period/Post IMP Treatment Period (Visit 15 to Visit 17).

	Post IMP treatment follow-up: Patients who complete the 12-week randomized IMP treatment period at Week 12 (Visit 14) EOT visit, as per protocol, resume their prescreening ICS/LABA therapy and enter the 20-week safety follow-up period/Post IMP Treatment Period (Visit 15 to Visit 17). Note: For patients who meet the criteria for a LOAC or discontinue IMP treatment early (due to other reasons) prior to 12 weeks of treatment, their ETD EOT visit and their individual 20-week Post IMP Treatment Period may start earlier than at Week 12. At any EOT visit, if a patient's asthma cannot be adequately controlled by the prescreening ICS/LABA therapy, additional controller therapies may be prescribed based on the Investigator's clinical judgement.
STUDY POPULATION **Main selection criteria**	**Inclusion criteria:** I 01. Adult patients with a physician diagnosis of asthma for at least 12 months based on the Global Initiative for Asthma (GINA) 2017 Guidelines I 02. Patients with existing treatment with medium to high dose ICS (≥250 mcg of fluticasone propionate 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 Visit 1. Please note that the lower limit of allowed ICS dose (500 mcg of fluticasone propionate daily) corresponds to upper limit of medium dose defined by GINA guidelines. Patients receiving medium ICS dose <500 mcg daily are not eligible. I 03. Patients with prebronchodilator FEV1 >40% of predicted normal at Visit 1/Screening. Prebronchodilator FEV1 ≥50% but ≤85% of predicted normal at Visit 2/Baseline. I 04. Patients with reversibility of at least 12% and 200 mL in FEV1 after administration of 2 to 4 puffs (200-400 mcg) of albuterol/salbutamol or levalbuterol/levosalbutamol during screening or documented history of a reversibility test that meets this criteria within 12 months prior to Visit 1 or documented positive response to methacholine challenge (a decrease in FEV by 20% [PC_{20}] of <8mg/mL) within 12 months prior to Visit 1/Screening is considered acceptable to meet this inclusion criterion. I 05. Patients must have experienced, within 1 year prior to Visit 1, any of the following events at least once: - Treatment with a systemic steroid (oral or parenteral) for worsening asthma. - Hospitalization or emergency medical care visit for worsening asthma. I 06. Signed written informed consent. **Exclusion criteria:** Patients who have met all the above inclusion criteria will be screened for the following key exclusion criteria: E 01. Patients <18 years or >70 years of age (ie, have reached the age of 71 at the screening visit) E 02. Patients with body mass index (BMI) <16 E 03. Chronic lung disease (for example, chronic obstructive pulmonary

	disease [COPD], or idiopathic pulmonary fibrosis [IPF]) which may impair lung function, or another diagnosed pulmonary or systemic disease associated with elevated peripheral eosinophil counts, for eg eosinophilic granulomatosis with polyangiitis. E 04. History of life threatening asthma (ie, severe exacerbation that requires intubation). E 05. Co-morbid disease that might interfere with the evaluation of IMP E 06. Patients with any of the following events within the 4 weeks prior to their Screening Visit 1 or during the screening period: - Treatment with 1 or more systemic (oral and/or parenteral) steroid bursts for worsening asthma - Hospitalization or emergency medical care visit for worsening asthma E 07. Asthma Control Questionnaire 5-question version (ACQ-5) score <1.25 or >3.0 at V2/randomization. During the screening period an ACQ-5 of up to ≤4 is acceptable. E 08. Anti-immunoglobulin E (IgE) therapy (eg, omalizumab [Xolair®]) within 130 days prior to Visit 1 or any other biologic therapy (including anti-IL5 monoclonal antibody [mAb]) or systemic immunosuppressant (eg, methotrexate) to treat inflammatory disease or autoimmune disease (eg, rheumatoid arthritis, inflammatory bowel disease, primary biliary cirrhosis, systemic lupus erythematosus, multiple sclerosis) and other diseases, within 2 months or 5 half-lives prior to Visit 1, whichever is longer. E 09. Patients with a history of a systemic hypersensitivity reaction to a monoclonal antibody. E 10. Patients on or initiation of bronchial thermoplasty within 2 years prior to Visit 1 or plan to begin therapy during the screening period or the randomized treatment period. E 11. Current smoker or cessation of smoking within the 6 months prior to Visit 1. E 12. Previous smoker with a smoking history >10 pack-years. For a complete list of exclusion criteria, see protocol.
Total expected number of patients	Approximately 240 patients, randomized in a 1:1:1:1 ratio to receive SAR440340 (60), dupilumab (60), SAR440340 and dupilumab (60), or placebo (60).
Expected number of sites:	80
STUDY TREATMENTS **Investigational medicinal products**	SAR440340 and matching placebo Dupilumab (SAR231893) and matching placebo
Formulation:	SAR440340 for SC administration: 1 vial of lyophilisate drug product (287 mg) is reconstituted with 2.5 mL of sterile water for injection resulting in 2.9 mL of 100 mg/mL SAR440340 DP. A volume of 1.5 mL per injection will be withdrawn from the vial. Sterile placebo will be provided in matched glass vials. Dupilumab for SC administration is supplied as 150 mg/mL in glass prefilled syringes to deliver 300 mg in 2.0 mL. Placebo matching dupilumab is prepared in the same formulation as dupilumab, without the addition of protein.

Route of administration:	SC. All IMP applications will be done as separate injections.
Dose regimen:	SAR440340 (300 mg) administered as 2 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
Noninvestigational medicinal products **Formulation:**	**Background Therapy** From Screening Visit 1 to Visit 2/randomization (4 weeks), all eligible patients will receive fluticasone/salmeterol as study-specific ICS/LABA background therapy. This background treatment is maintained for the first 4 weeks of randomized IMP treatment during the background therapy stabilization phase. At Week 4 (Visit 6) post-randomization, the LABA component (salmeterol) will be withdrawn, and patients will be switched from their BID fluticasone/salmeterol combination therapy to a clinically comparable ICS dose of fluticasone monotherapy. The ICS component (fluticasone) will be withdrawn by a step-wise dose reduction starting at Week 6 (Visit 8) and will continue at each Weeks 7, 8, and 9 (Visits 9, 10, and 11, respectively), provided that patients do not experience a LOAC event (ie, are prematurely withdrawn). One inhaler for the combination fluticasone/salmeterol and another inhaler for fluticasone alone will be provided while patient is in screening and on IMP treatment. Dry Powder Inhaler (DPI)/Metered Dose Inhaler (MDI), as applicable. **Reliever Medication** Patients may use albuterol/salbutamol or levalbuterol/levosalbutamol MDI as reliever medication as needed during the study. Nebulizer solutions may be used as an alternative delivery method.
Route of administration:	Oral inhalation, nebulizer for albuterol, levalbuterol, fluticasone/salmeterol combination therapy, and fluticasone monotherapy.
Dose regimen:	**Background therapy stable phase:** From Screening Visit 1 (Week -4) up to Visit 6 (Week 4) clinically comparable doses of the study-specific ICS/LABA combination therapy with fluticasone/salmeterol, as approved for region: Fluticasone/salmeterol – DPI: 1 puff of 250/50 mcg twice daily (BID) or 1 puff of 500/50 mcg BID OR Fluticasone/salmeterol – MDI: 2 puffs of 115/21 mcg (230/42 mcg) BID or 2 puffs of 230/21 mcg (460/42 mcg) BID

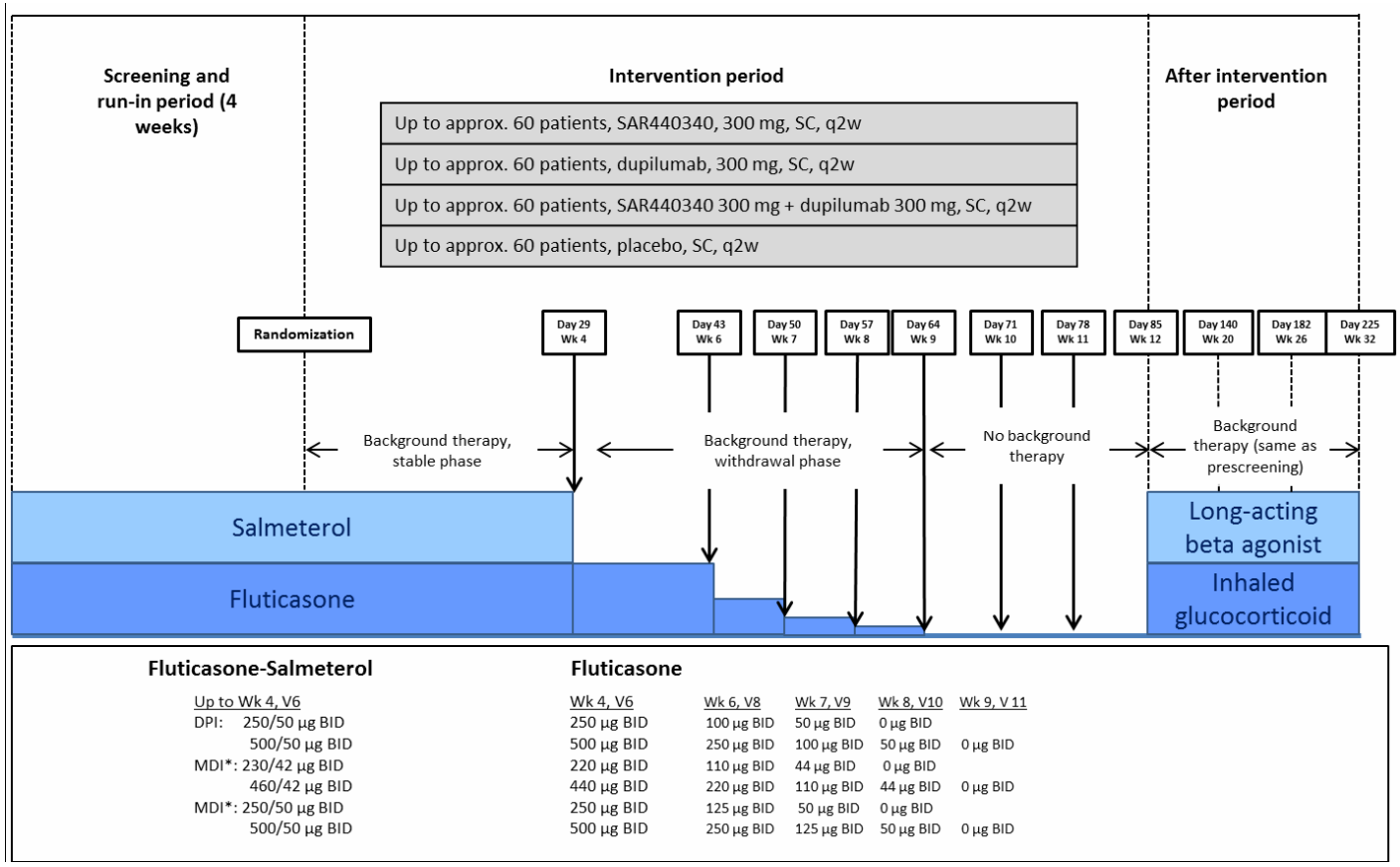
	OR Fluticasone/salmeterol – MDI: 2 puffs of 125/25 mcg (250/50 mcg) BID or 2 puffs of 250/25 mcg (500/50 mcg) BID. **Background therapy withdrawal phase:** Salmeterol will be withdrawn at Week 4 (Visit 6) post-randomization. Patients will be switched from their BID fluticasone/salmeterol combination therapy to a clinically comparable ICS dose of fluticasone BID 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 The ICS component (fluticasone) will be withdrawn by a step-wise dose reduction starting at Week 6/Visit 8 (DPI: 100 mcg BID or 250 mcg BID or MDI: 110 or 125 mcg BID or 220 or 250 mcg BID) and will continue at Week 7 (DPI: 50 mcg BID or 100 mcg BID or MDI: 44 or 50 mcg BID or 110 or 125 mcg BID), Week 8 (DPI: 0 mcg BID or 50 mcg BID or MDI: 0 mcg BID or 44 or 50 mcg BID) and Week 9 (DPI: 0 mcg BID or 0 mcg BID or MDI: 0 mcg BID or 0 mcg BID), provided that patients do not experience a LOAC event (ie, are prematurely withdrawn).
ENDPOINTS	**Primary endpoint:** The primary endpoint is the proportion of patients with LOAC. **Secondary endpoint:** FEV1 change from baseline at Week 12 (pre- and postbronchodilator). **Other efficacy endpoints:** Change from baseline in other lung function measurement (peak expiratory flow [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. Asthma Quality of Life Questionnaire with Standardized Activities (AQLQ [S]) Self-Administered change from baseline at Week 12 and at each assessment time point. Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) score change from baseline at Week 12 in patients with a secondary diagnosis 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.

	Safety evaluation: Adverse events (AEs)/treatment-emergent adverse events (TEAEs). Physical examination and body weight. Vital signs and 12-lead electrocardiogram. Clinical laboratory tests. Tolerability at IMP injection site. **Systemic drug concentration and Anti-drug antibodies:** Serum functional SAR440340 concentrations and PK profile. Serum functional dupilumab concentrations and PK profile. Antidrug antibodies (ADA) against SAR440340. ADA against dupilumab. **Biomarkers and other pharmacodynamics:** Blood eosinophil and neutrophil counts. Fraction of exhaled nitric oxide (FeNO) level compared with baseline. Total IL33, soluble IL33 receptor (sST2), periostin. Calcitonin. Pulmonary and activation-regulated chemokine (PARC) and eotaxin-3. Total IgE. Optional: Messenger ribonucleic acid (mRNA) sequencing or whole transcriptome analysis. Optional: Blood sample archival for exploratory research Optional: Deoxyribonucleic acid (DNA) for assessment of pharmacogenomic effects.
ASSESSMENT SCHEDULE	Screening Period (4 weeks [±3 days]). Randomized IMP Treatment Period (12 weeks [±3 days]). - Background (ICS/LABA) therapy stabilization phase (4 weeks, [±3 days]). - Background therapy withdrawal phase (4-5 weeks, [±3 days]). - No background therapy phase (3-4 weeks, [±3 days]). Post IMP treatment safety follow-up period (20 weeks [±5 days]).
STATISTICAL CONSIDERATIONS	**Sample size determination:** Data from a previous study with dupilumab with similar design (ACT11457) showed a 44% rate of LOAC in the placebo group in a 12-week study with a similar population and background treatment compared to a 6% rate of LOAC in the dupilumab group, for an 87% relative reduction with dupilumab. Therefore, the placebo incidence of LOAC events is assumed to be 40%, and with 50 patients per group the study will have 80% power to detect a 26% reduction in the rate of LOAC events (to 14% in the SAR440340 group) at the 5% significance level (two-sided). Allowing for approximately 15% dropouts, a sample size of 60 patients per group has been defined. Furthermore, based upon ACT11457 the standard deviation for the absolute change in FEV1 after 12 weeks is estimated to be 0.35 L. For the purpose of calculation 50 of the 60 randomized patients per group are assumed to have Week 12 data (based on ACT11457 where ~80% of patients had this data). Therefore at the 5% significance level there will be 80% power to detect differences of 0.2 L among the treatment groups. The smallest difference in the trial that will still be declared statistically significant at the 5% level is

	estimated to be 0.14 L. The observed effect of dupilumab versus placebo was 0.27 L. Randomization will be stratified by Screening Visit 1 eosinophil count and by country. To ensure enrollment according to intended distribution of baseline eosinophil count, alerts will be built into the interactive voice/web response system (IVRS/IWRS) to limit enrolling patients in the following 2 stratification groups: Eosinophil <150/mm^3: not more than approximately 25% (60) patients Eosinophil ≥300/mm^3: at least approximately 45% (108) patients **Analysis population:** The primary population for efficacy analysis will be all randomized patients receiving at least one dose of study drug, analyzed in their assigned group (modified intent-to-treat [mITT]). 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. **Primary analysis:** For the primary analysis of proportion of patients experiencing an LOAC event, a logistic regression model will be used to compare SAR440340 with placebo and the coadministration of SAR440340 and dupilumab with placebo. The model will include terms for treatment stratification factors, baseline background ICS dose level and number of exacerbation events within 1 year prior to screening. The odds ratio and 95% confidence interval will be estimated from this model. **Safety analysis:** Safety analyses will be descriptive, based on the safety population. The safety analysis will focus on the TEAE period. This period is defined as the time from the first administration of the IMP to the last administration of the IMP plus 22 weeks. **Interim analyses:** No formal interim analysis is planned. Analyses will be performed for safety monitoring and internal decision making. No formal stopping rules or adjustment for multiplicity will be applied.
DURATION OF STUDY PERIOD (per patient)	The total duration of the study (per patient) is expected to be up to 36 weeks: • 4 weeks (±3 days) of screening period • 12 weeks (±3 days) of randomized IMP treatment period 20 weeks (±5 days) of post IMP treatment safety follow-up period

1 FLOW CHARTS

1.1 GRAPHICAL STUDY DESIGN



* Depending on regional availability

Abbreviations: SC: subcutaneous, q2w: every 2 weeks, Wk: week, BID: twice daily, DPI: dry powder inhaler, MDI: metered dose inhaler, µg: microgram

1.2 STUDY FLOW CHART

Period	Screening (± 3 days)	Randomized IMP Treatment Period (± 3 days) Including the Following Background ICS/LABA Therapy Phases:													Post IMP Treatment Period (± 5 days)		
		ICS/LABA stabilization					ICS/LABA withdrawal[b,c]				No ICS/LABA[b]						
											No ICS/LABA[c]						
VISIT	**V1**	**V2 Randomization/ Baseline**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14 EOT[d,e]**	**V15**	**V16[f]**	**V17 EOS**
DAY[a]	**D-28 to D0**	**D1**	**D8**	**D15**	**D22**	**D29**	**D36**	**D43**	**D50**	**D57**	**D64**	**D71**	**D78**	**D85**	**D141**	**D183**	**D225**
WEEK	**W-4 to W0**	**W0**	**W1**	**W2**	**W3**	**W4**	**W5**	**W6**	**W7**	**W8**	**W9**	**W10**	**W11**	**W12**	**W20**	**W26**	**W32**
Informed consent	X																
Patient demography	X																
Previous medical and surgical history	X																
Inclusion/exclusion criteria	X	X															
Qualifying Spirometry and Reversibility[g]	X																
Prior & concomitant meds	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Switch from current ICS/LABA combination to Sponsor-supplied fluticasone/salmeterol combination	X																
Call IVRS/IWRS	X	X		X		X		X		X		X		X			X
Randomization		X															
Study treatment administration																	
IMP administration[h]		X		X		X		X		X		X					
Dispense or download electronic diary/PEF meter[i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X[d,e]			
Evaluation and LABA (salmeterol) withdrawal[j]						X[j]											
Evaluation and ICS (fluticasone) withdrawal[k]								X[k]	X[k]	X[k]	X[k]						
Resume original dose of ICS/LABA therapy[d]														X[d,e]			
Safety																	
Physical examination[l]	X	X				X				X				X	X		X
Vital signs[m]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Electrocardiogram (12-lead)	X					X								X			X

Period	Screening (± 3 days)	Randomized IMP Treatment Period (± 3 days) Including the Following Background ICS/LABA Therapy Phases:													Post IMP Treatment Period (± 5 days)		
		ICS/LABA stabilization					ICS/LABA withdrawal[b,c]				No ICS/LABA[b]						
											No ICS/LABA[c]						
VISIT	V1	V2 Randomization/ Baseline	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14 EOT[d,e]	V15	V16[f]	V17 EOS
DAY[a]	D-28 to D0	D1	D8	D15	D22	D29	D36	D43	D50	D57	D64	D71	D78	D85	D141	D183	D225
WEEK	W-4 to W0	W0	W1	W2	W3	W4	W5	W6	W7	W8	W9	W10	W11	W12	W20	W26	W32
Hematology, biochemistry, urinalysis[n]	X	X				X				X				X	X		X
Hepatitis and HIV Serology tests[n]	X																
Quantiferon gold testing[o]	X																
Pregnancy (β-hCG blood) test[p]	X																
Pregnancy (urine) test[p]		X				X				X				X			X
Adverse event reporting, including SAEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pharmacokinetics and Immunogenicity																	
Serum sample for SAR440340 concentration		X		X		X[q]				X				X	X		X
Serum sample for dupilumab concentration		X		X		X[q]				X				X	X		X
Anti-SAR440340 antibody and anti-dupilumab antibody		X				X[q]								X			X
Biomarkers																	
Blood eosinophils and neutrophils	X	X		X[r]		X		X[r]		X				X	X		X
FeNO[s]	X	X		X		X				X				X	X		X
Total IL33 and sST2 (Serum)	X	X				X				X				X	X		X
Calcitonin	X	X				X				X				X	X		X
PARC	X	X				X				X				X			
Eotaxin-3	X	X				X				X				X			
Total IgE	X	X				X								X			
Periostin	X	X				X								X			
RNA sample (optional)	X	X				X								X			
Blood sample archival for exploratory research (optional)	X	X				X								X			
PGx analysis (optional)		X															

Period	Screening (± 3 days)	Randomized IMP Treatment Period (± 3 days) Including the Following Background ICS/LABA Therapy Phases:													Post IMP Treatment Period (± 5 days)		
		ICS/LABA stabilization					ICS/LABA withdrawal[b,c]				No ICS/LABA[b]						
											No ICS/LABA[c]						
VISIT	V1	V2 Randomization/ Baseline	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14 EOT[d,e]	V15	V16[f]	V17 EOS
DAY[a]	D-28 to D0	D1	D8	D15	D22	D29	D36	D43	D50	D57	D64	D71	D78	D85	D141	D183	D225
WEEK	W-4 to W0	W0	W1	W2	W3	W4	W5	W6	W7	W8	W9	W10	W11	W12	W20	W26	W32
Efficacy																	
LOAC event reporting			X	X	X	X	X	X	X	X	X	X	X	X			
Spirometry (FEV1) (pre-BD)[t]		X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Spirometry (FEV1) (post-BD)[t]		X				X		X		X		X		X	X		X
ACQ-5[u]	X	X		X		X		X		X		X		X	X		X
AQLQ(S)[u]		X		X		X		X		X		X		X	X		X
RQLQ (patients with history of allergic rhinitis only)[u]		X		X		X		X		X		X		X	X		X

Abbreviations:ACQ-5 = asthma control questionnaire-5; AQLQ(S) = asthma quality of life questionnaire;β-hCG = beta human chorionic gonadotropin, D = day; DNA = deoxyribonucleic acid; EDTA = ethylene-diamine-tetra-acetic acid; EOT = End of Treatment; FEF = forced expiratory flow; FeNO = fraction of exhaled nitric oxide; FEV1 = forced expiratory volume in 1 second; ICS = inhaled corticosteroid; IgE = Immunoglobulin E; IMP = investigational medicinal product, IL33 = interleukin-33; IVRS/IWRS = Interactive Voice/Web Response System; LABA = long-acting β2 adrenergic agonist; LOAC = loss of asthma control; BD = bronchodilator; PARC = pulmonary and activation-regulated chemokine; PEF = peak expiratory flow; PGx = pharmacogenomics; PK = pharmacokinetic; RNA = ribonucleic acid; RQLQ = rhinoconjunctivitis quality of life questionnaire; SAE = serious adverse event; sST2 = soluble IL33 receptor; V = visit; W = week.

a The study visits occur on the planned dates (relative to the first injection), as scheduled. The visit schedule should be adhered to within ±3 days for the screening period and randomized IMP treatment period, and ±5 days for the visits during the post IMP treatment safety follow-up period.

b After 5 weeks of ICS/LABA withdrawal phase, patients with high dose ICS (fluticasone) backgound at Visit 2/baseline will be on IMP treatment without background therapy for 3 weeks.

c After 4 weeks of ICS/LABA withdrawal phase, patients with medium dose fluticasone backgound at Visit 2/baseline will be on IMP treatment without background therapy for 4 weeks.

d End of IMP treatment (EOT) visit: Patients who discontinue prematurely from the study (ie, early treatment discontinuation [ETD]), prior to completing the 12-week IMP treatment (eg, due to a LOAC event or due to other reasons), will be evaluated as soon as possible at the individual patients' EOT Visit, using procedures as planned for the EOT Visit at Week 12 (Visit 14). At their EOT visit, all patients will resume their prescreening ICS/LABA background therapy and enter the 20-week Post IMP Treatment Period (V15 to V17). If a patient's asthma cannot be adequately controlled by the prescreening ICS/LABA therapy, additional controller therapies may be prescribed based on the Investigator's clinical judgement.

e The Post IMP Treatment Period will start at Week 12 for patients who complete the IMP treatment period, and may start earlier than Week 12 for patients who meet the criteria for a LOAC or discontinue IMP treatment early (due to other reasons) prior to completing the 12-week IMP treatment.

f Visit 16 visit can be either an on-site visit or a phone-call.

g Patients with reversibility of at least 12% and 200 mL in FEV1 after administration of 2 to 4 puffs (200-400 mcg) of albuterol/salbutamol or levalbuterol/levosalbutamol during screening or documented history of a reversibility test that meets this criteria within 12 months prior to Visit 1 or documented positive response to methacholine challenge (a decrease in FEV by 20% [PC_{20}] of <8mg/mL) within 12 months prior to Visit 1/Screening is considered acceptable to meet this inclusion criterion. If the subject does not meet the qualifying criteria for reversibility at Visit 1/Screening, up to 2 additional attempts during the screening period,

each on a different day prior to Visit 2/Baseline, may be performed. When reversibility assessment is repeated during the screening period, the prebronchodilator FEV1 should again meet the inclusion criterion (I 03) of >40% of predicted normal.

h Patients should be monitored by site personnel for at least 30 minutes after administration of all IMP injections. Monitoring period may be extended as per country specific requirements.

i Electronic diary/PEF meter is a handheld device used for daily recording of salbutamol/albuterol or levosalbutamol/levalbuterol use, asthma controller drug use, asthma symptom score Numerical Rating Scale (NRS), nocturnal awakenings due to asthma symptoms and AM and PM PEF, and recording of patient's answers to the ACQ-5, AQLQ(S), and RQLQ questionnaires during the scheduled visits. This handheld device is dispensed at Visit 1 (including instructions for use) and recorded information is downloaded from this device on the other indicated days. If not already done so, patient will return electronic devices to the site at EOS. Electronic devices will be returned to the sponsor at EOS as the latest.

j After evaluation for LOAC events, all patients that do not meet the criteria for LOAC at Week 4/V6, will have the LABA (salmeterol) withdrawn from their background therapy and will be switched from fluticasone/salmeterol combination therapy to clinically comparable ICS dose of fluticasone monotherapy.

k After evaluation for LOAC events, all patients that do not meet the criteria for LOAC at V8, V9, V10 (and V11), will have ICS (fluticasone) withdrawn by 3 or 4 steps of dose reduction depending on their medium or high dose ICS (fluticasone) background treatment at Visit 2/baseline, respectively.

l Complete physical examinations will include skin, nasal cavities, eyes, ears, respiratory, cardiovascular, gastrointestinal, neurological, lymphatic, and musculoskeletal systems.

m Vital signs, including systolic and diastolic blood pressure (mmHg), pulse rate (beats per minute), and respiratory rate (breaths per minute) will be measured at all visits detailed in the flowchart. Height (cm) will be measured at screening (Visit 1) only. Body weight (kg) will be measured at Visit 1/Screening, Visit 2/Baseline and Visit 14/EOT.

n Hematology will include hemoglobin, hematocrit, platelet count, total white blood cell count, differential count, and total red blood cell count. Serum chemistry will include include creatinine, blood urea nitrogen, glucose, uric acid, total cholesterol, total protein, albumin, total bilirubin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, electrolytes (sodium, potassium, chloride), bicarbonate, and creatine phosphokinase. Urinalysis will include 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. Clinical laboratory testing at Screening 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), hepatitis C virus antibodies (HCV Ab), human immunodeficiency virus (HIV) screen (Anti-HIV-1 and HIV-2 antibodies) and anti-nuclear antibody (ANA). In case of results showing HBs Ag (negative), and HBc Ab (positive), an HBV DNA testing may be performed prior to randomization to rule out a false positivity if the Investigator believes the patient is a false positive, or to clarify the serological status if the investigator finds it unclear to interpret in absence of known HBV infection. In case of results showing HCV Ab (positive), an HCV RNA testing may be performed to rule out a false positivity, if the Investigator believes the patient is a false positive. Note: Anti-ds DNA antibody will be tested if ANA is positive (≥1:160 titer). The blood sample for serum chemistry must be taken with the patient in fasting state which means no intake of any food or drink except for water for at least 8 hours (if the visit can only be done at a different time of the day and the patient is not fasting, then he/she should be advised to eat light food and the site should document that serum chemistry was not obtained under fasting conditions).

o Quantiferon gold should be collected for all patients at the Screening Visit 1. If the result is confirmed positive, the patient should be referred to an Infectious Disease specialist. Please refer to the central laboratory manual for additional details.

p Only for women of childbearing potential: serum pregnancy test at Screening/V1 and urine pregnancy tests at V2, V6, V10, V14/EOT, and V17/EOS. A negative result must be obtained at V1 and at V2 prior to randomization. In case of positive urine test the study treatment will be withheld and a serum pregnancy test to confirm the pregnancy should be performed as soon as possible. Pregnancy will lead to definitive treatment discontinuation in all cases.

q 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.

r Hematology sample will be drawn for eosinophils and neutrophils (with other critical values reported per lab manual).

s Exhaled nitric oxide assessment will be conducted prior to spirometry and following a fast of at least 1 hour.

t Spirometry (pre-BD FEV1, post-BD FEV1, and PEF, FVC, FEF) should be performed not earlier than 6 hours after last dose of albuterol or levalbuterol (if any) and withholding the last dose of LABA for at least 12 hours, and prior to administration of investigational product. The postbronchodilator spirometry may be repeated several times within 30 minutes after administration of bronchodilator.

u The ACQ-5, AQLQ(S), and RQLQ are to be completed on the patient's handheld device during clinic visits.

2 TABLE OF CONTENTS

2.1 LIST OF TABLES

3 LIST OF ABBREVIATIONS

ACQ-5:	Asthma Control Questionnaire-5
ADA:	Anti-drug antibodies
AEs:	Adverse events
AESI:	Adverse events of special interest
ALT:	Alanine transaminase
AQLQ[S]:	Asthma Quality of Life Questionnaire with Standardized Activities
AST:	Aspartate transaminase
BID:	Twice daily
COPD:	Chronic obstructive pulmonary disease
DMC:	Data monitoring committee
DNA:	Deoxyribonucleic acid
DPI:	Dry powder inhaler
ECG:	Electrocardiogram
eCRF:	Electronic case report form
EOS:	End of study
FEV1:	Forced expiratory volume in 1 second
FIH:	First-in-human
FVC:	Forced vital capacity
GSO:	Global Safety Officer
HBc Ab:	Hepatitis B core antibody
HBs Ag:	Hepatitis B surface antigen
HDM:	House dust mite
HIV:	Human immunodeficiency virus
IB:	Investigator's brochure
ICF:	Informed consent form
ICH:	International Conference on Harmonisation
ICS:	Inhaled corticosteroids
IEC:	Independent Ethics Committee
Ig:	Immunoglobulin
IL:	Interleukin
ILC2:	Innate lymphoid cells type 2
IMP:	Investigational medicinal product
IRB:	Institutional Review Board
IRT:	Interactive Response Technology
ISR:	Injection site reaction
IV:	Intravenous
IVRS:	Interactive Voice Response System
IWRS:	Interactive Web Response System
LABA:	Long-acting β2 adrenergic agonist
LOAC:	Loss of asthma control
LS:	Least square

mAb:	Monoclonal antibody
MCID:	Minimal Clinically Important Difference
MDI:	Metered dose inhaler
mITT:	Modified intent-to-treat
NIMP:	Noninvestigational medicinal product
NRS:	Numerical Rating Scale
OCS:	Oral corticosteroid
PARC:	Pulmonary and activation-regulated chemokine
PCSA:	Potentially clinically significant abnormality
PEF:	Peak expiratory flow
PK:	Pharmacokinetics
ppb:	Parts per billion
q2w:	Every 2 weeks
RNA:	Ribonucleic acid
RQLQ:	Rhinoconjunctivitis Quality of Life Questionnaire
SAEs:	Serious adverse events
SC:	Subcutaneous
TB:	Tuberculosis
TEAE:	Treatment-emergent adverse event
Th2:	T-helper 2
ULN:	Upper limit of normal range

4 INTRODUCTION AND RATIONALE

4.1 ASTHMA

Asthma is a chronic inflammatory disease of the airways characterized by airway hyperresponsiveness, acute and chronic bronchoconstriction, airway edema and mucus plugging. The inflammation component of asthma is thought to involve many cell types including epithelial cells, T lymphocytes, eosinophils, mast cells, neutrophils, innate lymphoid cells type 2 (ILC2) and their biological products. Patients with asthma most often present with symptoms of wheezing, shortness of breath, cough, and chest tightness.

Despite current treatment options, uncontrolled asthma continues to carry a significant burden, with more than 1 million moderate-to-severe asthmatic adolescent and adults in the US having uncontrolled symptoms on inhaled corticosteroids (ICS) combined with a second controller or systemic corticosteroid therapy (1,2). These patients are prone to severe exacerbations, and contribute disproportionately to the overall morbidity in this condition, including more hospital days, emergency room visits, and lost work/school days than matched controls with good asthma control. Additionally, they are likely to experience co-morbidities such as anxiety, depression, and insomnia (3,4). Furthermore, systemic corticosteroids, while clinically effective, are associated with significant side effects, such as fluid retention and swelling, glaucoma, increased blood pressure, increased risk of infections, diabetes, osteoporosis, and impaired growth in children (5).

Due to the limitations of the standard of care therapy, there are a number of biologics in development for moderate-to-severe asthma (5,6,7,8,9, and 10). For severe uncontrolled asthma patients, there are four currently approved biologics. In the severe, corticosteroid-refractory allergy-induced asthma population, the anti-immunoglobulin E (IgE) agent omalizumab (XOLAIR®) has shown efficacy. Xolair is associated with a black box warning of potential for anaphylaxis. In the severe population with an eosinophilic phenotype, the two currently approved anti-interleukin (IL)-5 agents, mepolizumab (NUCALA®) and reslizumab (CINQAIR®), and the most recently approved anti-IL5 receptor benralizumab (Fasenra™) have shown efficacy as well. These anti-IL5 agents now provide an additional therapeutic option with important limitations though. Even in the high eosinophilic group, 36% of patients on mepolizumab had no decrease in oral corticosteroid (OCS) dose or had a lack of asthma control (11), suggesting that targeting a single cytokine in a heterogenous disease such as asthma is not sufficient. In this context, there is a need for identification of novel therapeutic targets and development of more efficacious and well tolerated treatments for severe asthma.

To address these limitations, dupilumab, an anti-IL4-Rα antibody that blocks the biologic activities of both IL4 and IL13, is currently being investigated in a Phase 3 program in moderate-to-severe asthma. In the pivotal Phase 2b study (10), it was demonstrated that in patients with moderate-to-severe uncontrolled asthma, treatment with dupilumab 200 mg or 300 mg every 2 weeks (q2w) as an add-on to ICS/long-acting β2 adrenergic agonist (LABA) combination therapy produced a clinically meaningful and statistically significant increase from baseline in forced expiratory volume in 1 second (FEV1) at Week 12 and Week 24 and a significant

reduction in the annualized rate of severe asthma exacerbations in both the high eosinophil population (≥300 cells/µL) (71.2% to 80.7% reductions in severe asthma exacerbations) and the overall population (70% to 70.5% reductions in severe asthma exacerbations) (10). A second pivotal study to evaluate the efficacy and safety of dupilumab in patients with persistent asthma is ongoing. Results from completed studies indicate that dupilumab is generally well-tolerated.

The main objective for new biologics is to further improve asthma symptoms, lung function, and prevent exacerbations, while optimizing adherence to the treatment. One of the reasons for the poor response to medication in some patients with severe asthma may be the heterogeneity of the disease, namely the mixed eosinophilic and neutrophilic inflammation, only partly responding to the current targeted therapies. Also, asthma exacerbations are associated with upper respiratory viral infections, mostly rhinoviruses, with frequency estimates of 85% and 60% for childhood and adult asthma, respectively. Underlying deficiencies in innate immunity and evidence of a synergism between viral infection and allergic mechanisms in increasing risk of exacerbations are all important mechanisms to target with novel treatments (12).

4.2 SAR440340 ANTI-IL33 MONOCLONAL ANTIBODY

SAR440340 is a human monoclonal antibody (mAb) that targets IL33 and is under development as a potential novel treatment for asthma and chronic obstructive pulmonary disease (COPD). IL33 is a proinflammatory cytokine that initiates and amplifies innate and adaptive inflammatory cascades (13), in response to epithelial cell stress or damage due to exposure to airborne allergens, viruses, cigarette smoke, and air pollutants. Human genetic susceptibility data as well as preclinical data suggest that SAR440340 may be efficacious in asthma via targeting of inflammatory pathways including T-helper 2 (Th2)/eosinophilic, neutrophilic, and ILC2 mediators.

The role of IL33 in asthma is supported by genetic association in humans and by preclinical studies in animal models. In humans, gene variants of IL33 and its receptor ST2 are associated with increased levels of peripheral eosinophils and greater risk for asthma (14), and increased levels of IL33 have been reported in bronchial cells of asthma patients (15). In mice, genetic deletion or blockade of IL33 or ST2 suppressed lung inflammation (16,17). IL33 has also been described as a potent suppressor of innate antiviral immunity, contributing to synergistic associations between frequent lower respiratory infections in early life and asthma onset in later childhood (18). In a House Dust Mite (HDM) extract-induced model of chronic airway inflammation in humanized IL33 mice (Il33hu/hu mice), SAR440340 blocked several pathologic markers of type 1 and type 2 immune responses. Chronic HDM exposure in mice induces severe lung inflammation of mixed type 1 and type 2 phenotypes such as tissue infiltration by type 1 inflammatory cells (neutrophils), induction of type 2 cytokines, severe lung remodeling, and type 2-characteristic increases in serum IgE and HDM-specific IgG1. Mice treated with SAR440340 had significantly reduced lung weights and lung consolidation, reduced pulmonary neutrophilic infiltration, decreased IL5 protein levels and IL13 messenger ribonucleic acid (mRNA) levels, and decreased serum amyloid A.

The first-in-human (FIH) study (R3500-HV-1551) to investigate safety and pharmacokinetics (PK) of a single intravenous (IV) infusion of 0.3, 1, 3, or 10 mg/kg or a single subcutaneous (SC) injection of 150 mg of SAR440340 in normal healthy volunteers was completed. Treatment with

SAR440340 was generally well-tolerated. No deaths and no serious adverse events (SAEs) were reported.

The first-in-patient study (R3500-AS-1619) to investigate safety, tolerability, PK, and pharmacodynamic (PD) effects of a repeated SC administration of SAR440340 at 2 dose levels (75 and 150 mg), every week for 4 weeks, in adult patients with moderate asthma is ongoing.

A PD study (R3500-AS-1633) to assess the effects of a single IV dose of 10 mg/kg SAR440340, 2 repeated q2w SC doses of dupilumab (600 mg loading dose then 300 mg dose), and the coadministration of SAR440340 with dupilumab on markers of inflammation after Bronchial Allergen Challenge in patients with mild allergic asthma is ongoing.

At the time of writing this protocol, acceptable safety and tolerability was observed from the blinded assessments in both these ongoing studies for asthma patients.

4.3 DUPILUMAB ANTI-IL4R ALPHA MONOCLONAL ANTIBODY

In the ACT15102 study, dupilumab will be used as an active calibrator since it was successfully tested in a similar ICS/LABA withdrawal design targeting high eosinophilic patients (ACT11457) (19) and also demonstrated a satisfactory efficacy profile in a broader spectrum of asthma patients in Phase 2b, with 70% reduction of annual exacerbation and 160 to 200 mL FEV1 improvement versus placebo (DRI12544) (10).

Based on the results of DRI12544 study, the 2 q2w dupilumab regimens (200 mg and 300 mg) are currently being evaluated in the ongoing Phase 3 pivotal study (EFC13579). EFC13579 is a study of dupilumab in a broad population of adult and adolescent patients with uncontrolled, persistent asthma. In September 2017, topline results showed this study met the 2 primary endpoints. Dupilumab, when added to standard therapies, reduced severe asthma attacks (exacerbations) and improved lung function. At 52 weeks, in the 300 mg dose group, dupilumab reduced severe asthma attacks by 46% in the overall population, 60% in patients with ≥150 eosinophilic cells/µL, and 67% in patients with ≥300 eosinophilic cells/µL ($p<0.001$ for all groups). At 12 weeks, in the 300 mg dupilumab dose group, mean improvement in lung function over placebo as assessed by FEV_1 was 130 mL (9%) in the overall population, 150 mL (11%) in patients with ≥150 eosinophilic cells/µL, and 240 mL (18%) in patients with ≥300 eosinophilic cells/µL ($p<0.001$ for all groups). The results for the 200 mg and 300 mg dupilumab dose groups were generally comparable on both LOACs and FEV_1. The extent of patient response correlated with allergic or atopic status as reflected by blood eosinophils and other markers. Less activity was observed in patients with < 150 eosinophilic cells/µL.

4.4 COADMINISTRATION OF SAR440340 WITH DUPILUMAB

Increasingly it is appreciated that severe asthma is a complex and heterogeneous condition. While OCS are often required in this condition due to their broad anti-inflammatory effects, the side effects of these agents are unacceptable for long term use. Targeted mAb approaches which block single pathways may not be sufficient to treat the most severe patients and hence it is suggested that combination of mAbs which target separate yet complementary pathways and which are safe

and efficacious may be a successful and safe approach to treat the most severe, complex asthma phenotypes. The mechanism of action of SAR440340 and dupilumab as well as preclinical data in a mouse model of chronic HDM allergic inflammation suggest that the coadministration of SAR440340 with dupilumab may have additive anti-inflammatory effects compared to either SAR440340 or dupilumab alone, due to both distinct and overlapping effects of each mAb.

Humanized mice expressing human IL33, IL4, and IL4Rα ($Il33_{hu/hu}$, $Il4_{hu/hu}$, $Il4ra_{hu/hu}$ mice) exposed to HDM extract thrice-weekly for 19 weeks were treated twice-weekly from Week 12 to Week 19 with SAR440340, dupilumab, coadministration of SAR440340 and dupilumab, or an isotype control antibody. Gross lung pathology type 1 and/or type 2 immune response markers were assessed. The combination of SAR440340 and dupilumab showed improved efficacy compared to either treatment alone at preventing HDM-induced increases in lung weight, at reducing HDM-induced lung inflammation, with statistical significance for lung hIL4, IL-6, tumor necrosis factor (TNFα), growth related oncogene (GROα), monocyte chemoattractant protein-1 (MCP-1) and myeloperoxidase (MPO) relative to control $IgG4^P$, and at reducing serum IgE and serum amyloid A protein (SAA). In addition, a recent publication has demonstrated in two well established murine models of asthma that dual inhibition of both IL33 and IL13 was more efficacious than inhibiting each cytokine alone in reducing airway eosinophilia, levels of IL5 in bronchoalveolar lavage as well as ILC2 cells in the lung (20).

Thus, it may be hypothesized that the coadministration of SAR440340 and dupilumab may offer additive effects on the prevention of LOAC events and improvement of FEV1 in patients with moderate-to-severe asthma. Based on the results of the combination toxicology study of REGN646 the surrogate antibody for dupilumab, with SAR440340 in cynomolgus monkey and the lack of additive or synergistic safety findings with the combination, the existing data are deemed adequate to support FIH combination studies of these 2 agents.

4.5 RISK/BENEFIT

As outlined above, results of preclinical studies and Phase 1 studies suggest that SAR440340 is well-tolerated at doses up to 10 mg/kg administered IV as a single dose. A repeated dose study of SAR440340 at 75 and 150 mg administered every week for 4 weeks in adult patients with moderate asthma is ongoing. SAR440340 is expected to inhibit the proinflammatory activity of IL33, which is elevated in asthma patients. Thus, the benefit/risk profile for SAR440340 in this study supports its evaluation as a potential agent for treatment of asthma.

Dupilumab, at the proposed dose of 300 mg q2w administered SC, has been shown to be well-tolerated, has an acceptable safety profile, and was associated with significant improvements in clinical outcomes and markers of asthma control in 2 Phase 2 studies, with Phase 3 studies currently ongoing (10,19).

In summary, SAR440340 or dupilumab, individually, have either been demonstrated to or predicted (based on genetic and preclinical data) to provide high benefit for asthma patients along with a low safety risk, and combining SAR440340 and dupilumab has potentially additive benefits for the treatment of severe asthma. As outlined in Section 4.4, there is a compelling rationale for evaluating the combination of SAR440340 and dupilumab for treatment of asthma, as compared with SAR440340 or dupilumab, alone.

There is a theoretical risk of infection associated with blocking of host defense pathways by the combination of SAR440340 plus dupilumab. The preliminary safety data from the FIH study of SAR440340 have revealed no safety signals. Dupilumab has been found in clinical studies to be generally well-tolerated with a favorable safety profile and was not associated with an increased risk of infections other than oral Herpes infections in patients with atopic dermatitis.

The combination toxicology study supports the use of the combination at doses above those proposed for the proof of concept (PoC) study. There are no preclinical safety findings or signs of overlapping toxicity that would preclude the combination of SAR440340 and dupilumab. Furthermore, no drug-drug interactions affecting drug metabolism or excretion are expected for 2 mAbs. Therefore, the anticipated safety of the combination SAR440340 plus dupilumab is considered reasonable, with close monitoring of adverse events (AEs) and laboratory results throughout the study and follow-up period. The safety data for SAR440340 and dupilumab are summarized in the Investigator's brochure (IB) for each of these agents.

4.6 RATIONALE FOR SELECTING THE DOSE

The proposed dose regimen of SAR440340 is 300 mg SC q2w. It has been chosen based on safety data from the first-in-human (FIH) study in healthy subjects (R3500-HV-1551) and modeling of 300 mg q2w using PK data from the FIH study showing coverage at steady state of 5-fold the plasma level concentration of 17 mg/L shown to be required for optimal in vivo efficacy in a chronic exposure to HDM asthma model in mice.

The regimen of dupilumab that will be used in this study, consisting of 300 mg SC dose q2w, is based upon doses that have been shown in pivotal studies to reduce the rate of exacerbations and demonstrated a satisfactory safety profile in patients with severe asthma (10) (See Section 4.3 for additional details).

The doses of SAR440340 and dupilumab within the coadministration arm are supported by the justification above as well. Maintaining these levels without dose adjustment is supported by the absence of signs of overlapping toxicity from the combination toxicology study and the fact that for these biological drugs no drug-drug interactions affecting drug metabolism or excretion are expected.

4.7 STUDY DESIGN

ACT15102 study will evaluate the efficacy and safety of SAR440340, and the coadministration of both SAR440340 and dupilumab, in the treatment of patients with moderate-to-severe asthma. SAR440340 and dupilumab will be administered as 2 and 1 SC injection, respectively, q2w over a 12-week randomized investigational medicinal product (IMP) treatment period. This 12-week randomized IMP treatment period consists of a 4-week standardized ICS/LABA background therapy stabilization phase, a 4-5 week background therapy withdrawal phase and a 3-4 week no background therapy phase, followed by a 20-week post IMP treatment safety follow-up period. This study design has been successfully deployed in a previous Phase 2a investigation of dupilumab (19).

This study will be a multinational, randomized, double-blind, placebo-controlled, parallel-group (4 groups), 12-week Proof of Concept (PoC) study conducted in adult patients aged of 18 to 70 years, suffering from asthma based on the Global Initiative for Asthma (GINA) 2017 Guidelines, and whose asthma is partially controlled or uncontrolled on ICS/LABA background therapy with medium to high dose ICS (≥250 mcg of fluticasone propionate 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 Visit 1.

To ensure enrollment according to intended distribution of baseline eosinophil count, alerts will be built into the Interactive Voice Response System (IVRS)/Interactive Web Response System (IWRS) to limit enrolling patients in the following 2 stratification subgroups:

- Eosinophil <150/mm^3 not more than approximately 25% (60) patients
- Eosinophil ≥300/mm^3 at least approximately 45% (108) patients

The 12-week treatment duration is based on published data from ACT11457 dupilumab study with similar design, and should allow the observation of a reduction of the LOAC (primary efficacy variable) with SAR440340, and the coadministration of SAR440340 with dupilumab, as compared to placebo, considering the severity of the target population, under medium to high dose ICS/LABA therapy. In addition, 12-weeks are deemed sufficient to demonstrate treatment-induced changes on reversibility of airflow limitation as measured by FEV1 (secondary efficacy variable).

Upon completing 12 weeks of treatment with the IMP (or following early discontinuation of investigational products), patients enter the 20-week safety follow-up period/Post IMP Treatment Period. The 20-week follow-up period post IMP treatment, which covers approximately to 5 half-lives of SAR440340, will allow safety follow-up and efficacy recording.

The safety analysis will focus on the IMP treatment-emergent adverse event (TEAE) period, from the first administration of the IMP to 22 weeks after the last administration of the IMP.

After the end of IMP treatment (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.

5 STUDY OBJECTIVES

5.1 PRIMARY OBJECTIVE

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 "loss of asthma control" (LOAC*) events.

5.2 SECONDARY OBJECTIVES

- Evaluate the effects of SAR440340 and coadministration of SAR440340 and dupilumab, compared with placebo, on 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.

5.3 OTHER OBJECTIVES

- Evaluation of the calibrator (dupilumab) arm performance.
- To evaluate the effects of SAR440340 and the coadministration of both compared to placebo on:
  - Other spirometric assessments (peak expiratory flow [PEF], forced vital capacity [FVC], forced expiratory flow [FEF] 25-75%).
  - Patient reported outcomes.
  - Immunogenicity (ie, anti-drug antibodies [ADA]).
  - The PK profile of SAR440340 and dupilumab in serum.
  - Selected biomarkers of the IL33 and IL4/IL13 pathway.
- Furthermore, the effects of the coadministration of SAR440340 and dupilumab on relevant endpoints compared to each monotherapy treatment arm will be assessed as well.

*** Definition of Loss of Asthma Control**

Loss of asthma control (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 V2 if background therapy withdrawal completed)
- Requiring use of systemic (oral and/or parenteral) steroid treatment
- Requiring hospitalization or emergency room visit.

6 STUDY DESIGN

6.1 DESCRIPTION OF THE STUDY

The multinational, randomized, double-blind, placebo-controlled, parallel-group (4 groups), 12-week PoC study that is designed to assess the efficacy, safety, and tolerability of SAR440340 (an anti-IL33 monoclonal antibody), and the coadministration of SAR440340 and dupilumab (an anti-IL4-Rα monoclonal antibody that blocks the biologic activities of both IL4 and IL13) in patients with moderate-to-severe asthma who are not well controlled on ICS/LABA therapy. Study treatment includes IMP (SAR440340 and/or dupilumab and/or placebo) added-on to a background therapy of ICS/LABA (fluticasone/salmeterol [Noninvestigational medicinal product {NIMP}], standardized at screening). Background therapy of ICS/LABA is to be withdrawn during the 12-week randomized treatment period and resumed at the end of the IMP treatment period for the 20-week safety follow-up period (Section 1.1 and Section 1.2), as outlined below:

- Screening period (4 weeks ± 3 days)
- Randomized IMP Treatment Period (12 weeks ± 3 days)
  - Background therapy stabilization phase (4 weeks)
  - Background therapy withdrawal phase (4-5 weeks, see Section 6.1.1 and for more details see Section 8.2.1)
  - No background therapy phase (3-4 weeks, see Section 1.2)
- Post IMP treatment safety follow-up period (20 weeks ± 5 days)

At the Screening Visit 1, all patients must be on a stable therapy for their asthma which must include any 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 1.

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 background therapy with fluticasone/salmeterol, as approved for region:

- Fluticasone/salmeterol - dry powder inhaler (DPI):
  1 puff of 250/50 mcg twice daily (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

Please note that patients should use the same inhaler type (either DPI or MDI) throughout 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 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.

Visits during the 12-week IMP treatment period will occur every week and will be followed by a 20-week observational follow-up period.

6.1.1 Background therapy (ICS/LABA) withdrawal phase

Withdrawal of background therapy with the ICS fluticasone and the LABA salmeterol, during the 12-week IMP treatment period, will be performed as described in Section 8.2.1, and summarized below (for overview please refer to Section 1.1 and Section 1.2).

At Week 4 (Visit 6) post-randomization, the LABA component (salmeterol) will be withdrawn, and patients will be switched from their BID fluticasone/salmeterol combination therapy to a clinically comparable ICS dose of fluticasone BID 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

The ICS component (fluticasone) will be withdrawn by a step-wise dose reduction starting at Week 6 (Visit 8) and will continue at each Weeks 7, 8, and 9 (Visits 9, 10, and 11, respectively), provided that patients do not experience a LOAC event.

An appropriate inhaler for each required ICS dose while patient is in screening and on IMP treatment will be provided by the Sponsor per local regulation.

Patients that meet the criteria for a LOAC, at any time during the randomized IMP treatment phase, will (be):

- Discontinue early from IMP treatment,
- Evaluated and receive treatment by the Investigator with standard of care according to standard medical practice,
- Resume their individual prescreening ICS/LABA background therapy and
- Followed for safety during the 20-week Post IMP Treatment Period.

6.1.2 Early treatment discontinuation (ETD) follow-up

Patients who discontinue IMP treatment prior to completing the 12-week IMP treatment (due to LOAC or due to early treatment discontinuation [ETD]), will be evaluated as soon as possible at the individual patients' End of Treatment (EOT) Visit, using procedures as planned for the EOT Visit at Week 12 (Visit 14). At their EOT visit, patients will resume their prescreening ICS/LABA background therapy and enter the 20-week safety follow-up period/Post IMP Treatment Period (Visit 15 to Visit 17).

6.1.3 Post IMP treatment follow-up

Patients who complete the 12-week randomized IMP treatment period at Week 12 (Visit 14) EOT visit, as per protocol, resume their prescreening ICS/LABA therapy and enter the 20-week safety follow-up period/Post IMP Treatment Period (Visit 15 to Visit 17).

Note: For patients who meet the criteria for a LOAC or discontinue IMP treatment early (due to other reasons) prior to 12 weeks of treatment, their ETD EOT visit and their individual 20-week Post IMP Treatment Period may start earlier than at Week 12.

At any EOT visit, if a patient's asthma cannot be adequately controlled by the prescreening ICS/LABA therapy, additional controller therapies may be prescribed based on the Investigator's clinical judgement.

6.2 DURATION OF STUDY PARTICIPATION

6.2.1 Duration of study participation for each patient

Study participation for each patient will be a total of 252 days (approximately 36 weeks) including 28 days screening, 84 days IMP treatment period, and 140 days post IMP treatment safety follow-up period.

6.2.2 Determination of end of clinical trial (all patients)

The last patient last visit (the End of Study (EOS) Visit at Week 32, Day 225) will occur at the end of a 20-week safety follow-up period for those patients who complete the study as per protocol.

Patients who discontinue prematurely from the study (prior to completing the 12-week IMP treatment) will be evaluated as soon as possible using the procedure normally planned for the EOT Visit at Week 12 (Visit 14), and return to the study site for the post IMP treatment safety follow-up period (Visit 15 to Visit 17).

6.3 INTERIM ANALYSIS

No formal interim analysis is planned. Analyses will be performed for safety monitoring and internal decision making. No formal stopping rules or adjustment for multiplicity will be applied.

6.4 STUDY COMMITTEES

6.4.1 Data monitoring committee

An internal data monitoring committee (DMC) will be unblinded and comprised of individuals with expertise in the diseases under study, biostatistics, or clinical research. The DMC members are independent of the project/study teams and are not involved in the study conduct. The primary responsibilities of the DMC are to review and evaluate the study data during the course of the trial and make appropriate recommendations regarding the conduct of the clinical trial to the project/study team.

The DMC procedures and data to be reviewed by the DMC are described in the DMC charter.

6.5 DISCUSSION OF STUDY DESIGN AND CHOICE OF CONTROL GROUPS

ACT15102 study will evaluate the efficacy and safety of SAR440340, and the coadministration of the same dose level of both SAR440340 and dupilumab (for more details please refer to Section 4.4), administered SC q2w over a 12-week treatment period for the treatment of patients with moderate-to-severe asthma. This study design has been successfully deployed in a previous Phase 2a investigation of dupilumab (19).

The 12-week treatment duration is based on published data from ACT11457 dupilumab study with similar design, and should allow the observation of a reduction of the LOAC (primary efficacy variable) with SAR440340, and the coadministration of SAR440340 with dupilumab, as compared to placebo, considering the severity of the target population, under medium to high dose ICS/LABA therapy. In addition, 12-weeks are deemed sufficient to demonstrate treatment-induced changes on reversibility of airflow limitation as measured by FEV1 (secondary efficacy variable).

A follow-up period of 20 weeks, which covers approximately to 5 half-lives of SAR440340, will allow safety and efficacy recording after the end of the intervention period. The safety analysis will focus on the TEAE period, from the first administration of the IMP to 22 weeks after the last administration of the IMP.

7 SELECTION OF PATIENTS

A total of up to approximately 240 subjects (up to approximately 60 subjects per treatment arm) are expected to be randomized and treated in up to approximately 80 sites worldwide.

The Screening Visit blood eosinophils count will be assessed at baseline and it is planned that at least approximately 45% of patients will have blood eosinophil counts of $\geq 300/mm^3$ and no more than approximately 25% of patients will have blood eosinophil counts $<150/mm^3$ (stratified randomization).

7.1 INCLUSION CRITERIA

I 01. Adult patients with a physician diagnosis of asthma for at least 12 months based on the Global Initiative for Asthma (GINA) 2017 Guidelines (1).

I 02. Patients with existing treatment with medium to high dose ICS (≥250 mcg of fluticasone propionate 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 Visit 1. Please note that the lower limit of allowed ICS dose (500 mcg of fluticasone propionate daily) corresponds to upper limit of medium dose defined by GINA guidelines. Patients receiving medium ICS dose <500 mcg daily are not eligible.

I 03. Patients with prebronchodilator forced expiratory volume (FEV1) >40% of predicted normal at Visit 1/Screening. Prebronchodilator FEV1 ≥50% but ≤85% of predicted normal at Visit 2/Baseline.

I 04. Patients with reversibility of at least 12% and 200 mL in FEV1 after administration of 2 to 4 puffs (200-400 mcg) of albuterol/salbutamol or levalbuterol/levosalbutamol during screening or documented history of a reversibility test that meets this criteria within 12 months prior to Visit 1 or documented positive response to methacholine challenge (a decrease in FEV by 20% [PC_{20}] of < 8mg/mL) within 12 months prior to Visit 1/Screening is considered acceptable to meet this inclusion criterion.

I 05. Patients must have experienced, within 1 year prior to Visit 1, any of the following events at least once:

- Treatment with a systemic steroid (oral or parenteral) for worsening asthma.
- Hospitalization or emergency medical care visit for worsening asthma.

I 06. Signed written informed consent.

7.2 EXCLUSION CRITERIA

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

7.2.1 Exclusion criteria related to study methodology

E 01. Patients less than 18 years or >70 years of age (ie, have reached the age of 71 at the screening visit).

E 02. Patients with body mass index (BMI) <16.

E 03. Chronic lung disease (for example, chronic obstructive pulmonary disease [COPD], or idiopathic pulmonary fibrosis [IPF]), which may impair lung function, or another diagnosed pulmonary or systemic disease associated with elevated peripheral eosinophil counts, for eg eosinophilic granulomatosis with polyangiitis.

E 04. History of life threatening asthma (ie, severe exacerbation that requires intubation).

E 05. Co-morbid disease that might interfere with the evaluation of IMP.

E 06. Patients with any of the following events within the 4 weeks prior to their Screening Visit 1 or during the screening period:

- Treatment with 1 or more systemic steroid (oral or parenteral) bursts for worsening asthma.
- Hospitalization or an emergency medical care visit for worsening asthma.

E 07. Asthma Control Questionnaire 5-question version (ACQ-5) score <1.25 or >3.0 at V2/randomization. During the screening period an ACQ-5 of up to ≤4 is acceptable.

E 08. Anti-IgE therapy (eg, omalizumab [Xolair®]) within 130 days prior to Visit 1 or any other biologic therapy (including anti-IL5 mAb) or systemic immunosuppressant (eg, methotrexate, any anti-TNF mAbs, B and/or T cell targeted immunosuppressive therapies) to treat inflammatory disease or autoimmune disease (eg, rheumatoid arthritis, inflammatory bowel disease, primary biliary cirrhosis, systemic lupus erythematosus, multiple sclerosis) and other diseases, within 2 months or 5 half-lives prior to Visit 1, whichever is longer.

E 09. Patients with a history of a systemic hypersensitivity reaction to a monoclonal antibody.

E 10. Patients on or initiation of bronchial thermoplasty within 2 years prior to Visit 1 or plan to begin therapy during the screening period or the randomized IMP treatment period.

E 11. Current smoker or cessation of smoking within the 6 months prior to Visit 1.

E 12. Previous smoker with a smoking history >10 pack-years.

E 13. Current history of substance and/or alcohol abuse.

E 14. Inability to follow the procedures of the study (eg, due to language problems, psychological disorders) or unable to read, understand and fill a questionnaire or use an electronic diary without any help.

E 15. Exposure to another investigative drug (small molecules as well as monoclonal antibodies) within a time period prior to Visit 1 that is <5 PK half-lives of the antibody. In case the half-life is not known, then the minimum interval since the exposure to the prior investigative antibody is 6 months. The minimum interval since exposure to any other (non-antibody) investigative study medication is 30 days prior to Visit 1.

E 16. Clinically relevant abnormal laboratory values suggesting an unknown disease and requiring further evaluation.

E 17. Patients who have previously been treated in any clinical trial of SAR440340 or dupilumab, or have been treated with commercially available dupilumab.

E 18. Patient is the Investigator, or any Subinvestigator, research assistant, pharmacist, study coordinator, other staff or relative thereof directly involved in the conduct of the study.

E 19. Prisoners and patients who are legally institutionalized.

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

E 20. Clinically significant abnormal electrocardiogram (ECG) at Visit 1 that may affect the conduct of the study in the judgment of the Investigator.

E 21. Concomitant severe diseases or diseases for which the use of ICS (eg, active and inactive pulmonary tuberculosis) or LABA based on judgment of Investigator are contraindicated.

E 22. Use of injectable glucocorticosteroids or oral systemic glucocorticosteroids within 1 month prior to Visit 1/Screening or more than 4 courses of IV glucocorticosteroids within the 6 months prior to Visit 1.

E 23. Patients during the screening period that require medications or therapy that are prohibited as concomitant medications (see Section 8.8).

E 24. A patient with a history of clinically significant renal, hepatic, cardiovascular, metabolic, neurologic, hematologic, ophthalmologic, respiratory, gastrointestinal, cerebrovascular or other significant medical illness or disorder which, in the judgment of the Investigator, could interfere with the study or require treatment that might interfere with the study. Specific examples include but are not limited to uncontrolled diabetes, severe hypertension, severe ischemic heart disease, unstable angina in the last 6 months, unstable cardiac arrhythmias, and Class IV heart failure.

E 25. Exclusion related to tuberculosis (TB):

- Active TB or a history of incompletely treated TB.
- Confirmed Quantiferon-positive patients (no active disease) are excluded from the study unless all of the following conditions are met:
  - Patients with a history of prior documented completed chemoprophylaxis for latent tuberculosis infection (TBI) (with a treatment regimen as per local guidelines) or treatment of active TBI, and
  - Has obtained consultation with a specialist to rule out or treat active TBI, and
  - Review and approval from Sponsor has been granted.
- Suspected extrapulmonary TB infection.
- Patients at high risk of contracting TB, such as close contact with individuals with active or latent TB.
- Patient who received Bacille Calmette Guerin (BCG)-vaccination within 12 months prior to Screening Visit 1.

E 26. Patients on DPI controller within 1 month prior to visit 1 in those countries where the study specified doses of controllers are not available in the DPI formulation

7.2.3 Exclusion criteria related to the current knowledge of SAR440340

E 27. Known allergy to doxycycline or related compounds or known allergy to SAR440340 excipients.

E 28. Females who are lactating, breastfeeding or who are pregnant.

E 29. Women of childbearing potential (premenopausal female biologically capable of becoming pregnant) who:

- Do not have:
  - A confirmed negative serum β-human chorionic gonadotropin (β-hCG) test at Visit 1.
  - Negative urine pregnancy test prior to Visit 2/Randomization.
- Who are not protected by one of the acceptable forms of effective contraception (See Appendix A) during the protocol-defined time frame (Section 6.2.1).

Postmenopausal women (defined as at least 12 consecutive months without menses) are not required to use additional contraception.

For men in the study:

- Male participants with female partners of childbearing potential are not eligible to participate unless they agree to ONE of the following (during the protocol-defined time frame [Section 6.2.1]):

- Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent.
- Agree to use a male condom plus partner use of a contraceptive method with a failure rate of <1% per year (see Appendix A) when having penile-vaginal intercourse with a woman of childbearing potential who is not currently pregnant.

- Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration (during the protocol-defined time frame [Section 6.2.1]).

E 30. Diagnosed active parasitic infection (helminthes), suspected or high risk of parasitic infection, unless clinical and (if necessary) laboratory assessments have ruled out active infection before randomization.

E 31. History of human immunodeficiency virus (HIV) infection or positive HIV 1/2 serology at Visit 1.

E 32. Known or suspected history of immunosuppression, including history of invasive opportunistic infections (eg, tuberculosis, histoplasmosis, listeriosis, coccidioidomycosis, penumocystosis, aspergillosis), despite infection resolution; or unusually frequent, recurrent or prolonged infections, per Investigator's judgment.

E 33. Evidence of acute or chronic infection requiring treatment with antibacterials, antivirals, antifungals, antiparasitics, or antiprotozoals within 4 weeks before Visit 1, significant viral infections within 4 weeks before Visit 1 that may not have received antiviral treatment (eg, influenza receiving only symptomatic treatment).

E 34. Live attenuated vaccinations within 12 weeks prior to Visit 1 or planned live, attenuated vaccinations during the study; see Appendix B for list of prohibited live, attenuated vaccines.

E 35. Patients with autoimmune disease or patients using systemic immunosuppressive therapy for autoimmune disease (eg, rheumatoid arthritis, inflammatory bowel disease, primary biliary cirrhosis, systemic lupus erythematosus, multiple sclerosis, etc) or patients with high titer autoantibodies at screening who are suspected of having high risk for developing autoimmune disease at the discretion of the Investigator or the Sponsor.

E 36. Patients requiring maintenance treatment with non-selective β-1 adrenergic receptor blockers.

E 37. Active hepatitis or patients with positive or indeterminate hepatitis B surface antigen (HBs Ag), hepatitis B core antibody (HBc Ab) (Confirmed with presence of hepatitis B virus [HBV] deoxyribonucleic acid [DNA]) or positive hepatitis C virus antibody (HCV Ab) (Confirmed with presence of HCV RNA [RNA]) at Screening Visit 1.

E 38. Any prior history of malignancy or active malignancy, including lymphoproliferative diseases (except successfully treated carcinoma in-situ of the cervix, non-metastatic

squamous cell or basal cell carcinoma of the skin) within 5 years prior to Screening Visit 1.

E 39. Clinically significant laboratory tests at Visit 1:

- Alanine transaminase (ALT) or aspartate transaminase (AST) >3 times upper limit of normal range (ULN),
- Hemoglobin <10 g/dL for male and <9 g/dL for female,
- Neutrophils <1.5 K/mm^3 (except <1.0 /mm^3 for those of African descent),
- Platelets <100 K/mm^3,
- Creatinine ≥150 µmol/L.

7.2.4 Additional exclusion criteria during or at the end of the screening period

E 40. Patient who has withdrawn consent before enrollment/randomization.

E 41. Despite screening of the patient, enrollment/randomization is stopped at the study level.

8 STUDY TREATMENTS

8.1 INVESTIGATIONAL MEDICINAL PRODUCT(S)

8.1.1 SAR440340

Sterile SAR440340 will be provided in one 20 mL vial containing 287 mg of lyophilisate drug product.

8.1.2 SAR440340 matching placebo

Sterile placebo for SAR440340 will be provided in matched 20 mL vial containing lyophilisate placebo.

8.1.3 Dupilumab

Sterile dupilumab (ie, SAR231893) will be provided as 150 mg/mL in glass prefilled syringe to deliver 300 mg in 2.0 mL.

8.1.4 Placebo matching dupilumab

Sterile placebo for dupilumab will be provided in matched glass prefilled syringe to deliver 2.0 mL.

8.1.5 Preparation of investigational product

SAR440340 or matching placebo lyophilisate will be reconstituted by an unmasked site pharmacist or designee (not involved with study) as per instruction provided in study pharmacy manual.

Administration will be performed by blinded nurse or designee as per instruction provided in study pharmacy manual.

Dupilumab or matching placebo in glass prefilled syringes will be dispensed to the Investigator or designee for administration to the respective patient. Additional information will be provided in the pharmacy manual.

8.1.6 Dosing schedule

The IMP is administered every 14±3 days (q2w) by the Investigator or designee during visits to the study site.

Investigational medicinal product will be administered by the Investigator or designee following clinic procedures and blood collection. Patients should be monitored for any signs or symptoms of a hypersensitivity reaction for at least 30 minutes after all IMP injections are administered. The monitoring period may be extended up to 2 hours as per country specific requirements. Trained personnel and medications should be available to treat anaphylaxis or any severe allergic reaction if it occurs.

Subcutaneous injection sites should alternate between the upper thighs, 4 quadrants of the abdomen or the upper arms, so that the same site is not injected twice during 2 consecutive visits.

8.2 NONINVESTIGATIONAL MEDICINAL PRODUCT(S)

Noninvestigational medicinal product (Asthma Control Therapy) during screening and treatment will be locally sourced at site level. In the case site will not be able to locally manage the provision of the product, the clinical study unit or local depot will assist the site by providing the products to the sites or voucher to the patients.

At the Screening Visit 1, all patients must be on a stable therapy for their asthma which must include any medium or high dose ICS therapy (see Appendix C) in combination with a LABA as second controller for at least 3 months with a stable dose ≥1 month prior to screening. Please note that eligible medium ICS dose of 250 mcg of fluticasone propionate BID or equipotent ICS daily dosage corresponds to upper limit of medium dose defined by GINA guidelines in Appendix C. Please note that doses may be country-specific depending on labelling requirements.

The third controller is not allowed during the screening and treatment phase of the study, and may not be used for an additional 4 weeks prior to screening visit (V1). After completion of screening procedures, all eligible patients will be switched to a clinically comparable dose of the study-specific ICS/LABA background therapy with fluticasone/salmeterol, as approved for region:

- Fluticasone/salmeterol – dry powder inhaler (DPI):
  1 puff of 250/50 mcg twice daily (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 – metered dose inhaler (MDI):
  2 puffs of 125/25 mcg (250/50 mcg) BID or
  2 puffs of 250/25 mcg (500/50 mcg) BID

Please note that patients should use the same inhaler type (either DPI or MDI) throughout the study.

From Screening Visit 1 to Visit 2/randomization (4 weeks), all eligible patients will receive fluticasone/salmeterol as study-specific ICS/LABA background therapy. This background treatment is maintained for the first 4 weeks of randomized IMP treatment during the background therapy stabilization phase.

8.2.1 Background therapy (ICS/LABA) withdrawal phase

Withdrawal of background therapy with the ICS fluticasone and the LABA salmeterol, during the 12-week IMP treatment period, will be performed as described below in detail for each visit from Week 4 through Week 9 (for overview please refer to Section 1.1 and Section 1.2).

Week 4 (Visit 6) – LABA withdrawal:

At Week 4 (Visit 6) post-randomization, the LABA component (salmeterol) will be withdrawn, and patients will be switched from their BID fluticasone/salmeterol combination therapy to a clinically comparable ICS dose of fluticasone BID 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

Week 6 (Visit 8) – ICS withdrawal

The ICS component (fluticasone) will be withdrawn by a step-wise dose reduction (see Table 1) starting at Week 6 (Visit 8) and will continue at each Weeks 7, 8, and 9 (Visits 9, 10, and 11, respectively), provided that patients do not experience a LOAC event (see description below Table 1).

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 a LOAC at any time during this ICS/LABA withdrawal phase (and randomized treatment period), he/she will be withdrawn from IMP and treated by the Investigator with standard of care according to standard medical practice. The patient will resume his/her original ICS/LABA (ie, prior to screening) background therapy and will be followed for safety, if possible, for the subsequent 20-week Post IMP Treatment Period as planned per protocol.

End of IMP Treatment Visit 14 (Week 12) – prescreening ICS/LABA is resumed

Upon completing the 12-week randomized IMP treatment (or following early discontinuation of investigational products), 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.

8.2.2 Reliever medication

The reliever medication will not be dispensed or supplied by the Sponsor.

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.

The description of the criterion for qualifying an asthma exacerbation event based on nebulizer using, will use the nebulizer-to-puff conversion factor for application to loss of asthma control (LOAC) definition.

Salbutamol/albuterol nebulizer and levosalbutamol/levalbuterol nebulizer use will be converted 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 = 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 = 3.75 mg or 12 puffs.

After conversion of nebulizer-to-puff, and for every instance, where the number of puffs is ≥6 additional puffs of salbutamol/albuterol or levosalbutamol/levalbuterol in a 24-hour period (compared to Baseline) on 2 consecutive days in any week, a LOAC event should be documented.

8.3 BLINDING PROCEDURES

8.3.1 Methods of blinding

SAR440340 and placebo will be provided in treatment kits indistinguishable in appearance and will be labeled with a treatment kit number. The randomized treatment kit number list will be generated by Sanofi.

In accordance with the double-blind design, study patients, Investigators, and study site personnel (except the personnel who conduct the reconstitution of the IMP and preparation of syringes for injection) will remain blinded except under circumstances described in Section 8.3.2.

To maintain blinding, the personnel involved with dose preparation will be required to agree not to reveal to other study personnel the type of IMP solution (SAR440340 or dupilumab versus placebo) in the vials/syringes.

Dupilumab and placebo will be provided in identically matched prefilled syringes. To protect the blind, each treatment kit of glass prefilled syringes (dupilumab/placebo) will be prepared such that the treatments (dupilumab and its matching placebo) are identical and indistinguishable and will be labeled with a treatment kit number. The randomized treatment kit number list will be generated by Sanofi.

Patients, Investigators, and study site personnel will not have access to the randomization (treatment codes) except under circumstances described in Section 8.3.2.

8.3.2 Randomization code breaking during the study

In case of an AE, the code must only be broken in circumstances when knowledge of the IMP is required for treating the patient.

Code breaking can be performed at any time by using the proper module of the Interactive Response Technology (IRT) and/or by calling any other phone number provided by the Sponsor for that purpose. If the blind is broken, the Investigator must document the date, time of day, and reason for code breaking.

Subject withdrawal will only occur when the code break call is made at the site level, not the study level. This means that if the Emergency Unblinding transaction is performed by the Investigator (ie, at the site level), then the subject will be withdrawn from treatment. However, if the Emergency Unblinding transaction is performed by the Global Safety Officer (GSO) (ie, at the study level, as the GSO is not site based), then the subject will not be withdrawn from treatment.

8.4 METHOD OF ASSIGNING PATIENTS TO TREATMENT GROUP

Randomized treatment kit number lists will be generated centrally by Sanofi. The investigational product (SAR440340 or matching placebo and dupilumab or matching placebo) will be packaged in accordance with these lists. The Sanofi clinical supplies team will provide the randomized

treatment kit number lists and the randomization scheme to the centralized treatment allocation system (IVRS/IWRS). This centralized treatment allocation system will generate the patient randomization list according to which it will allocate the treatment to the patients. Patients who meet the entry criteria will be randomized to receive either SAR440340 or matching placebo in combination with either dupilumab or matching placebo. The Investigator obtains treatment kit numbers at randomization and subsequent scheduled visits via an IVRS/IWRS that will be available 24 hours a day. Patients will be randomized in a 1:1:1:1 ratio to receive SC administrations of either:

- SAR440340 300 mg q2w, and coadministration of dupilumab placebo or
- Dupilumab 300 mg q2w and coadministration of SAR440340 placebo or
- SAR440340 300 mg and dupilumab 300 mg q2w coadministration or
- Placebo to both SAR440340 and dupilumab q2w coadministration.

If certain dynamic laboratory tests do not meet the eligibility criteria, these laboratory assessments may be repeated, at the discretion of the Investigator, if it is judged to be likely to return to acceptable range for study inclusion within the screening visit window (28 days) prior to Day 1. These patients do not need to sign a new informed consent form (ICF) and be allocated a new patient number within this same screening window.

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

Randomization will be stratified by Screening Visit 1 eosinophil count and by country.

To ensure enrollment according to intended distribution of baseline eosinophil count, alerts will be built into the IVRS/IWRS system to limit enrolling patients in the following 2 stratification groups:

- Eosinophil <150 /mm^3 not more than approximately 25% (60) patients
- Eosinophil ≥ 300 /mm^3 at least approximately 45% (108) patients

8.5 INVESTIGATIONAL MEDICINAL PRODUCT PACKAGING AND LABELING

SAR440340 and placebo will be supplied as 1 glass vial packed in a patient kit box. Both glass vial and box will be labeled.

Dupilumab and placebo will be supplied as 1 glass prefilled syringe packed in a patient kit box. Both glass prefilled syringe and box will be labeled.

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

8.6 STORAGE CONDITIONS AND SHELF LIFE

Investigators or other authorized persons (eg, pharmacists) are responsible for storing the IMP/NIMP in a secure and safe place in accordance with local regulations, labeling specifications, policies, and procedures.

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

8.7 RESPONSIBILITIES

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

All IMP/NIMP will be dispensed in accordance with the Investigator's prescription and it is the Investigator's responsibility to ensure that an accurate record of IMP/NIMP issued and returned is maintained.

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

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

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

8.7.1 Treatment accountability and compliance

The Investigator or pharmacist will also keep accurate records of the quantities of the IMP/NIMP dispensed, used, and unused. The IMP/NIMP tracking log and inventory form is to be updated each time IMP/NIMP is dispensed. The study monitor will periodically check the supplies of the IMP/NIMP held by the Investigator or pharmacist to verify accountability. Treatment kit number has to be recorded on the appropriate page of the electronic Case Report Form (eCRF) and also on the IMP/NIMP tracking log and inventory log form.

The monitoring team in charge of the study will have to check case report form data comparing them with the centralized treatment allocation system information, the IMP kit and IMP tracking log and inventory form.

For NIMP not provided by the Sponsor, tracking and reconciliation has to be achieved by the Investigator and must be captured in standard site documents and records (eg, medical notes).

8.7.2 Return and/or destruction of treatments

All partially used or unused treatment kits will be retrieved by the Sponsor or destroyed at study site. The Investigator will not destroy any unused IMP unless the Sponsor provides written authorization.

A detailed treatment log of the destroyed IMP will be established with the Investigator (or the pharmacist) and countersigned by the Investigator and the monitoring team.

For NIMP not provided by the Sponsor, tracking and reconciliation has to be achieved by the Investigator and need to be captured in standard site documents and records (eg, medical notes).

8.8 CONCOMITANT MEDICATION

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

The following concomitant treatments are not permitted during the screening or treatment phases:

- Any inhaled steroid other than the standardized fluticasone/salmeterol or fluticasone background therapy administered as per protocol
- Systemic steroids (except systemic steroids to treat asthma exacerbations)
- LABA other than the salmeterol component of the fixed dose combination administered per protocol
- Ipratropium bromide or other inhaled anti-cholinergic agents (tiotropium)*
- Methylxanthines (theophylline, aminophyllines)*
- Leukotriene receptor antagonists or leukotriene synthesis inhibitors*
- Lipoxygenase inhibitors
- Cromones
- Anti-IL5 mAb
- Anti-IgE therapy (eg, omalizumab [Xolair®])
- Systemic immunosuppressant (eg, methotrexate, any anti-TNF mAbs, B and/or T cell targeted immunosuppressive therapies)
- Bronchial thermoplasty
- Intravenous Ig (IVIG) therapy
- Live Attenuated Vaccines: refer to Appendix B
- Beta-adrenergic receptor blockers (except for a selective beta-1 adrenergic receptor blocker used with dose stabled 1 month prior to Visit 1)
- Asthma relievers other than salbutamol/albuterol or levosalbutamol/levalbuterol: their use is not recommended during the study period. In case of use in exceptional circumstances

(eg, prescribed by a physician not participating in the study), their use will be documented in the patient's file and reported in the eCRF.

- Other investigational drugs

Note: The following is a list of permitted concomitant medications during the study

- Antihistamines are permitted as concomitant medication.
- Ocular, intranasal, and topical corticosteroids are permitted during the study.

* The third controller is not allowed to be used for an additional 4 weeks prior to screening visit (V1).

9 ASSESSMENT OF INVESTIGATIONAL MEDICINAL PRODUCT

9.1 PRIMARY ENDPOINT

The primary endpoint is the proportion of patients with LOAC (for definition, see Section 5).

9.2 SECONDARY AND OTHER EFFICACY ENDPOINTS

The secondary endpoint for this study is:

- FEV1 change from baseline at Week 12 (pre- and post-bronchodilator).

9.2.1 Other efficacy endpoints

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

9.2.2 Disease-specific efficacy measures

9.2.2.1 Spirometry

Spirometry should be performed in accordance with the American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines (21) and prior to administration of investigational product.

For prebronchodilator measured 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.

Reversibility is defined as an increase of the absolute FEV1 after administration of bronchodilator, and is measured by spirometry as postbronchodilator increase of FEV1 in percent of the prebronchodilator FEV1. After spirometry for measuring prebronchodilator 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 postbronchodilator spirometry may be repeated several times within 30 minutes after administration of bronchodilator. If the subject does not meet reversibility at Visit 1/Screening, up to 2 additional attempts during the screening period, each on a different day prior to Visit 2/Baseline, may be performed. When reversibility assessment is repeated during the screening period, the prebronchodilator FEV1 should again meet the inclusion criterion (I 03) of >40% of predicted normal.

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

9.2.2.2 Disease-specific, daily efficacy assessments

9.2.2.2.1 Electronic diary/PEF meter

The electronic diary/PEF meter is dispensed at Visit 1 and recorded information is downloaded from this device on the other indicated days (Section 1.2). The electronic diary/PEF meter is used for daily recording of salbutamol/albuterol or levosalbutamol/levalbuterol use, asthma controller drug use, asthma symptoms, nocturnal awakenings due to asthma symptoms and AM and PM PEF.

On a daily basis throughout the study (except 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.
- Indicate the number of inhalations/day of salbutamol/albuterol or levosalbutamol/levalbuterol for symptom relief.
- Record the number of inhalations/day of ICS/LABA or ICS background therapy.
- Record the number of nocturnal awakenings due to asthma symptoms.

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 PEF will be the mean AM measurement recorded for the 7 days prior to the first dose of IMP, and baseline PM PEF will be the mean PM measurement recorded for the 7 days prior to the first dose of investigational product. Period stability limit is defined as the respective mean AM or PM PEF obtained over the last 7 days prior to Day 1. There should be at least 4 days of measurements for setting up the stability limit, and the first dosing visit may be rescheduled until data for 4 days are available.

Information derived from the electronic PEF meter will be evaluated by the Investigator at study visits.

In the Post IMP Treatment Period, the patient's response in the electronic diary/PEF meter will not be recorded daily; questionnaires will only be administered at on-site visits.

9.2.2.3 ACQ (Asthma Control Questionnaire)

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 (see Appendix D).

Measurement properties such as reliability and ability to detect change have been documented in the literature (22).

The ACQ-5 is short version of ACQ-7, and ACQ-5 score is the mean of the first 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 is the smallest change that can be considered clinically important, corresponding to the Minimal Clinically Important Difference (MCID) defined by the developer.

9.2.2.4 Asthma Quality Of Life Questionnaire with Standardized Activities Self-Administered

The Asthma Quality Of Life Questionnaire with Standardized Activities (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 (23).

The instrument is comprised of 32 items (see Appendix E), each rated on a 7-point Likert scales from 1 to 7. The AQLQ(S) has 4 domains. The domains and the number of items in each domain are as follows:

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

Patients are asked to recall how their asthma has been during the previous 2 weeks.

A global score is calculated ranging from 1 to 7 and a score by domain. Higher scores indicate better quality of life.

The magnitude of effect of asthma treatments is measured by the mean change from baseline between treatment and control groups. The instrument has been used in many clinical trials, and it has been shown to be reliable, valid (patient interviews), and sensitive to change. 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. Measurement properties such as reliability and ability to detect change have been documented in the literature. The proportion of patients achieving clinically relevant responder thresholds is defined as the percentage of patients with a change or difference in individual score of at least 0.5. In addition, the total score on each domain could be useful for the interpretation of the magnitude of effect.

9.2.2.5 Standardized Rhinoconjunctivitis Quality of Life Questionnaire in those patients with comorbid allergic rhinitis

Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ[S]) is a self-administered questionnaire (Appendix F) with standardized activities developed to measure health-related quality of life signs and symptoms that are most problematic in adults, as a result of perennial or seasonal allergic rhinitis (24).

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). Higher scores indicated more health-related quality of life impairment (lower scores better).

The magnitude of effect of asthma treatment is measured by the mean change from baseline between treatment and control groups. An MCID of 0.5 has been established as the minimal important difference indicative of a clinically meaningful change defining responders. The proportion of patients achieving clinically relevant responder thresholds is defined as the percentage of patients with a change or difference in individual score of at least 0.5. In addition, the total score on each domain could be useful for the interpretation of the magnitude of effect.

9.2.2.6 Asthma Symptom Score Numerical Rating Scale (NRS)

Patients will record overall symptom scores in an electronic diary/PEF meter 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). Baseline symptom scores will be the mean AM and mean PM scores recorded for the 7 days prior to randomization. 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. There is no global score, just an AM score and a PM score. An MCID of 0.35 is being used (25) (see Appendix G).

9.2.3 Safety and tolerability endpoints

The same safety assessments will be applied across all arms. Adverse events, including SAEs and AEs of special interest (AESI), will be collected at every visit. The Investigator will ask the patient how he/she has felt since the last study visit. The study-specific and general safety criteria are detailed in Section 10.6.

9.2.3.1 Adverse events

Adverse events for each patient will be monitored and documented from the time the patient gives informed consent at Visit 1 until the End-of-Study visit (Visit 17) except for:

- Serious AEs
- Adverse events that are ongoing at database lock

Adverse events, AESI, and SAEs will be reported as described in Section 10.4.3.

9.2.3.1.1 Physical examination

Complete physical examinations will include an assessment of skin, nasal cavities, eyes, ears, respiratory, cardiovascular, gastrointestinal, neurological, lymphatic, and musculoskeletal systems. All deviations from normal will be recorded, including those attributable to the patient's disease.

Refer to Section 1.2 for the schedule of physical examinations performed throughout this study.

9.2.3.2 Vital signs

Vital signs, including systolic and diastolic blood pressure (mmHg), pulse rate (beats per minute), and respiratory rate (breaths per minute) and body temperature will be measured at all visits. Vital signs will be measured in the sitting position using the same arm (preferably). Height (cm) will be measured at screening (Visit 1) only.

Body weight (kg) will be measured at screening (Visit 1), baseline (Visit 2), and EOT (Visit 14). Refer to Section 1.2 for the schedule of vital signs performed throughout this study.

9.2.3.3 Electrocardiogram

Recording of a standard 12-lead ECG will be performed at the clinical site. Refer to Section 1.2 for the schedule of ECG performed throughout this study. At the postrandomization 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. Refer to ECG reading manual for more details. All ECG recordings will be centrally read by independent experts.

9.2.3.4 Clinical laboratory tests

The clinical laboratory tests will be conducted by an accredited (College of American Pathologists or equivalent) central laboratory with national and regional clinical licenses as required for diagnostic testing and must provide evidence of participation in proficiency testing, as appropriate. After reviewing the laboratory report and evaluating any results that are outside the normal range, the Investigator must sign and date the laboratory report.

Abnormal laboratory values that are considered to be clinically significant by the Investigator must be repeated as soon as possible after receiving the laboratory report to rule out laboratory error. Persistent abnormal laboratory values should be repeated until they return to normal or until an etiology of the persistent abnormality is determined.

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

The clinical laboratory parameters that will be measured are:

- Hematology: To include hemoglobin, hematocrit, platelet count, total white blood cell (WBC) count with 5-part differential count, and total red blood cell (RBC) count. Neutrophil and eosinophil counts (study biomarkers) will also be evaluated as a part of hematology testing.
- Serum chemistry: To include creatinine, blood urea nitrogen, glucose, uric acid, total cholesterol, total protein, albumin, total bilirubin (in case of values above the normal range, differentiation in conjugated and nonconjugated bilirubin), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, electrolytes (sodium, potassium, chloride), bicarbonate, and creatine phosphokinase (CPK).
- Urinalysis will include 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.
- Clinical laboratory testing at Screening Visit 1 will include hepatitis screen covering HBs Ag, hepatitis B surface antibody (HBs Ab), HBc Ab, hepatitis C virus antibodies (HCV Ab), HIV screen (Anti-HIV-1 and HIV-2 antibodies) and anti-nuclear antibody (ANA). In case of results showing HBs Ag (negative), and HBc Ab (positive), an HBV DNA testing may be performed prior to randomization to rule out a false positivity if the Investigator believes the patient is a false positive, or to clarify the serological status if the Investigator finds it unclear to interpret in absence of known HBV infection. In case of results showing HCV Ab (positive), an HCV RNA testing may be performed to rule out a false positivity, if the Investigator believes the patient is a false positive.
  Note: Anti-ds DNA antibody will be tested if ANA is positive (≥1:160 titer).
- Clinical laboratory testing at Screening Visit 1 will also include Quantiferon gold testing for all patients. If the result is confirmed positive, the patient should be referred to an Infectious Disease specialist. Please refer to the central laboratory manual for additional details.

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

9.2.3.5 Pregnancy test

For women of childbearing potential only: serum pregnancy test at Screening/Visit 1 and urine pregnancy tests at Visits 2, 6, 10, 14/EOT and Visit 17/EOS. A negative result must be obtained at Visit 1 and at Visit 2 prior to randomization. In case of positive urinary test, the study treatment will be withheld and a serum pregnancy test should be performed as soon as possible to confirm the pregnancy. Pregnancy will lead to definitive treatment discontinuation in all cases. Refer to Section 1.2 for the schedule of pregnancy test performed throughout this study.

9.3 OTHER ENDPOINTS

9.3.1 Systemic drug concentration and anti-drug antibodies

- Serum functional SAR440340 or dupilumab concentrations
- Anti-drug antibodies (ADA) against SAR440340
- Anti-drug antibodies (ADA) against dupilumab

9.3.1.1 Sampling time

Predose blood samples will be collected for determination of functional SAR440340 and dupilumab concentrations in serum (PK profile) and ADA against SAR440340 and dupilumab in serum (immunogenicity and safety) as summarized in the study flow chart (Section 1.2). The date of collection should be recorded in the patient eCRF. In a patient with treatment-emergent ADA response, if the sample at week 12 or the first post-treatment time point analyzed is positive in the ADA assay, then ADA assessments may be performed on PK samples collected at Week 4.

If an SAE or listed AESI (anaphylaxis, systemic hypersensitivity reaction, and severe injection site reaction [ISR] lasting 24 hours), occurs in a patient, blood samples should be collected for determination of functional IMP concentration, and ADA assessment at or near the onset and completion of the occurrence of the event, if possible. The exact date and time of sample collection must be recorded and entered into the database by the central laboratory. An unscheduled systemic drug concentration page in the eCRF must be completed as well. If necessary for safety monitoring, additional additional blood for an ADA sample may be drawn after the EOS Visit until resolution of AE.

Further follow-up of individual patients will be considered based on the overall assessment of antibody titers and clinical presentation.

9.3.1.2 Handling procedures

Special procedures for collection, storage, and shipping of serum are described in separate operational manuals. An overview of handling procedure for samples used in the determination of systemic drug concentration and ADA is provided in Table 2.

Table 2 - Summary of handling procedures for samples

Sample type	PK (SAR440340 or dupilumab)	ADA (SAR440340 or Dupilumab)
Matrix	Serum	Serum
Blood sample volume	5 mL	5 mL
Anticoagulant	None	None
Blood handling procedures	See Operational Manual	See Operational Manual
Serum aliquot split	Two aliquots	Two aliquots
Serum shipment condition	In dry ice	In dry ice

Additional samples can be collected for safety.

9.3.1.3 Bioanalytical method

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

Table 3 - Summary of bioanalytical methods for pharmacokinetics and antidrug antibody

Analyte	PK (SAR440340 or dupilumab)	ADA (SAR440340 or dupilumab)
Matrix	Serum	Serum
Analytical technique	ELISA	Electrochemiluminescence
Site of bioanalysis	Regeneron	Regeneron

ADA = anti-drug antibody; ELISA: enzyme-linked immunosorbent assay; PK: pharmacokinetics.

9.3.2 Pharmacodynamics and phenotyping

9.3.2.1 Pharmacodynamic variables

- Blood eosinophil and neutrophil counts (Section 9.3.2.2)
- Fraction of exhaled nitric oxide (FeNO) level compared with baseline (Section 9.3.2.3)
- Total IL33 and soluble IL33 receptor (sST2; serum sample)
- Calcitonin (serum sample)
- Pulmonary and activation-regulated chemokine (PARC) (serum samples)
- Eotaxin-3 (sodium heparinized samples)
- Total IgE (serum samples)
- Periostin (serum samples)

- Optional: Messenger ribonucleic acid (mRNA) sequencing or whole transcriptome analysis (PaxGene samples)
- Optional: Blood sample archival for exploratory research (serum and plasma)
- Optional: Deoxyribonucleic acid (DNA) sample will be collected for assessment of pharmacogenomic effects (blood sample)

For timing of pharmacodynamic sample collection refer to study flow chart Section 1.2.

Assay methodologies are briefly summarized below. More detailed information on the collection, handling, transport, and preservation of samples (eg, minimum volumes required for blood collection and for aliquots for each biomarker assay) will be provided in a separate laboratory manual.

9.3.2.2 Whole blood biomarkers

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

9.3.2.3 Exhaled nitric oxide

Fractional exhaled nitric oxide (FeNO) will be analyzed using a NIOX instrument (Aerocrine AB, Solna, Sweden), or similar analyzer using a flow rate of 50 mL/s, and reported in parts per billion (ppb). This assessment should be conducted prior to spirometry and following a fast of at least 1 hour. Further details on the procedure for measuring exhaled nitric oxide with NIOX will be provided in a separate instruction manual.

9.3.2.4 Plasma/serum biomarkers

Total IL33 and sST2 will be measured in serum samples. Pulmonary and activation-regulated chemokine (PARC) will be assayed using a validated enzyme immunoassay. Periostin will be assessed using the SHINO test.

For calcitonin, developement of the method is currently ongoing.

Eotaxin-3 will be measured in heparinized plasma with a validated enzyme immunoassay (Human Eotaxin-3 Quantikine ELISA kit).

Total IgE will be measured with a fluorenzyme immunoassay (Phadia 1000) approved for diagnostic testing.

9.3.3 Pharmacogenetics

9.3.3.1 Stored DNA (optional) and RNA (optional) samples

Pharmacogenetic testing is optional and voluntary. Written informed consent must be obtained before sampling.

For those patients who provided written consent to the collection of the optional pharmacogenetic 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. Specific procedures for collection, storage, and shipping of pharmacogenetic samples will be provided in a lab manual.

Deoxyribonucleic acid (DNA) samples for the genomics sub study will be used to identify genomic associations with clinical or biomarker response, other clinical outcome measures and possible AEs. In addition, association between genomic variants and prognosis or progression of diseases may also be studied. These data may be used or combined with data collected from other studies to identify and validate genomic markers related to the study drug or diseases. The DNA may be subjected to a genome-wide association study by whole exome sequencing, single nucleotide polymorphism studies of candidate genes, DNA copy number variations or whole genome analysis in order to thoroughly explore genetic associations with disease progression or treatment response. The list of methods may be expanded to include novel methodology that may be developed during the course of this study or sample storage period.

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

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

The aliquots of DNA sent to the bioanalytical laboratories for specific genetic testing will be destroyed after completion of that specific analysis and issuance of the related analytical data.

9.4 FUTURE USE OF SAMPLES

Not all of the samples collected during this study may be required for the tests planned in this clinical trial. For patient(s) who have consented to it, the samples that are archived, unused or left over after planned testing may be used for additional research purposes (any genetic analysis subject to additional consent per Section 9.3.3). For patients who have consented to it, archival

blood samples will be collected at the visits specified in the study flow chart. Additional details will be provided in the laboratory manual.

These archived serum and plasma samples, and any residual or leftover serum, plasma or blood remaining from planned laboratory work, may be used for research purposes related to inflammatory diseases (eg, exploratory biomarkers of disease or drug effect), pathway biology, additional drug safety assessments or development and validation of bioassay methods beyond those defined in the present protocol. These samples will remain labelled with the same identifiers as the ones used during the study (ie, patient ID, sample ID). They will be transferred to a Sanofi site (or a subcontractor site) which can be located outside of the country where the study is conducted. The Sponsor has included safeguards for protecting patient confidentiality and personal data (see Section 14.3 and Section 14.5).

9.5 APPROPRIATENESS OF MEASUREMENTS

The efficacy and safety assessments used in this study are standard for the evaluation of therapy in patients with asthma.

10 STUDY PROCEDURES

10.1 VISIT SCHEDULE

The clinical trial consist of 3 periods, including an add-on ICS/LABA (fluticasone/salmeterol, standardized at screening) background therapy that is withdrawn during the 12-week randomized IMP (SAR440340 and/or dupilumab and/or placebo) treatment period and resumed at the end of the IMP treatment period for the 20-week safety follow-up period (Section 1.1 and Section 1.2), as outlined below:

- Screening period (4 weeks [±3 days])
- Randomized IMP treatment (12 weeks [±3 days])
  - Background therapy stable phase (4 weeks)
  - Background therapy withdrawal phase (4-5 weeks, see Section 6.1.1 and for more details see Section 8.2.1)
  - No background therapy phase (3-4 weeks, see Section 1.2)
- Post IMP treatment safety follow-up period (20 weeks [±5 days])

The study visits occur on the planned dates (relative to the first injection), as scheduled. The visit schedule should be adhered to within ±3 days for the screening period and randomized IMP treatment period and ±5 days for the 3 visits during the post IMP treatment safety follow-up period.

Spirometry should be performed at approximately the same time of the day (either in the AM or PM, but preferably in the AM, as detailed in Section 9.2.2.1) at each visit throughout the study.

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 EOT assessments and participate in follow-up assessments according to the visit schedule.

Reminder: sexually active patients (both male and female) of reproductive potential are required to practice an effective contraception throughout the participation in the study including follow-up period. Sites should counsel all study patients, regarding the importance of practicing responsible and effective contraception throughout the participation in the study including follow-up period.

Prior to all screening assessments, after discussion of participation in the study, the written consent form (including voluntary participation in pharmacogenetic testing/future use of blood samples) must be signed and dated.

Although the screening assessments for this study are grouped under the heading of a single visit in this protocol, it is possible for them to be performed over more than 1 site visit if necessary, as long as the screening visit window prior to randomization (Day 1) is respected. If certain dynamic laboratory tests do not meet the eligibility criteria, these laboratory assessments may be repeated,

at the discretion of the Investigator, if it is judged to be likely to return to acceptable range for study inclusion within the screening visit window (4 weeks ± 3 days) prior to Day 1. These patients do not need to sign a new ICF or be allocated a new patient number within this same screening window.

If the subject does not meet the qualifying criteria for reversibility at Visit 1/Screening, up to 2 additional attempts during the screening period, each on a different day prior to Visit 2/Baseline, may be performed. When reversibility assessment is repeated during the screening period, the prebronchodilator FEV1 should again meet the inclusion criterion (I 03) of >40% of predicted normal.

Patients that fail the initial screening for exclusion criteria (eg, concomitant medications) may be rescreened for study eligibility 1 additional time. Patients that are rescreened must sign a new consent form and will be allocated a new patient number; all of the Visit 1 procedures must be repeated (refer to Section 8.4 for further instructions related to rescreening) unless a prior assessment is performed within the time frame permitted prior to study entry.

It is recommended that assessments/procedures at a site visit are performed in the following order if applicable and possible:

1. Patient-reported outcomes and other questionnaires
2. ECG
3. Procedures:
   a) FeNO
   b) Spirometry (FEV1) and Reversibility
   c) Electronic Diary download
4. Safety and laboratory assessments
5. Administration of IMP

10.1.1 Visit 1/Screening (Week -4 to Week 0 [zero], Day -28 to Day 0) – Screening Visit

Following a discussion of participation in the clinical trial, informed consent must be obtained and documented. These steps precede any study procedures. The visit schedule should be adhered to within the ±3 day visit window allowed during the treatment phase of the study.

The following procedures will then be performed:

- Call IVRS/IWRS to assign patient number and register screening visit.
- Interview to collect patient demographic information, asthma history (including smoking habits), previous medical history and surgical history, and prior and concomitant medications. Inquire about AEs/SAEs.
- Administer ACQ-5 via handheld device
- Perform 12-lead ECG

- Review entry criteria to assess eligibility (Section 7.1 for details) , with special attention to verify the following:
  - Existing treatment with medium to high dose ICS (≥250 mcg of fluticasone propionate 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 Visit 1.
- Perform Spirometry (review eligibility criteria) and measure exhaled nitric oxide:
  - Exhaled nitric oxide assessment is conducted prior to spirometry and following a fast of ≥1 hour.
  - Spirometry will be performed after a washout period of bronchodilators according to their action duration, for example, withholding the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours and withholding the last dose of LABA for at least 12 hours. This will be verified before performing the measurements.
  - Patients with reversibility of at least 12% and 200 mL in FEV1 after administration of 2 to 4 puffs (200-400 mcg) of albuterol/salbutamol or levalbuterol/levosalbutamol during screening or documented history of a reversibility test that meets this criteria within 12 months prior to Visit 1 or documented positive response to methacholine challenge (a decrease in FEV by 20% [PC_{20}] of <8mg/mL) within 12 months prior to Visit 1/Screening is considered acceptable to meet this inclusion criterion.

    Note: If the subject does not meet the qualifying criteria for reversibility at Visit 1/Screening, up to 2 additional attempts during the screening period, each on a different day prior to Visit 2/Baseline, may be performed. When reversibility assessment is repeated during the screening period, the prebronchodilator FEV1 should again meet the inclusion criterion (I 03) of >40% of predicted normal.
- Perform physical examination (refer to Section 9.2.3.1.1). Complete physical examination will include skin, nasal cavities, eyes, ears, respiratory, cardiovascular, gastrointestinal, neurological, lymphatic, and musculoskeletal systems.
- Measure vital signs (including systolic and diastolic blood pressure [mmHg], heart rate [beats per minute], respiration rate [breaths per minute], body temperature [°C], body weight [kg], and height [cm]).

After determination of preliminary eligibility:

- Obtain blood samples for screening clinical laboratory (see Section 9.2.3.4 for details) determinations: hematology and serum chemistry.
- Obtain blood samples for screening serology: HBs Ag, HBs Ab, HBc Ab, hepatitis C virus antibodies (HCV Ab), anti-HIV-1 and HIV-2 antibodies, and ANA.
- Obtain urine sample for urinalysis.
- Quantiferon gold testing.

  Note: If the result is confirmed positive, the patient should be referred to an Infectious Disease specialist.

- Obtain serum β-hCG pregnancy test if female of childbearing potential
- Perform blood sampling for the following tests:
  - Biomarker set: blood eosinophils and neutrophils, total IL33, sST2, calcitonin, PARC, eotaxin-3, total IgE and periostin (refer to Section 9.3.2.4),
  - Optional: Sample for RNA panel testing for those patients who have consented to it
  - Optional: Archival of serum and plasma for those patients who have consented to Future Use of Specimens (refer to Section 9.4)
- Dispense electronic diary/PEF meter handheld device, provide instructions for daily use, and remind patient to bring the device to the next visit.

  The electronic diary/PEF meter is a handheld device used for daily recording of salbutamol/albuterol or levosalbutamol/levalbuterol use, asthma controller drug use, nocturnal awakenings due to asthma symptoms and AM and PM PEF, and recordings of patient's answers to the ACQ-5, AQLQ(S), and RQLQ questionnaires during the scheduled visits. These handheld devices are dispensed at Visit 1 (including instructions for use) and recorded information is downloaded from the devices on the other indicated days (Section 1.2). At Visit 14/EOT, recorded information is downloaded from the handheld devices and the devices are returned at EOS as the lastest.
- All eligible patients will be switched to the study-specific ICS/LABA background therapy, which consists of BID fluticasone/salmeterol inhalations, at clinically comparable doses (to each individual patient's prescribed ICS/LABA dose level prior to screening, ie, meeting the preprotocol definition of medium or high dose ICS/LABA; Section 7.1), as approved for region (Section 8.2):
  - Fluticasone/salmeterol – dry powder inhaler (DPI):
    1 puff of 250/50 mcg twice daily (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 – metered dose inhaler (MDI):
    2 puffs of 125/25 mcg (250/50 mcg) BID or
    2 puffs of 250/25 mcg (500/50 mcg) BID
- Dispense study-specific ICS/LABA medication (DPI or MDI).
- Remind patients to use fluticasone/salmeterol combination as background therapy medication. Instruct patient to record daily usage in the electronic diary.
- Remind patients to use salbutamol/albuterol or levosalbutamol/levalbuterol as reliever medication throughout the study. Instruct patient to record usage in the electronic diary.

- Remind patient to withhold albuterol or levalbuterol (if any) for at least 6 hours and LABA for at least 12 hours prior to next visit.
- Schedule a site visit for Visit 2, Day 1 and request patient to come at approximately the same time of day as this visit.

10.1.2 Randomized IMP Treatment Phase – Week 0 to Week 12

10.1.2.1 Background therapy stabilization phase – Week 0 to Week 3 (Visits 2 to 5)

The visit schedule should be adhered to within the ±3 day visit window allowed during the treatment phase of the study.

10.1.2.1.1 Visit 2/Randomization/Baseline (Week 0/Day 1)

- Record all concomitant medication use with start date and dose in eCRF; inquire about AEs/SAEs and background asthma therapy tolerability and compliance.
- Administer ACQ-5, AQLQ(S), and, only to patients with history of allergic rhinitis, RQLQ(S) via handheld device.
- Perform spirometry and measure exhaled nitric oxide:
  - Exhaled nitric oxide assessment is conducted prior to spirometry and following a fast of ≥1 hour.
  - Spirometry will be performed at approximately the same time of day as the last visit, prior to administration of IMP and after withholding the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours and withholding the last dose of LABA for at least 12 hours. This will be verified before performing the measurements.
  - Prebronchodilator FEV1 should be determined.
  - Postbronchodilator FEV1 should be determined.
- Download electronic diary information from the handheld device, and remind patient to bring the device to the next visit.
- Perform physical examination.
- Perform urine pregnancy test (for women of childbearing potential)
- Measure vital signs (including systolic and diastolic blood pressure [mmHg], pulse rate [beats per minute], body weight [kg], respiratory rate [breaths per minute] and body temperature [°C]).

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

- Call IVRS/IWRS to register visit, randomize the patient if entry criteria are met, and receive the first assignment for treatment kit numbers.
  - Note: Please screen-fail the patient if entry criteria are not met.

- Perform baseline blood sampling (prior to administration of IMP) for the following tests:
  - PK analysis
  - Hematology and serum chemistry
  - Anti-SAR440340 antibody and anti-dupilumab antibody
  - Biomarker set: blood eosinophils and neutrophils, total IL33, sST2, calcitonin, PARC, eotaxin-3, total IgE, and periostin (refer to Section 9.3.2.4)
  - Optional: Sample for RNA panel testing
  - Optional: Archival of serum and plasma for those patients who have consented to Future Use of Specimens (refer to Section 9.4)
  - Optional: Sample for DNA for those patients who have consented to pharmacogentics, please refer to Section 9.3.3)
- Obtain urine sample for urinalysis.
- Administration of IMP.
  - Patients should be monitored by site personnel for at least 30 minutes after administration of all IMP injections. Monitoring period may be extended up to 2 hours as per country specific requirements.
- Remind patients to use fluticasone/salmeterol combination as background therapy medication. Instruct patient to record daily usage in the electronic diary.
- Remind patients to use salbutamol/albuterol or levosalbutamol/levalbuterol as reliever medication throughout the study. Instruct patient to record usage in the electronic diary.
- Remind patient to withhold albuterol or levalbuterol (if any) for at least 6 hours and LABA for at least 12 hours prior to next visit.
- Schedule a site visit for Visit 3 (Day 8, Week 1) and request patient to come at approximately the same time of day as this visit.

10.1.2.1.2 Visit 3, Day 8 (Week 1)

- Record all concomitant medication use; inquire about AEs/SAEs and asthma therapy tolerability.
- Evaluate patient for a LOAC event.
- Perform spirometry:
  - Spirometry will be performed at approximately the same time of day as the last visit, prior to administration of IMP and after withholding the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours and withholding the last dose of LABA for at least 12 hours. This will be verified before performing the measurements.
  - Prebronchodilator FEV1 should be determined.

- Download electronic diary information from the handheld device and remind patient to bring the device to the next visit.
- Measure vital signs (including systolic and diastolic blood pressure [mmHg], pulse rate [beats per minute], respiratory rate and body temperature [°C]).
- Remind patients to use fluticasone/salmeterol combination as background therapy medication. Instruct patient to record daily usage in the electronic diary.
- Remind patients to use salbutamol/albuterol or levosalbutamol/levalbuterol as reliever medication throughout the study. Instruct patient to record usage in the electronic diary.
- Remind patient to withhold albuterol or levalbuterol (if any) for at least 6 hours and LABA for at least 12 hours prior to next visit.
- Schedule a site visit for Visit 4, Day 15 and request patient to come at approximately the same time of day as this visit.

10.1.2.1.3 Visit 4, Day 15 (Week 2)

- Record all concomitant medication use; inquire about AEs/SAEs and asthma therapy tolerability.
- Evaluate patient for a LOAC event.
- Administer ACQ-5, AQLQ(S), and, only to patients with history of allergic rhinitis, RQLQ(S) via handheld device.
- Perform spirometry and measure exhaled nitric oxide:
  - Exhaled nitric oxide assessment is conducted prior to spirometry and following a fast of ≥1 hour.
  - Spirometry will be performed at approximately the same time of day as the last visit, prior to administration of IMP and after withholding the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours and withholding the last dose of LABA for at least 12 hours. This will be verified before performing the measurements.
  - Prebronchodilator FEV1 should be determined.
- Download electronic diary information from the handheld device and remind patient to bring the device to the next visit
- Measure vital signs (including systolic and diastolic blood pressure [mmHg], pulse rate [beats per minute], respiratory rate and body temperature [°C]).
- Perform blood sampling (prior to administration of IMP) for the following tests:
  - PK analysis
  - Biomarkers: blood eosinophils and neutrophils
- Call IVRS/IWRS to register visit and obtain next treatment kit numbers
- Administration of IMP.

- Patients should be monitored by site personnel for at least 30 minutes after administration of all IMP injections. Monitoring period may be extended up to 2 hours as per country specific requirements.

- Remind patients to use fluticasone/salmeterol combination as background therapy medication. Instruct patient to record daily usage in the electronic diary.
- Remind patients to use salbutamol/albuterol or levosalbutamol/levalbuterol as reliever medication throughout the study. Instruct patient to record usage in the electronic diary.
- Remind patient to withhold albuterol or levalbuterol (if any) for at least 6 hours prior to next visit.
- Schedule a site visit for Visit 5, Day 22 and request patient to come at approximately the same time of day as this visit.

10.1.2.1.4 Visit 5, Day 22 (Week 3)

- Record all concomitant medication use with start date and dose in eCRF; inquire about AEs/SAEs and asthma therapy tolerability and compliance.
- Evaluate patient for a LOAC event.
- Perform spirometry:
  - Spirometry will be performed at approximately the same time of day as the last visit, prior to administration of IMP and after withholding the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours and withholding the last dose of LABA for at least 12 hours. This will be verified before performing the measurements.
  - Prebronchodilator FEV1 should be determined.
- Download electronic diary information from the handheld device and remind patient to bring the device to the next visit.
- Measure vital signs (including systolic and diastolic blood pressure [mmHg], pulse rate [beats per minute], respiratory rate and body temperature [°C]).
- Remind patients to use fluticasone/salmeterol combination as background therapy medication. Instruct patient to record daily usage in the electronic diary.
- Remind patients to use salbutamol/albuterol or levosalbutamol/levalbuterol as reliever medication throughout the study. Instruct patient to record usage in the electronic diary.
- Remind patient to withhold albuterol or levalbuterol (if any) for at least 6 hours prior to next visit.
- Schedule a site visit for Visit 6, Day 29 and request patient to come at approximately the same time of day as this visit (fasting if morning visit).

10.1.2.2 Background therapy withdrawal phase – Week 4 to Week 9 (Visits 6 to 11): LABA withdrawal at Week 4, ICS step-wise withdrawal starting at Week 6

PLEASE NOTE: depending on high or medium dose fluticasone backgound therapy at Visit 2/baseline, patients will have a 5- or 4-week ICS/LABA withdrawal phase, respectively, and thus will be on IMP treatment without background therapy for 3 or 4 weeks, respectively, before resuming original (prescreening) ICS/LABA therapy at Visit 14/EOT (for overview, please see Section 1.1, Section 1.2, Section 8.2.1 and Table 1).

10.1.2.2.1 Visit 6, Day 29 (Week 4) – Withdrawal of LABA

- Record all concomitant medication use with start date and dose in eCRF; inquire about AEs/SAEs and asthma therapy tolerability and compliance.
- Evaluate patient for a LOAC event.
- Administer ACQ-5, AQLQ(S), and, only to patients with history of allergic rhinitis, RQLQ(S) via handheld device.
- Perform 12-lead ECG.
- Perform spirometry and measure exhaled nitric oxide:
  - Exhaled nitric oxide assessment is conducted prior to spirometry and following a fast of ≥1 hour.
  - Spirometry will be performed at approximately the same time of day as the last visit, prior to administration of IMP and after withholding the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours and withholding the last dose of LABA for at least 12 hours. This will be verified before performing the measurements.
  - Prebronchodilator FEV1 should be determined.
  - Postbronchodilator FEV1 should be determined.
- Download electronic diary information from the handheld device and remind patient to bring the device to the next visit.
- Perform physical examination.
- Perform urine pregnancy test (for women of childbearing potential).
- Measure vital signs (including systolic and diastolic blood pressure [mmHg], pulse rate [beats per minute], respiratory rate [breaths per minute] and body temperature [°C]).
- Perform blood sampling (prior to administration of IMP) for the following tests:
  - PK analysis
  - Hematology and serum chemistry
  - Biomarker set: blood eosinophils and neutrophils, total IL33, sST2, calcitonin, PARC, eotaxin-3, total IgE, periostin (refer to Section 9.3.2.4)
  - RNA panel testing (optional)

- Archival serum for those patients who have consented to collection for Future Use of Specimens (refer to Section 9.4)

- Obtain urine sample for urinalysis
- Call IVRS/IWRS to register visit and obtain next treatment kit numbers
- Administration of IMP
  - Patients should be monitored by site personnel for at least 30 minutes after administration of all IMP injections. Monitoring period may be extended up to 2 hours as per country specific requirements.
- At Week 4 (Visit 6), the LABA component (salmeterol) will be withdrawn, and all patients will be switched from their BID fluticasone/salmeterol combination therapy (from Screening Visit 1 up to Visit 6) to a clinically comparable ICS dose of fluticasone BID monotherapy (Section 8.2.1), 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
- Dispense ICS monotherapy MDI or DPI (see above) for use in the evening of this visit day and until morning of the next visit day. Please update controller profile in the electronic diary web portal accordingly.
- Remind patients to use fluticasone monotherapy as background therapy medication. Instruct patient to record daily usage in the electronic diary.
- Remind patients to use salbutamol/albuterol or levosalbutamol/levalbuterol as reliever medication throughout the study. Instruct patient to record usage in the electronic diary.
- Remind patient to withhold albuterol or levalbuterol (if any) for at least 6 hours prior to next visit.
- Schedule a site visit for Visit 7, Day 36 and request patient to come at approximately the same time of day as this visit.

10.1.2.2.2 Visit 7, Day 36 (Week 5)

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

- Evaluate patient for a LOAC event.
- Perform spirometry:
  - Spirometry will be performed at approximately the same time of day as the last visit, prior to administration of IMP and after withholding the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours. This will be verified before performing the measurements.
  - Prebronchodilator FEV1 should be determined.
- Download electronic diary information from the handheld device and remind patient to bring the device to the next visit.
- Measure vital signs (including systolic and diastolic blood pressure [mmHg], pulse rate [beats per minute], respiratory rate and body temperature [°C]).
- Remind patients to use fluticasone monotherapy as background therapy medication. Instruct patient to record daily usage in the electronic diary.
- Remind patients to use salbutamol/albuterol or levosalbutamol/levalbuterol as reliever medication throughout the study. Instruct patient to record usage in the electronic diary.
- Remind patient to withhold albuterol or levalbuterol (if any) for at least 6 hours prior to next visit.
- Schedule a site visit for Visit 8, Day 43 and request patient to come at approximately the same time of day as this visit.

10.1.2.2.3 Visit 8, Day 43 (Week 6) – Begin ICS withdrawal steps

- Record all concomitant medication use with start date and dose in eCRF; inquire about AEs/SAEs and asthma therapy tolerability and compliance.
- Evaluate patient for a LOAC event.
- Administer ACQ-5, AQLQ(S), and, only to patients with history of allergic rhinitis, RQLQ(S) via handheld device.
- Perform spirometry:
  - Spirometry will be performed at approximately the same time of day as the last visit, prior to administration of IMP and after withholding the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours. This will be verified before performing the measurements.
  - Prebronchodilator FEV1 should be determined.
  - Postbronchodilator FEV1 should be determined.
- Download electronic diary information from the handheld device and remind patient to bring the device to the next visit.
- Measure vital signs (including systolic and diastolic blood pressure [mmHg], pulse rate [beats per minute], respiratory rate [breaths per minute], and body temperature [°C]).

- Collection of blood samples for:
  - Biomarkers: blood eosinophils and neutrophils
- Call IVRS/IWRS to register visit and obtain next treatment kit numbers
- Administration of IMP
  - Patients should be monitored by site personnel for at least 30 minutes after administration of all IMP injections. Monitoring period may be extended up to 2 hours as per country specific requirements.

Step-wise ICS fluticasone withdrawal commences at this Visit 8 (Week 6):

- If no new LOAC event, proceed with next lower ICS dose level of fluticasone for each individual patient (Week 6, Visit 8). Please update controller profile in the electronic diary web portal accordingly.
- Dispense ICS monotherapy at the next lower ICS dose level of fluticasone for each individual patient, as approved for region (please refer to Table 1), for use in the evening of this visit day and until morning of the next visit day.
- Remind patients to use fluticasone monotherapy as background therapy medication. Instruct patient to record daily usage in the electronic diary.
- Remind patients to use salbutamol/albuterol or levosalbutamol/levalbuterol as reliever medication throughout the study. Instruct patient to record usage in the electronic diary.
- Remind patient to withhold albuterol or levalbuterol (if any) for at least 6 hours prior to next visit.
- Schedule a site visit for Visit 9, Day 50 and request patient to come at approximately the same time of day as this visit.

10.1.2.2.4 Visit 9, Day 50 (Week 7)

- Record all concomitant medication use with start date and dose in eCRF; inquire about AEs/SAEs and asthma therapy tolerability and compliance.
- Evaluate patient for a LOAC event.
- Perform spirometry:
  - Spirometry will be performed at approximately the same time of day as the last visit, prior to administration of IMP and after withholding the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours. This will be verified before performing the measurements.
  - Prebronchodilator FEV1 should be determined.
- Download electronic diary information from the handheld device and remind patient to bring the device to the next visit.
- Measure vital signs (including systolic and diastolic blood pressure [mmHg], pulse rate [beats per minute], respiratory rate and body temperature [°C]).

- If no new LOAC event, proceed with next lower ICS dose level of fluticasone for each individual patient (Week 7, Visit 9).
- Dispense ICS monotherapy at the next lower ICS dose level of fluticasone for each individual patient, as approved for region (please refer to Table 1), for use in the evening of this visit day and until morning of the next visit day. Please update controller profile in the electronic diary web portal accordingly.
- Remind patients to use fluticasone monotherapy as background therapy medication. Instruct patient to record daily usage in the electronic diary.
- Remind patients to use salbutamol/albuterol or levosalbutamol/levalbuterol as reliever medication throughout the study. Instruct patient to record usage in the electronic diary.
- Remind patient to withhold albuterol or levalbuterol (if any) for at least 6 hours prior to next visit.
- Schedule a site visit for Visit 10, Day 57 and request patient to come at approximately the same time of day as this visit (fasting if morning visit).

10.1.2.2.5 Visit 10, Day 57 (Week 8)

- Record all concomitant medication use with start date and dose in eCRF; inquire about AEs/SAEs and asthma therapy tolerability and compliance.
- Evaluate patient for a LOAC event.
- Administer ACQ-5, AQLQ(S), and, only to patients with history of allergic rhinitis, RQLQ(S) via handheld device.
- Perform spirometry and measure exhaled nitric oxide:
  - Exhaled nitric oxide assessment is conducted prior to spirometry and following a fast of ≥1 hour.
  - Spirometry will be performed at approximately the same time of day as the last visit, prior to administration of IMP and after withholding the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours. This will be verified before performing the measurements.
  - Prebronchodilator FEV1 should be determined.
  - Postbronchodilator FEV1 should be determined.
- Download electronic diary information from the handheld device and remind patient to bring the device to the next visit.
- Perform physical examination.
- Perform urine pregnancy test (for women of childbearing potential)
- Measure vital signs (including systolic and diastolic blood pressure [mmHg], pulse rate [beats per minute], respiratory rate [breaths per minute] and body temperature [°C]).

- Perform blood sampling (fasting if morning visit, prior to administration of IMP) for the following tests:
  - PK analysis
  - Biomarker set: blood eosinophils and neutrophils, total IL33, sST2, calcitonin, PARC, eotaxin-3 (refer to Section 9.3.2.4)
  - Hematology and serum chemistry
- Obtain urine sample for urinalysis.
- Call IVRS/IWRS to register visit and obtain next treatment kit number
- Administration of IMP
  - Patients should be monitored by site personnel for at least 30 minutes after administration of all IMP injections. Monitoring period may be extended up to 2 hours as per country specific requirements.
- If no new LOAC event, proceed with next lower ICS dose level of fluticasone for each individual patient (Week 8, Visit 10), or proceed with no background therapy (please refer to Table 1) until LOAC or Visit 14 (Week 12), whichever comes first.
- Dispense ICS monotherapy at the next lower ICS dose level of fluticasone for each individual patient on high dose ICS, as approved for region (please refer to Table 1), for use in the evening of this visit day and until morning of the next visit day. Please update controller profile in the electronic diary web portal accordingly.
- Remind patients on lowest ICS dose to use fluticasone monotherapy as background therapy medication. Instruct patient to record daily usage in the electronic diary.
- Remind patients to use salbutamol/albuterol or levosalbutamol/levalbuterol as reliever medication throughout the study. Instruct patient to record usage in the electronic diary.
- Remind patient to withhold albuterol or levalbuterol (if any) for at least 6 hours prior to next visit.
- Schedule a site visit for Visit 11, Day 64 and request patient to come at approximately the same time of day as this visit.

10.1.2.3 No ICS/LABA background therapy phase – Week 9 to Week 12 (Visits 11 to 14)

PLEASE NOTE: depending on high or medium dose fluticasone backgound therapy at Visit 2/baseline, patients will have a 5- or 4-week ICS/LABA withdrawal phase, respectively, and thus will be on IMP treatment without background therapy for 3 or 4 weeks, respectively, before resuming original (prescreening) ICS/LABA therapy at Visit 14/EOT (for more details, see Section 1.2 and Table 1).

10.1.2.3.1 Visit 11, Day 64 (Week 9)

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

- Evaluate patient for a LOAC event.
- Perform spirometry:
  - Spirometry will be performed at approximately the same time of day as the last visit, prior to administration of IMP and after withholding the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours. This will be verified before performing the measurements.
  - Prebronchodilator FEV1 should be determined.
- Download electronic diary information from the handheld device and remind patient to bring the device to the next visit.
- Measure vital signs (including systolic and diastolic blood pressure [mmHg], pulse rate [beats per minute], respiratory rate and body temperature [°C]).
- If no new LOAC event, proceed without background therapy (see Table 1) until LOAC or Visit 14 (Week 12), whichever comes first. Please update controller profile in the electronic diary web portal accordingly if appropriate.
- Remind patients to use salbutamol/albuterol or levosalbutamol/levalbuterol as reliever medication throughout the study. Instruct patient to record usage in the electronic diary.
- Remind patient to withhold albuterol or levalbuterol (if any) for at least 6 hours prior to next visit.
- Schedule a site visit for Visit 12, Day 71 and request patient to come at approximately the same time of day as this visit.

10.1.2.3.2 Visit 12, Day 71 (Week 10)

- Record all concomitant medication use with start date and dose in eCRF; inquire about AEs/SAEs and asthma therapy tolerability and compliance.
- Evaluate patient for a LOAC event.
- Administer ACQ-5, AQLQ(S), and, only to patients with history of allergic rhinitis, RQLQ(S) via handheld device.
- Perform spirometry:
  - Spirometry will be performed at approximately the same time of day as the last visit, prior to administration of IMP and after withholding the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours. This will be verified before performing the measurements.
  - Prebronchodilator FEV1 should be determined.
  - Postbronchodilator FEV1 should be determined.
- Download electronic diary information from the handheld device and remind patient to bring the device to the next visit.

- Measure vital signs (including systolic and diastolic blood pressure [mmHg], pulse rate [beats per minute], respiratory rate [breaths per minute] and body temperature [°C]).
- Call IVRS/IWRS to register visit and obtain next treatment kit numbers
- Administration of IMP
  - Patients should be monitored by site personnel for at least 30 minutes after administration of all IMP injections. Monitoring period may be extended up to 2 hours as per country specific requirements.
- Remind patients to use salbutamol/albuterol or levosalbutamol/levalbuterol as reliever medication throughout the study. Instruct patient to record usage in the electronic diary.
- Remind patient to withhold albuterol or levalbuterol (if any) for at least 6 hours prior to next visit.
- Schedule a site visit for Visit 13, Day 78 and request patient to come at approximately the same time of day as this visit.

10.1.2.3.3 Visit 13, Day 78 (Week 11)

- Record all concomitant medication use with start date and dose in eCRF; inquire about AEs/SAEs and asthma therapy tolerability and compliance.
- Evaluate patient for a LOAC event.
- Perform spirometry:
  - Spirometry will be performed at approximately the same time of day as the last visit, prior to administration of IMP and after withholding the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours. This will be verified before performing the measurements.
  - Prebronchodilator FEV1 should be determined.
- Download electronic diary information from the handheld device and remind patient to bring the device to the next visit.
- Measure vital signs (including systolic and diastolic blood pressure [mmHg], pulse rate [beats per minute], respiratory rate and body temperature [°C]).
- Remind patients to use salbutamol/albuterol or levosalbutamol/levalbuterol as reliever medication throughout the study. Instruct patient to record usage in the electronic diary.
- Remind patient to withhold albuterol or levalbuterol (if any) for at least 6 hours prior to next visit.
- Schedule a site visit for Visit 14, Day 85 and request patient to come at approximately the same time of day as this visit (fasting if morning visit).

10.1.2.4 Week 12 (Visit 14) – End of Treatment – End of Randomized IMP Treatment Period

10.1.2.4.1 Visit 14, Day 85 (Week 12)/EOT Visit/for Patients that Discontinue Study Treatment Prematurely: Individual EOT Visit – Begin of Post-IMP-treatment Safety Follow-up Period with Resumed Prescreening ICS/LABA Background Therapy

- Record all concomitant medication use with start date and dose in eCRF; inquire about AEs/SAEs and asthma therapy tolerability and compliance.
- Evaluate patient for a LOAC event.
- Administer ACQ-5, AQLQ(S), and, only to patients with history of allergic rhinitis, RQLQ(S).
- Perform 12-lead ECG
- Perform spirometry and measure exhaled nitric oxide:
  - Exhaled nitric oxide assessment is conducted prior to spirometry and following a fast of ≥1 hour.
  - Spirometry will be performed at approximately the same time of day as the last visit, prior to administration of IMP and after withholding the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours. This will be verified before performing the measurements.
  - Prebronchodilator FEV1 should be determined.
  - Postbronchodilator FEV1 should be determined.
- Download electronic diary information from the handheld device, and collect the PEF and e-diary devices from the patient, or ensure collection at EOS.
- Perform physical examination.
- Perform urine pregnancy test (for women of childbearing potential, including women that discontinue IMP treatment early due to any reason)
- Measure vital signs (including systolic and diastolic blood pressure [mmHg], pulse rate [beats per minute], body weight [kg], respiratory rate [breaths per minute] and body temperature [°C]).
- Perform blood sampling (fasting if morning visit, prior to administration of IMP) for the following tests:
  - PK analysis
  - Hematology and serum chemistry
  - Anti-SAR440340 antibody and anti-dupilumab antibody
  - Biomarker set: Blood eosinophils and neutrophils, total IL33, sST2, calcitonin, PARC, eotaxin-3, total IgE, and periostin (refer to Section 9.3.2.4)
  - RNA panel testing (optional)

- Archival serum for those patients who have consented to collection for Future Use of Specimens (refer to Section 9.4)

- Obtain urine sample for urinalysis

Upon completing 12 weeks of treatment with IMP (or following early discontinuation of IMP), patients enter the 20-week Post IMP Treatment Period. During the Post IMP Treatment Period patients should resume original dose of ICS/LABA combination therapy. If asthma is unable to be consistently controlled on original therapy and there is a safety concern, additional controller therapies may be prescribed based upon Investigator clinical judgement.

- Patients resume their original ICS/LABA treatment, with the same prescriptions as prior to the Screening Visit 1.
- Remind patients to use their original ICS/LABA background therapy medication.
- Remind patients to use salbutamol/albuterol or levosalbutamol/levalbuterol as reliever medication throughout the study.
- Remind patient to withhold albuterol or levalbuterol (if any) for at least 6 hours and LABA for at least 12 hours prior to next visit.
- Call IVRS/IWRS to register EOT or Premature Treatment Withdrawal.
- Schedule a site visit for Visit 15, Day 141 and request patient to come at approximately the same time of day as this visit (fasting if morning visit).

Note: Patients who discontinue IMP treatment early (prior to completing the 12-week IMP treatment) due to a LOAC event or due to other reasons, will be evaluated as soon as possible at the individual patients' EOT Visit, using procedures as planned for the EOT Visit at Week 12 (Visit 14). At their EOT visit, patients will resume their prescreening ICS/LABA background therapy and enter the 20-week Post IMP Treatment Period (Visit 15 to Visit 17).

10.1.2.5 Post IMP treatment observation period (Visits 15 and 17)

10.1.2.5.1 Visit 15, Day 141 (Week 20)

- Record all concomitant medication use with start date and dose in eCRF; inquire about AEs/SAEs and asthma therapy tolerability and compliance.
- Administer ACQ-5, AQLQ(S), and, only to patients with history of allergic rhinitis, RQLQ(S).
- Perform spirometry and measure exhaled nitric oxide:
  - Exhaled nitric oxide assessment is conducted prior to spirometry and following a fast of ≥1 hour.
  - Spirometry will be performed at approximately the same time of day as the last visit, prior to administration of IMP and after withholding the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours and withholding the last dose of LABA for at least 12 hours. This will be verified before performing the measurements.

- Prebronchodilator FEV1 should be determined.
- Postbronchodilator FEV1 should be determined.

- Perform physical examination.
- Measure vital signs (including systolic and diastolic blood pressure [mmHg], pulse rate [beats per minute], respiratory rate [breaths per minute] and body temperature [°C])
- Perform blood sampling (fasting if morning visit, prior to administration of IMP) for the following tests:
  - PK analysis
  - Hematology and serum chemistry
  - Biomarker set: Blood eosinophils and neutrophils, total IL33, and sST2, Calcitonin (refer to Section 9.3.2.4)
- Obtain urine sample for urinalysis
- Remind patients to use their original ICS/LABA background therapy medication.
- Remind patients to use salbutamol/albuterol or levosalbutamol/levalbuterol as reliever medication throughout the study.
- Schedule a site visit or phone call (Visit 16, Day 183) within a maximum of 47 days.

10.1.2.5.2 Visit 16, Day 183 (Week 26)

This visit can be either on site visit or phone call.

- Inquire about AEs/SAEs, new concomitant medications and asthma therapy tolerability and compliance.
- Remind patients to use their original ICS/LABA background therapy medication.
- Remind patients to use salbutamol/albuterol or levosalbutamol/levalbuterol as reliever medication throughout the study.
- Remind patient to withhold albuterol or levalbuterol (if any) for at least 6 hours and LABA for at least 12 hours prior to next visit.
- Schedule a site visit (Visit 17, Day 225) within a maximum of 47 days and request patient to come at approximately the same time of day as prior visits (fasting if morning visit).

10.1.2.6 Visit 17, Day 225 (Week 32) – End of Study Visit

- Record all concomitant medication use with start date and dose in eCRF; inquire about AEs/SAEs and asthma therapy tolerability and compliance.
- Administer ACQ-5, AQLQ(S), and, only to patients with history of allergic rhinitis, RQLQ(S).
- Perform 12-lead ECG

- Perform spirometry and measure exhaled nitric oxide:
  - Exhaled nitric oxide assessment is conducted following a fast of ≥1 hour.
  - Spirometry will be performed at approximately the same time of day as the last visit, prior to administration of IMP and after withholding the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours and withholding the last dose of LABA for at least 12 hours. This will be verified before performing the measurements.
  - Prebronchodilator FEV1 should be determined.
  - Postbronchodilator FEV1 should be determined.
- Perform physical examination.
- Perform urine pregnancy test (for women of childbearing potential)
- Measure vital signs (including systolic and diastolic blood pressure [mmHg], pulse rate [beats per minute], respiratory rate [breaths per minute] and body temperature [°C]).
- Perform blood sampling (fasting if morning visit, prior to administration of IMP) for the following tests:
  - PK analysis
  - Hematology and serum chemistry
  - Anti-SAR440340 antibody and anti-dupilumab antibody
  - Biomarker set: Blood eosinophils and neutrophils, total IL33, and sST2, Calcitonin (refer to Section 9.3.2.4)
- Obtain urine sample for urinalysis
- If not already done so at Visit 14/EOT, patient will return electronic devices to the site at this EOS visit. Electronic devices will be returned to the sponsor after EOS.
- Call IVRS/IWRS to register the EOS date

10.2 DEFINITION OF SOURCE DATA

Source data is all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Source documents are original documents, data and records are but not limited to hospital records, clinic and office charts, laboratory notes, memorandum, pharmacy dispensing records, recorded data from automated instruments, etc.

All the data collected in the eCRF should be transcribed directly from source documents. Data downloaded from the study-associated central laboratories, electronic data/information sources including IVRS/IWRS notifications, and computer generated print-outs, spirometry, nitric oxide measurement, ECG, patient questionnaire forms, and patient electronic diary/PEF meter, will be considered as source data.

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

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

10.3.1 Temporary treatment discontinuation with investigational medicinal product(s)

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

Following a temporary interruption the drug should be reinitiated at the next scheduled visit, maintaining the original dosing schedule.

10.3.2 Permanent treatment discontinuation with investigational medicinal product(s)

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

10.3.3 List of criteria for permanent treatment discontinuation

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

Patients must be withdrawn from the study treatment for the following reasons:

- At their own request or at the request of their legally authorized representative (legally authorized representative means an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective patient to the patient's participation in the procedure(s) involved in the research).
- If, in the Investigator's opinion, continuation in the study would be detrimental to the patient's well-being.
- At the specific request of the Sponsor.
- In the event of a protocol deviation, at the discretion of the Investigator or the Sponsor.
- Pregnancy.

- Loss of asthma control: Patients will be instructed to contact the Investigator if a patient feels that his or her asthma is not adequately controlled (clinical exacerbation, intolerable or incapacitating symptoms, frequent nocturnal awakenings, frequent albuterol or levalbuterol use).

  If a patient meets the criteria for a LOAC at any time during the 12-week IMP treatment period, he/she will be permanently withdrawn from IMP treatment and treated by the Investigator with standard of care according to standard medical practice.
- Anaphylactic reactions or systemic allergic reactions that are related to IMP and require treatment (see Appendix J).
- Diagnosis of a malignancy during study, excluding squamous or basal cell carcinoma of the skin.
- Any situation that meets permanent discontinuation rule as outlined in Appendix H. 'General Guidance for the follow-up of laboratory abnormalities by Sanofi'.
- Any opportunistic infection, such as TB or other infections whose nature or course may suggest an immunocompromised status (see Appendix I).
- Serum ALT >3 ULN and total bilirubin >2 ULN (see Appendix H).
- Serum ALT >5 ULN if baseline ALT ≤2 ULN or ALT >8 ULN if baseline ALT >2 ULN (see Appendix H).

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

10.3.4 Handling of patients after permanent treatment discontinuation

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

At the time of permanent treatment discontinuation before the EOT visit, patients will perform early treatment discontinuation visit with all the assessment designed for the EOT visit. At the time of study discontinuation after EOT visit, patients will perform early study discontinuation visit with all the assessment designed for the EOS visit.

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. Samples for biomarker analysis should be collected following EOT visit. Biomarker samples for future research could be suspended.

Patients who permanently discontinue the study medication will be asked and encouraged to return to the clinic and participate in follow-up assessments according to the visit schedule described in the Post IMP Treatment Period. The Post IMP Treatment Period will start at Week 12

for patients who complete the IMP treatment period, and may start earlier than Week 12 for patients who meet the criteria for a LOAC and discontinue IMP prior to 12 weeks of treatment.

For patients who permanently discontinue the study, under exceptional circumstances where there is no possibility for a patient to come to the site for the scheduled follow-up visit, a phone contact may be made after Sponsor's approval is given (with exception of Visit 16 that is allowed to be a phone visit as per protocol). During that phone contact, at least information about AEs, concomitant medication, and asthma exacerbation events must be collected and the schedule for these calls should still reflect the visit schedule described in the Post IMP Treatment Period.

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

10.3.5 Procedure and consequence for patient withdrawal from study

The patients may withdraw from the study before study completion if they decide to do so, at any time and irrespective of the reason. Withdrawal of consent for discontinuation of study treatment should be distinguished from withdrawal of consent for follow-up visits and from withdrawal of consent for non patient contact follow-up, eg, medical records check. Patients will be told that they are free to withdraw from the study at any time without any adverse effect on their care. However, if they no longer wish to take the IMP, they will be encouraged to remain in the study and attend the follow-up visits. The value of all their critical study data collected during their continued involvement will be emphasized as important to the public health value of the study.

The patient will resume his/her original ICS/LABA (ie, prior to screening) background therapy and will be followed for safety, if possible, for the 20-week Post IMP Treatment Period, as planned per protocol. 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.

Patients who withdraw should be explicitly asked about the contribution of possible AEs to their decision to withdraw consent, and any AE information elicited should be documented. Preferably the patient should withdraw consent in writing and, if the patient or the patient's representative refuses or is physically unavailable, the site should document and sign the reason for the patient's failure to withdraw consent in writing.

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

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

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

10.4 OBLIGATION OF THE INVESTIGATOR REGARDING SAFETY REPORTING

10.4.1 Definitions of adverse events

10.4.1.1 Adverse event

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

Asthma exacerbations should only be reported as AEs if they fulfill a seriousness criterion.

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

10.4.1.2 Serious adverse event

A **SAE** is any untoward medical occurrence that at any dose:

- Results in death, or
- Is life-threatening, or
  Note: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization, or
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect
- Is a medically important event
  Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require medical or surgical intervention (ie, specific measures or corrective treatment) to prevent one of the other outcomes listed in the definition above.

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

- Intensive treatment in an emergency medical care visit or at home for:
  - Allergic bronchospasm

- Anaphylaxis (refer to Appendix J for the definition of anaphylaxis)
- Blood dyscrasias (ie, agranulocytosis, aplastic anemia, bone marrow aplasia, myelodysplasia, pancytopenia, etc),

- Convulsions (seizures, epilepsy, epileptic fit, absence, etc).
- Development of drug dependence or drug abuse
- ALT >3 x the upper limit of normal (ULN) + total bilirubin >2 x ULN or asymptomatic ALT increase >10 x ULN
- Suicide attempt or any event suggestive of suicidality
- Syncope, loss of consciousness (except if documented as a consequence of blood sampling)
- Bullous cutaneous eruptions
- Cancers diagnosed during the study
- Chronic neurodegenerative diseases (newly diagnosed)

10.4.1.3 Adverse event of special interest

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

For these AESIs, the Sponsor will be informed immediately (ie, within 24 hours), per SAE notification described Section 10.4.4, even if not fulfilling a seriousness criterion, using the corresponding pages in the CRF (to be sent) or screens in the eCRF.

- Anaphylactic reactions, systemic allergic reactions that require treatment (refer to Appendix J for Definition of Anaphylaxis)
- Severe ISRs that last longer than 24 hours

  Note: A severe ISR (for AE reporting) is any event that meets one of the following criteria:

  - With a diameter of at least 10 cm.
  - Impacting daily activities.
  - With ulceration or necrosis.
  - For which operative intervention is required.
- Any infection meeting at least one of the following criteria:
  - Any serious infection (SAE).

- Requires parenteral (IV, intramuscular, SC) antimicrobial therapy
  Note: Antimicrobial therapy refers to antibiotic, antiviral, and antifungal agents.
- Requires oral antimicrobial therapy for longer than 14 days.
- Is a parasitic infection.
- Is an opportunistic infection (see Appendix I).

- Significant ALT elevation (see Appendix H)
  - ALT >3 x the ULN associated with total bilirubin >2 x ULN; or
  - ALT >5 x ULN if baseline ALT ≤2 x ULN; or
  - ALT >8 x ULN and baseline >2 x ULN.
- Malignancy
- Pregnancy occurring in a female patient enrolled in a study or in a female partner of a male patient enrolled in the study with IMP/NIMP. It will be qualified as an SAE only if it fulfills one of the seriousness criteria (see Section 10.4.1.2).
  - In the event of pregnancy in a female participant, IMP should be discontinued.
  - Follow-up of the pregnancy in a female participant or in a female partner of a male participant is mandatory until the outcome has been determined.
- Symptomatic overdose (serious or nonserious) with IMP/NIMP
  - An overdose (accidental or intentional) with the IMP is an event suspected by the Investigator or spontaneously notified by the patient and defined as at least twice the intended dose during an interval of <8 days. The circumstances (ie, accidental or intentional) should be clearly specified in the verbatim and symptoms, if any, entered on separate AE forms.
  - An overdose (accidental or intentional) with any NIMP is an event suspected by the Investigator or spontaneously notified by the patient and defined as at least twice the maximum daily dose as specified in a drug label, within the intended therapeutic interval. The circumstances (ie, accidental or intentional) should be clearly specified in the in the overdose form and symptoms, if any, entered on separate AE forms.
  - Of note, asymptomatic overdose has to be reported as a standard AE.

10.4.2 Serious adverse events waived from expedited regulatory reporting to regulatory authorities

Not applicable.

10.4.3 General guidelines for reporting adverse events

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

- When a safety event is categorized as a primary outcome, the event will be reported as an AE but will be waived from reporting to regulatory authorities provided an agreement has been reached with them.
- Whenever possible, diagnosis or single syndrome should be reported instead of symptoms. The Investigator should specify the date of onset, intensity, action taken with respect to IMP, corrective treatment/therapy given, additional investigations performed, outcome, and his/her opinion as to whether there is a reasonable possibility that the AE was caused by the IMP or by the study procedure(s). In studies that require the use of combined/multiple IMPs/NIMPs, the GSO with input from other appropriate study team members must determine if the causal relationship will either be assessed for the combined product as a regimen or as distinct entities. The GSO must communicate this decision to the study team for inclusion in the protocol and AE CRF.
- The Investigator should take appropriate measures to follow all AEs until clinical recovery is complete and laboratory results have returned to normal, or until progression has been stabilized, or until death, in order to ensure the safety of the patients. This may imply that observations will continue beyond the last planned visit per protocol, and that additional investigations may be requested by the monitoring team up to as noticed by the Sponsor. Patients who experience an ongoing SAE or an AESI, at the prespecified study end-date, should be followed until resolution, stabilization, or death and related data will be collected. The duration of poststudy follow-up and reporting of AEs will be specified (eg, until AE CRF).
- When treatment is prematurely discontinued, the patient's observations will continue until the end of the study as defined by the protocol for that patient.
- Laboratory, vital signs or ECG abnormalities are to be recorded as AEs only if:
  - Symptomatic and/or
  - Requiring either corrective treatment or consultation, and/or
  - Leading to IMP discontinuation or modification of dosing, and/or
  - Fulfilling a seriousness criterion, and/or
  - Defined as an AESI

Table 4 summarizes the reporting timelines:

Table 4 - Adverse event reporting

Adverse event/laboratory abnormality		Reporting timeframe
Serious adverse event		Within 24 hours
Pregnancy		Within 24 hours
Overdose	Symptomatic	Within 24 hours
	Asymptomatic	Routine
ALT elevation		
	ALT >3 x ULN and associated with total bilirubin >2 x ULN	Within 24 hours
	ALT >5 ULN if baseline ALT is ≤2 ULN	Within 24 hours
	ALT >8 ULN if baseline ALT is >2 ULN	Within 24 hours
Anaphylactic or systemic allergic reactions that require treatment.		Within 24 hours
Severe injection site reactions that last longer than 24 hours.		Within 24 hours
Infections as defined in Section 10.4.1.3		Within 24 hours
Malignancy		Within 24 hours

ALT: alanine aminotransaminase; ULN: upper limit of normal.

10.4.4 Instructions for reporting serious adverse events

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

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

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

10.4.5 Guidelines for reporting adverse events of special interest

For AESIs, the Sponsor must be informed immediately (ie, within 24 hours), as per SAE notification guidelines described in Section 10.4.4, even if not fulfilling a seriousness criterion, using the AE reporting instructions summarized in Section 10.4.3.

10.4.6 Guidelines for management of specific laboratory abnormalities

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

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

- Neutropenia
- Thrombocytopenia
- Increase in ALT
- Increase in serum creatinine
- Increase in CPK

Note: In some clinical trials these laboratory abnormalities can be considered as AESIs. For this study, only significant ALT increase will be considered as AESIs (see Section 10.4.1.3)

In addition, on treatment eosinophil counts >3000/mm^3 (3.0 giga/L) (confirmed by retest) are to be reported as AEs.

10.4.7 Guidelines for reporting product complaints (IMP/NIMP)

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

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

10.5 OBLIGATIONS OF THE SPONSOR

During the course of the study, the Sponsor will report in an expedited manner:

- All SAEs that are both unexpected and at least reasonably related to the IMP (suspected unexpected adverse drug reaction [SUSAR]), to the regulatory authorities, Independent

Ethics Committee (IECs)/Institutional Review Boards (IRBs) as appropriate and to the Investigators.

- All SAEs that are expected and at least reasonably related to the IMPs to the regulatory authorities, according to local regulations.

In this study, some AEs are considered related to the underlying condition and thus will not be considered unexpected (eg, wheezing related to asthma).

Any other AE not listed as an expected event in the IB or in this protocol or AE by itself is listed as expected in the IB but upon case assessment will be noted to be more severe or has an outcome of death (unless specified in the protocol), will be considered unexpected.

For safety, the treatment code will be unblinded by the Sponsor for reporting to the Health Authority of any SUSAR and reasonably associated with the use of the IMP according to either the judgment of the Investigator and/or the Sponsor.

In case of a SUSAR, Sanofi Global Pharmacovigilance and Epidemiology will utilize XGRID to reveal medication assignment for regulatory reporting requirements for the particular case.

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

10.6 SAFETY INSTRUCTIONS

10.6.1 Hypersensitivity

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

Acute allergic reactions may be defined as allergic reaction-mediated signs and symptoms experienced by patients during or shortly after the pharmacologic or biologic agent given. These reactions may present in a variety of ways, including dizziness, headache, anxiety, dyspnea, hypotension, tachycardia, pruritus, rash, urticaria/angioedema, flushing, nausea, or vomiting. Anaphylaxis may represent the most severe form of allergic reaction, but these events may also occur via non-IgE mediated mechanisms (eg, anaphylactoid reactions), or may occur via other immune-mediated mechanisms (eg, cytokine-mediated). Allergic reactions may begin within a few hours and persist up to 24 hours post dosing. Refer to Appendix J. “Definition of Anaphylaxis”, which describes the clinical criteria for the diagnosis of anaphylaxis. Delayed onset or late phase hypersensitivity reactions (ie, Type 1 hypersensitivity reaction) may manifest between 10 and 12 hours post dosing.

Patients should be monitored for at least 30 minutes after IMP dose administration for any signs or symptoms of a hypersensitivity reaction throughout the study. Trained personnel and medications should be available to treat anaphylaxis or any severe allergic reaction if it occurs. Anaphylactic reactions, systemic allergic reactions that require treatment must be reported as an AESI with immediate notification (for further details see Section 10.4.1.3 and Appendix J). If an

anaphylactic reaction, systemic allergic reaction requiring treatment occurs and is considered related to IMP by the investigator the study treatment should be permanently discontinued.

Anti-drug antibodies and PK samples will be collected near the onset and resolution of the AESI for any additional analysis.

10.6.2 Severe injection site reactions

Based on the SC mode of administration of high doses of protein ISRs are considered as a potential risk for SAR440340.

In dupilumab clinical studies, the incidence of ISRs was higher in the dupilumab treated patients compare to placebo treated patients. The ISRs were generally non serious, mild to moderate intensity.

Patients who experience an ISR must be closely monitored for the possibility of a more intense ISR with a future injection. Any severe ISR that lasts over 24 hours will be reported as an AESI with immediate notification (for further details please see Section 10.4.1.2). Anti-drug antibodies and PK samples will be collected near the onset and resolution of the AESI for any additional analysis

If there is any consideration being given to premedicating before the next dose (for preceding an ISR), please contact Sponsor prior to dosing patients.

10.6.3 Infections, including parasitic infections

Some biologic therapies have been associated with an increased risk of infection, including opportunistic infection.

IL33 is a proinflammatory cytokine released by damaged epithelial cells in response to insults such as allergens, viruses, or bacteria. IL33 signaling initiates and amplifies multiple downstream inflammatory pathways resulting in effects characteristic of both Type 1 and Type 2 immune inflammations. Although blockade or knockout of IL33 signaling in mice did not reveal any unique role for IL33 in mounting an acute immune response to viral challenge and did not lead to worsening of symptoms or outcome, subjects will be monitored for signs or symptoms of infection.

Dupilumab and SAR440340 inhibit the T-helper 2 (Th2) cytokines production. Infections with a diversity of helminthic parasites elicit eosinophilia via stimulation of Th2-like lymphocyte responses. The Th2 response is characterized by production of IL4, IL13, and IL5, subsequently generating IgG1 and IgE-secreting cells, and eliciting eosinophilia. Eosinophilia is prominent in a number of helminthic parasitic diseases. The eosinophilic response to helminths is determined both by the host's immune response and by the parasite, including its distribution, migration, and development within the infected host. Therefore, patients treated with dupilumab and/or SAR440340 may potentially have an increased risk of parasitic infection.

To minimize the risk, patients with certain type of infections are not allowed to participate in the study (eg, patients with active opportunistic or parasitic infections or at high risk of developing the infections, patients with medical history of invasive opportunistic infections, patients with HIV infection or HIV seropositivity, patients with positive screening for hepatitis B and C).

As a precautionary measure, the Investigator is required to carefully monitor for any signs or symptoms of infection such as, but not limited to, increased body temperature, malaise, weight loss, sweats, cough, dyspnea, pulmonary infiltrates, or serious febrile systemic illness.

During the study, appearance of signs or symptoms (such as abdominal pain, cough, diarrhea, fever, fatigue hepatosplenomegaly) that could be associated with a parasitic infection should be carefully evaluated, especially if there is a history of parasitic exposure through recent travel to/or residence in endemic areas, especially when conditions are conducive to infection (eg, extended stay, rural or slum areas, lack of running water, consumption of uncooked, undercooked, or otherwise potentially contaminated food, close contact with carriers and vectors, etc). Subsequent medical assessments (eg, stool exam, blood tests, etc) must be performed in order to rule out parasitic infection/infestation.

Infections defined in Section 10.4.1.3 should be reported as AESIs with immediate notification. A complete diagnostic work-up should be performed (ie, cultures, histopathological or cytological evaluation, antigen detection and serum antibody titers). Patients should be referred to an infectious disease specialist if deemed necessary for diagnostic work up and appropriate treatment.

Infections or infestations that do not respond to medical treatment should have study drug discontinued until the infection is resolved.

For any opportunistic infection, such as TB, or other infections whose nature or course may suggest an immunocompromised status (see Appendix I), patients must be permanently discontinued from study medication.

10.6.4 Elevated liver function tests

No preclinical and clinical data has suggested any hepatic toxicity of SAR440340 or dupilumab; however, as a general consideration of clinical development, the administration of immunosuppressant or immunomodulating agents may represent an additional risk factor for hepatotoxicity.

In order to closely follow liver function tests (LFT), assessment of total protein, albumin, total bilirubin (in case of values above the normal range, differentiation in conjugated and nonconjugated bilirubin), alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase are measured as part of the clinical laboratory testing.

Guidance for the investigation of elevated LFTs as well as concurrent management of IMP is provided in Appendix H.

Alanine transaminase elevations defined in Section 10.4.1.3 should be reported as AESIs with immediate notification.

10.6.5 Malignancy

Available literature data related to the IL-4Rα inhibition, and data from animal toxicology studies in which monkeys received chronic treatment with an IL-4Rα blocker, do not support an increased risk of cancer for dupilumab. There is no evidence from the clinical studies to date that the treatment with dupilumab increases the risk of malignancy. In toxicology studies on REGN3500-mediated IL33 blockade, the effect of REGN3500 administration has not demonstrated the development of malignancy. Long-term use has not been studied.

The investigator should carefully monitor for any signs or symptoms of malignancy. Malignancy should be reported as AESI with immediate notification.

10.7 ADVERSE EVENTS MONITORING

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

11 STATISTICAL CONSIDERATIONS

11.1 DETERMINATION OF SAMPLE SIZE

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

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, based on a previous study with dupilumab with similar design (ACT11457) (19)
- A 26% reduction in the rate of LOAC (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.

Patients will be randomized using a 1:1:1:1 ratio to one of the 4 treatment groups. Randomization will be stratified by Screening Visit 1 eosinophil count (using the following 3 strata: <150 /mm^3 [not more than approximately 25% or 60 patients], 150-299 /mm^3, ≥300 /mm^3 [at least approximately 45% or 108 patients]) and by country. For eosinophil count, alerts will be built into the IVRS/IWRS system to limit enrolling patients in 2 of the 3 eosinophil count strata.

11.2 DISPOSITION OF PATIENTS

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

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

Patients treated without being randomized will not be considered as randomized and will not be included in any efficacy population. Data from these patients will be summarized separately.

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.

11.3 ANALYSIS POPULATIONS

11.3.1 Efficacy populations

11.3.1.1 Modified intent-to-treat population

The analysis population for the efficacy endpoints will be the modified intent-to-treat (mITT) population: 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.

11.3.2 Safety population

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.

11.3.3 Pharmacokinetic analysis population

The PK population will consist of all patients in the safety population with at least one postdose, nonmissing serum SAR440340 or serum dupilumab concentration.

11.3.3.1 Antidrug antibody population

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.

11.4 STATISTICAL METHODS

11.4.1 Extent of study treatment exposure and compliance

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

11.4.1.1 Extent of investigational medicinal product exposure

Duration of IMP exposure is defined as: last dose date – first dose date +14 day, regardless of unplanned intermittent discontinuations.

11.4.1.2 Compliance

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

Treatment compliance will be summarized descriptively (N, mean, standard deviation [SD], median, first quartile [Q1], third quartile [Q3], min, and max). The percentage of patients with compliance <80% will be summarized.

11.4.2 Analyses of efficacy endpoints

11.4.2.1 Analysis of primary efficacy endpoint

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 country), baseline background ICS dose level and number of exacerbation events within 1 year prior to screening.

Each of the comparisons will be tested at a two-sided 5% significance level:

- SAR440340 versus placebo
- Coadministration of SAR440340 and dupilumab versus placebo

The odds ratio and 95% confidence interval (CI) for each comparison will be estimated from this model.

Comparisons between other treatment groups on incidence of LOAC will be analyzed in a similar fashion in an exploratory manner.

As a supportive analysis, time to LOAC postrandomization will be analyzed using a Cox regression model with treatment, baseline eosinophil strata, and region (pooled country) as covariates. The Kaplan-Meier (KM) method will be used to estimate the probabilities of the event at specific time points for each treatment group. P-value from log-rank test stratified by baseline eosinophil strata and region will also be provided.

11.4.2.2 Analyses of secondary and other efficacy endpoints

The change from baseline for continuous endpoints (eg. FEV1, PEF, ACQ-5 score, asthma symptom scores, nocturnal awakenings, number of inhalations/day of albuterol or levalbuterol) will be analyzed using a mixed effect model with repeated measures (MMRM) approach. Details regarding the inclusion of values for analysis depending on concurrent events/treatments that could be confounded with efficacy will be detailed in the SAP. No imputation will be performed on missing values. The covariates to be included are treatment, baseline eosinophil strata, region (pooled country), baseline background ICS dose level, visit, treatment-by-visit interaction, the corresponding baseline value and baseline-by-visit interaction. Additionally, gender and height will be included in the models for spirometry variables. The repeated measures analysis will be

based on the restricted maximum likelihood method assuming an unstructured covariance structure 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. In addition, differences in LS means, the corresponding 95% CI and p-value will be derived from the MMRM model.

11.4.2.3 Multiplicity considerations

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 endpoint(s) and no adjustments will be made for the subgroup analyses. Reported p-values will be nominal p-values.

11.4.2.4 Handling of missing data

Missing data handling and sensitivity analyses for the primary and secondary endpoints will be detailed in the SAP.

11.4.3 Analyses of safety data

The summary of safety results will be presented by treatment group. All safety analyses will be performed on the safety population using the following common rules:

The baseline value is defined generally as the last available value before the first dose of IMP.

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

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

11.4.3.1 Adverse events

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

The proportion of patients with at least 1 TEAE, serious TEAE, and TEAE leading to discontinuation of the study will be tabulated by treatment group. In addition, TEAEs will be described according to maximum intensity and relation to the study drug. Serious AEs and AEs leading to study discontinuation that occur outside the treatment-emergent period will be summarized separately.

11.4.3.1.1 Adverse events of special interests

The following summaries will be generated:

- Incidence of each AESI will be tabulated by treatment group
- The time-to-first event analyzed using K-M methods and displayed as K-M plots (cumulative incidence (%) versus time based on K-M estimates) will be provided to depict the course of onset over time. When TEAE start date or worsening date is partially available, the maximum of the earliest possible TEAE start date and the treatment start date will be used. When TEAE start date or worsening date is completely missing, the treatment start date will be used.
- An overview summary of the number (%) of patients with
  - any TEAE
  - any SAE (regardless of treatment-emergent status)
  - any treatment-emergent SAE
  - any AE leading to death
  - any TEAE leading to permanent study drug discontinuation
  - any TEAE by maximum intensity, corrective treatment, and final outcome

Definitions of AESIs and the method to identify AESIs will be specified in the SAP.

11.4.3.1.2 *Death*

The following summaries will be generated depending on the overall incidence:

- Number (%) of patients who died by study period (TEAE, on-study) and reasons for death summarized on the safety population
- Death in nonrandomized patients or randomized and not treated patients
- Treatment-emergent adverse events (TEAE) leading to death (death as an outcome on the AE CRF/eCRF page as reported by the Investigator) by primary SOC, HLGT, HLT, and PT showing number (%) of patients sorted by internationally agreed order of SOC and alphabetic order of HLGT, HLT, and PT.

Patient data listings will be provided for all TEAEs, treatment-emergent SAEs, AEs leading to treatment discontinuation, AESIs, and deaths.

11.4.3.1.3 Clinical laboratory evaluation, vital signs, and electrocardiogram data

Results and change from baseline for the parameters will be summarized by treatment group for baseline and each post baseline time point, endpoint, minimum, and maximum value. Summary statistics will include number of patients, mean, SD, median, Q1, Q3, minimum, and maximum.

The proportion of patients who had at least 1 incidence of PCSA at any time during the treatment emergent period will be summarized by treatment group. Shift tables showing changes with respect to the baseline status will be provided.

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

11.4.4 Pharmacokinetics, pharmacodynamics, and analyses of antidrug antibodies

11.4.4.1 Pharmacokinetic analysis

Serum concentrations of functional SAR440340 and dupilumab will be summarized using arithmetic and geometric means, SD, standard error of the mean (SEM), coefficient of variation (CV%), minimum, median, and maximum by treatment per visit.

11.4.4.2 Anti-drug antibodies analysis

The ADA analysis will be detailed in the SAP.

11.4.4.3 Pharmacodynamics

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

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

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

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

Change from baseline in the following variables: global measure and the 4 domains of AQLQ and RQLQ will be analyzed using an MMRM approach, described previously for the continuous efficacy variables. Descriptive statistics including number of patients, mean, standard error, and LS means will be provided. In addition, the difference in LS means, the corresponding 95% CIs, and the p-values will be provided.

11.5 INTERIM ANALYSIS

No formal interim analysis is planned. Analyses will be performed for safety monitoring and internal decision making. No formal stopping rules or adjustment for multiplicity will be applied.

12 ETHICAL AND REGULATORY CONSIDERATIONS

12.1 ETHICAL AND REGULATORY STANDARDS

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

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

12.2 INFORMED CONSENT

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

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

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

Prior to collection of blood for pharmacogenetics, the optional pharmacogenetic section of ICF (written) should be completed by the patient or by the subject’s legally acceptable representative, and by the person who conducted the informed consent discussion.

The ICF, including the optional pharmacogenetic sample and optional future use of samples, used by the Investigator for obtaining the patient's informed consent must be reviewed and approved by the Sponsor prior to submission to the appropriate ethics committee (IRB/IEC) for approval/favorable opinion.

12.3 HEALTH AUTHORITIES AND INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE (IRB/IEC)

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

The clinical trial (study number, clinical trial protocol title, and version number), the documents reviewed (clinical trial protocol, ICF, IB with any addenda or labeling documents [summary of product characteristics, package insert], Investigator's curriculum vitae [CV], etc) and the date of the review should be clearly stated on the written (IRB/IEC) approval/favorable opinion.

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

During the clinical trial, any amendment or modification to the clinical trial protocol should be submitted to the health authorities (competent regulatory authority), as required by local regulation, in addition to the IRB/IEC before implementation, unless the change is necessary to eliminate an immediate hazard to the patients, in which case the health authorities (competent regulatory authority) and the IRB/IEC should be informed as soon as possible. They should also be informed of any event likely to affect the safety of patients or the continued conduct of the clinical trial, in particular any change in safety. All updates to the IB or labeling information will be sent to the IRB/IEC and to health authorities (competent regulatory authority), as required by local regulation.

A progress report is sent to the IRB/IEC at least annually and a summary of the clinical trial's outcome at the end of the clinical trial.

13 STUDY MONITORING

13.1 RESPONSIBILITIES OF THE INVESTIGATOR(S)

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

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

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

13.2 RESPONSIBILITIES OF THE SPONSOR

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

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

13.3 SOURCE DOCUMENT REQUIREMENTS

According to the ICH GCP, the monitoring team must check the eCRF entries against the source documents, except for the preidentified source data directly recorded in the eCRF. The ICF will include a statement by which the patient allows the Sponsor’s duly authorized personnel, the

ethics committee (IRB/IEC), and the regulatory authorities to have direct access to original medical records which support the data on the eCRFs (eg, patient's medical file, appointment books, original laboratory records, etc). These personnel, bound by professional secrecy, must maintain the confidentiality of all personal identity or personal medical information (according to confidentiality and personal data protection rules).

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

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

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

Data are available within the system to the Sponsor as soon as they are entered in the eCRF.

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

13.5 USE OF COMPUTERIZED SYSTEMS

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

14 ADDITIONAL REQUIREMENTS

14.1 CURRICULUM VITAE

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

14.2 RECORD RETENTION IN STUDY SITES

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

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

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

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

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

14.3 CONFIDENTIALITY

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

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

The Subinvestigators shall be bound by the same obligation as the Investigator. The Investigator shall inform the Subinvestigators of the confidential nature of the clinical trial.

The Investigator and the Subinvestigators shall use the information solely for the purposes of the clinical trial, to the exclusion of any use for their own or for a third party's account.

14.4 PROPERTY RIGHTS

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

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

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

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

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

14.5 DATA PROTECTION

- The patient's personal data, which are included in the Sponsor database shall be treated in compliance with all applicable laws and regulations
- When archiving or processing personal data pertaining to the Investigator and/or to the patients, the Sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party
- The Sponsor also collects specific data regarding Investigator as well as personal data from any person involved in the study which may be included in the Sponsor’s databases, shall be treated by both the Sponsor and the Investigator in compliance with all applicable laws and regulations

Analyses of patient genetic data will be conducted as described in the protocol as this is needed for pharmacogenetics analyses required for the purposes of the study or by regulatory authorities.

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

14.6 INSURANCE COMPENSATION

The Sponsor certifies that it has taken out a liability insurance policy covering all clinical trials under its sponsorship. This insurance policy is in accordance with local laws and requirements. The insurance of the Sponsor does not relieve the Investigator and the collaborators from any

obligation to maintain their own liability insurance policy. An insurance certificate will be provided to the IECs/IRBs or regulatory authorities in countries requiring this document.

14.7 SPONSOR AUDITS AND INSPECTIONS BY REGULATORY AGENCIES

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

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

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

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

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

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

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

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

14.8.1 By the Sponsor

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

- The information on the product leads to doubt as to the benefit/risk ratio
- Patient enrollment is unsatisfactory
- The Investigator has received from the Sponsor all IMP, means, and information necessary to perform the clinical trial and has not included any patient after a reasonable period of time mutually agreed upon
- Noncompliance of the Investigator or Subinvestigator, delegated staff with any provision of the clinical trial protocol, and breach of the applicable laws and regulations or breach of the ICH GCP

- The total number of patients are included earlier than expected

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

14.8.2 By the Investigator

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

In the event of premature discontinuation of the study or premature close-out of a site, for any reason whatsoever, the appropriate IRB/IEC and regulatory authorities should be informed according to applicable regulatory requirements.

14.9 CLINICAL TRIAL RESULTS

The Sponsor will be responsible for preparing a CSR and to provide a summary of study results to the Investigator.

14.10 PUBLICATIONS AND COMMUNICATIONS

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

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

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

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

15 CLINICAL TRIAL PROTOCOL AMENDMENTS

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

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

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

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

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

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17 APPENDICES

Appendix A Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User Dependent[a]

Failure rate of <1% per year when used consistently and correctly

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b]
  - oral
  - intravaginal
  - transdermal

- Progestogen-only hormone contraception associated with inhibition of ovulation
  - oral
  - injectable

Highly Effective Methods That Are User Independent[a]

- Implantable progestogen-only hormonal contraception associated with inhibition of ovulation
  - Intrauterine device (IUD)
  - Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion

Vasectomized partner

A vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.

Sexual abstinence

Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

NOTES:

a) Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies.

Appendix B List of Prohibited Live Attenuated Vaccines

Bacillus Calmette-Guérin (BCG) antituberculosis vaccine

Chickenpox (Varicella)

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

Measles (Rubeola)

Measles-mumps-rubella (MMR) combination

Measles-mumps-rubella-varicella (MMRV) combination

Mumps

Oral polio (Sabin)

Oral typhoid

Rotavirus

Rubella

Smallpox (Vaccinia)

Varicella Zoster (shingles)

Yellow fever

This list is indicative and not exhaustive.

Appendix C Low, medium, and high dose inhaled corticosteroids

Inhaled Corticosteroid	Total Daily Dose (mcg)		
	Low	Medium	High
Beclometasone dipropionate (CFC)	200–500	>500–1000	>1000
Beclometasone dipropionate (HFA)	100–200	>200–400	>400
Budesonide (DPI)	200–400	>400–800	>800
Ciclesonide (HFA)	80-160	>160–320	>320
Fluticasone furoate (DPI)	100*	n.a.	200
Fluticasone propionate (DPI)	100–250	>250–500	>500
Fluticasone propionate (HFA)	100–250	>250–500	>500
Mometasone furoate	110–220	>220–440	>440
Triamcinolone acetonide	400–1000	>1000–2000	>2000

CFC = chlorofluorocarbon propellant; DPI = dry powder inhaler; HFA = hydrofluoroalkane propellant; n.a. = not applicable; nebules = nebulized solution
Source: Adapted from Global Initiative for Asthma (GINA) 2017 guidelines
*It has been shown that fluticasone furoate 100 mcg daily is clinically comparable to fluticasone proprionate 500 mcg daily and thus fluticasone furoate 100 mcg daily is considered medium inhaled corticosteroid dose in the ACT15102 study (26, 27).

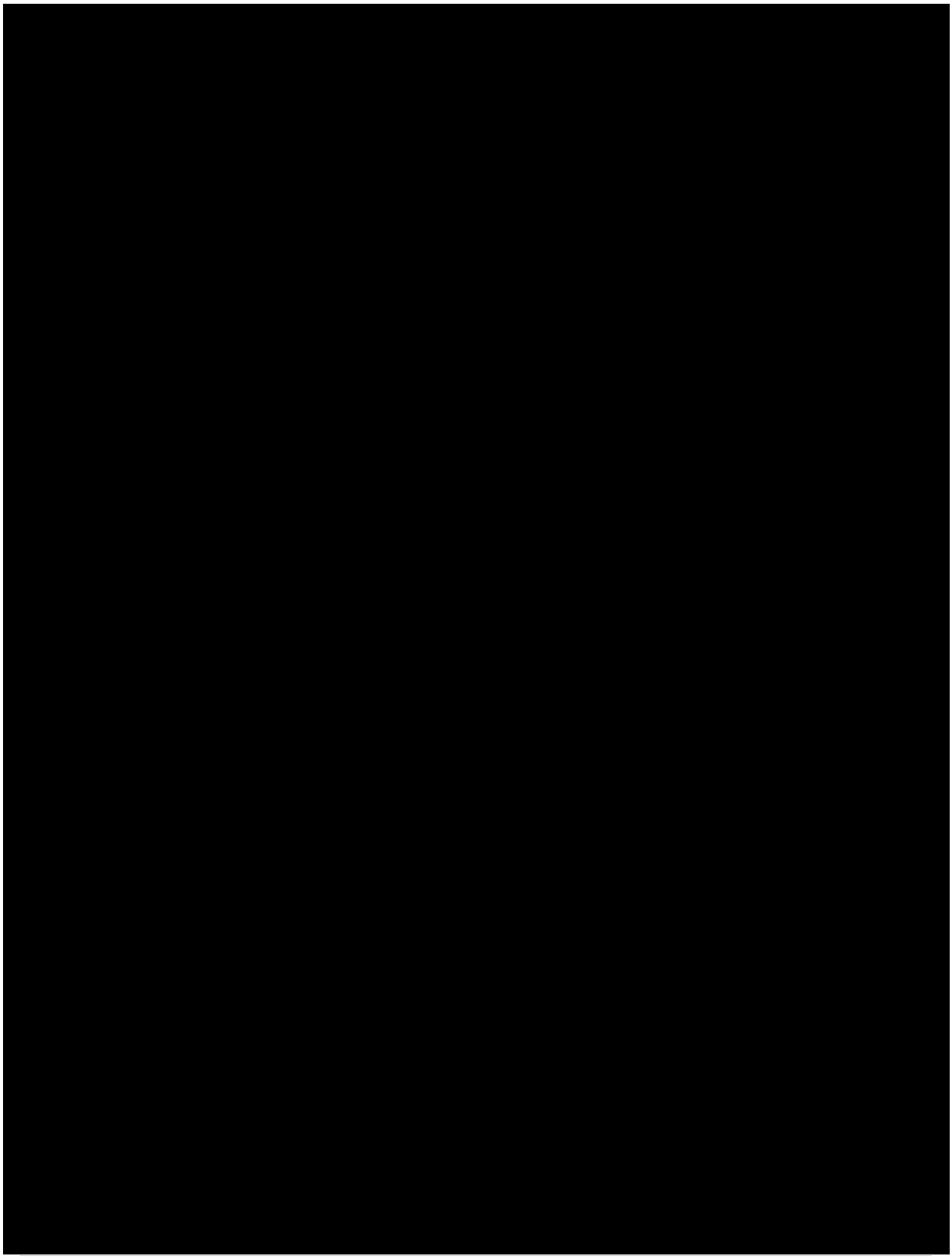
Appendix D Asthma Control Questionnaire (ACQ)

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

[redacted]

December 2002

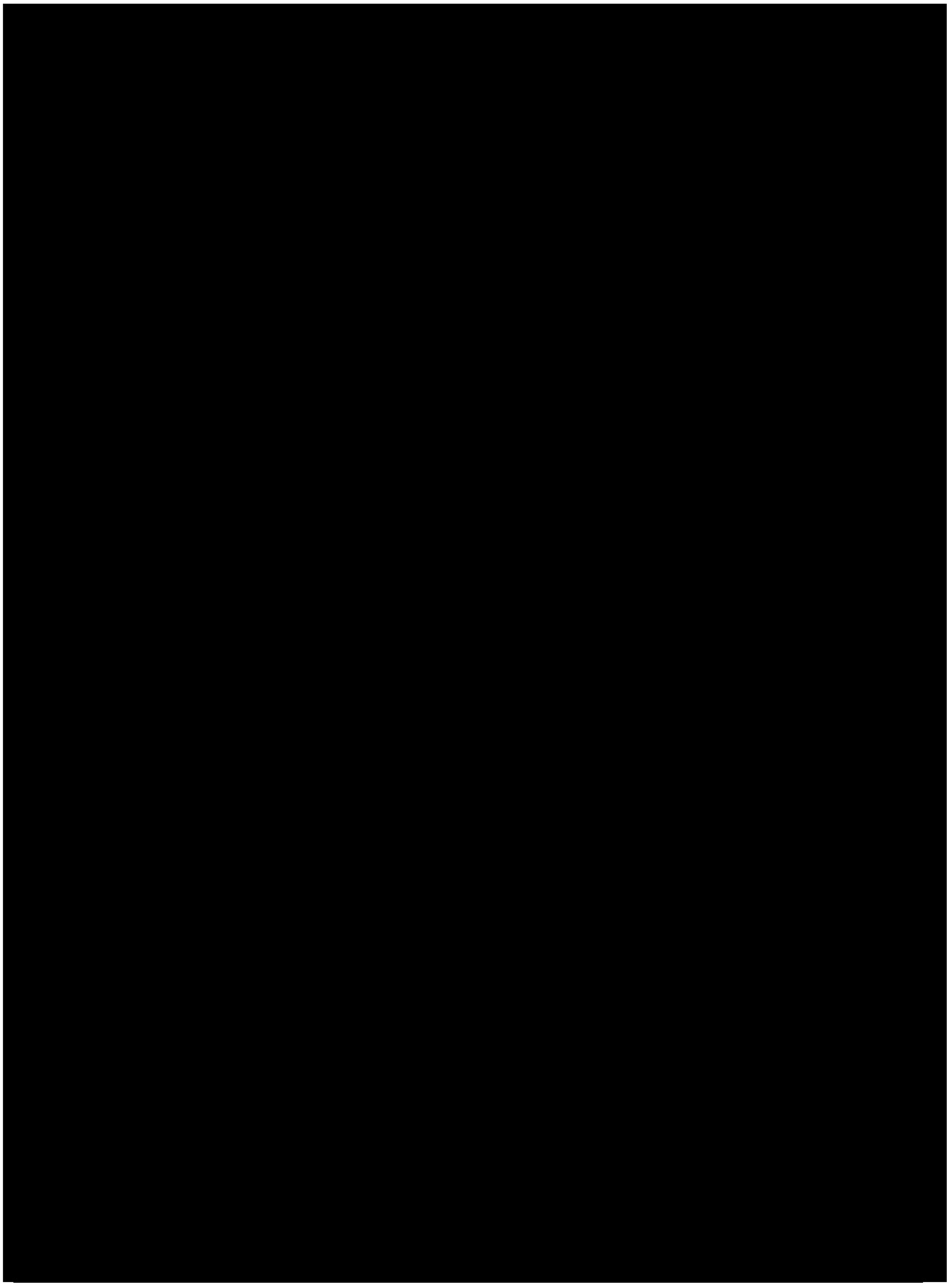
SYMPTOMS ONLY MODIFIED 30 JAN 04 NORTH AMERICAN ENGLISH

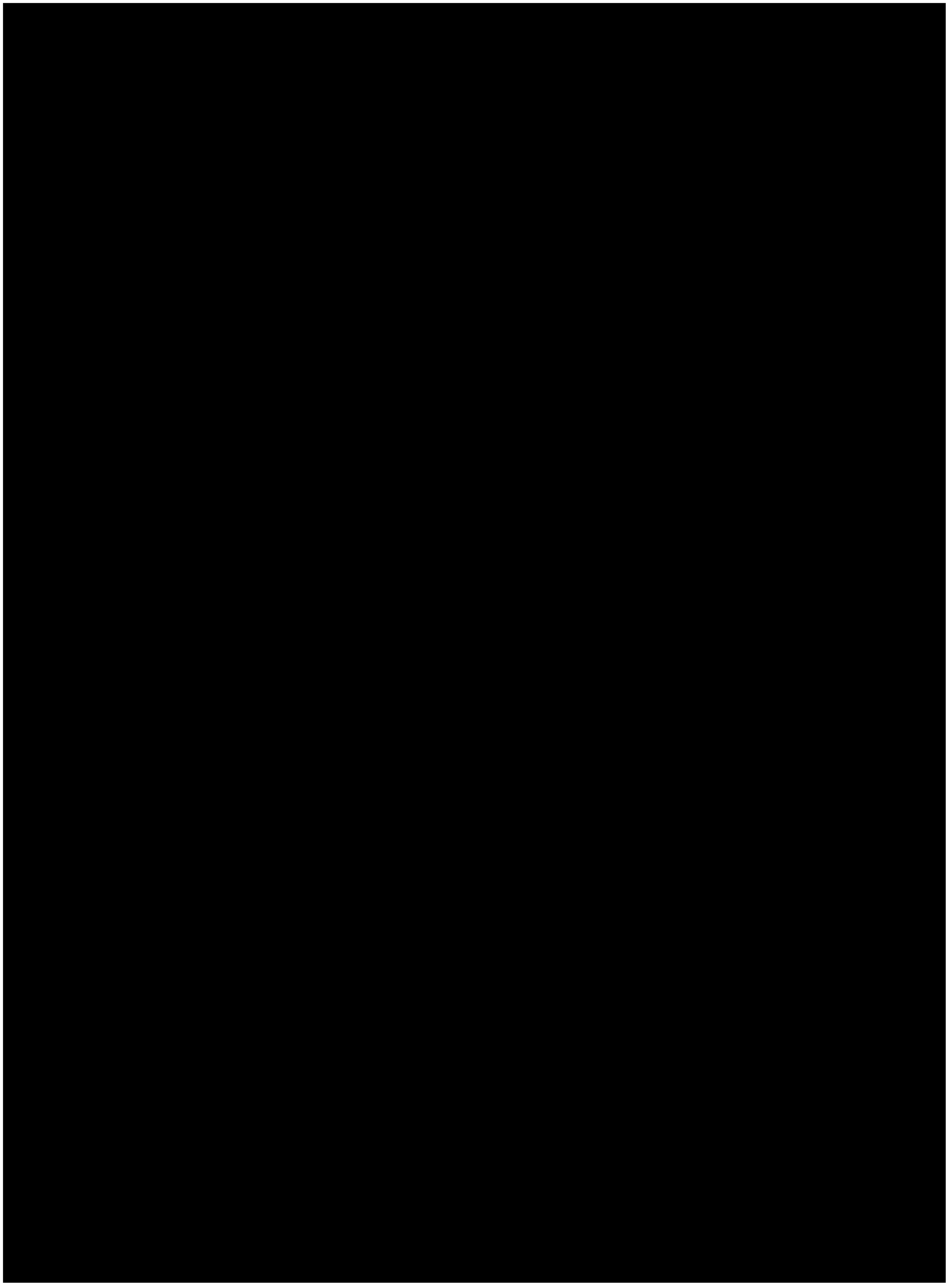


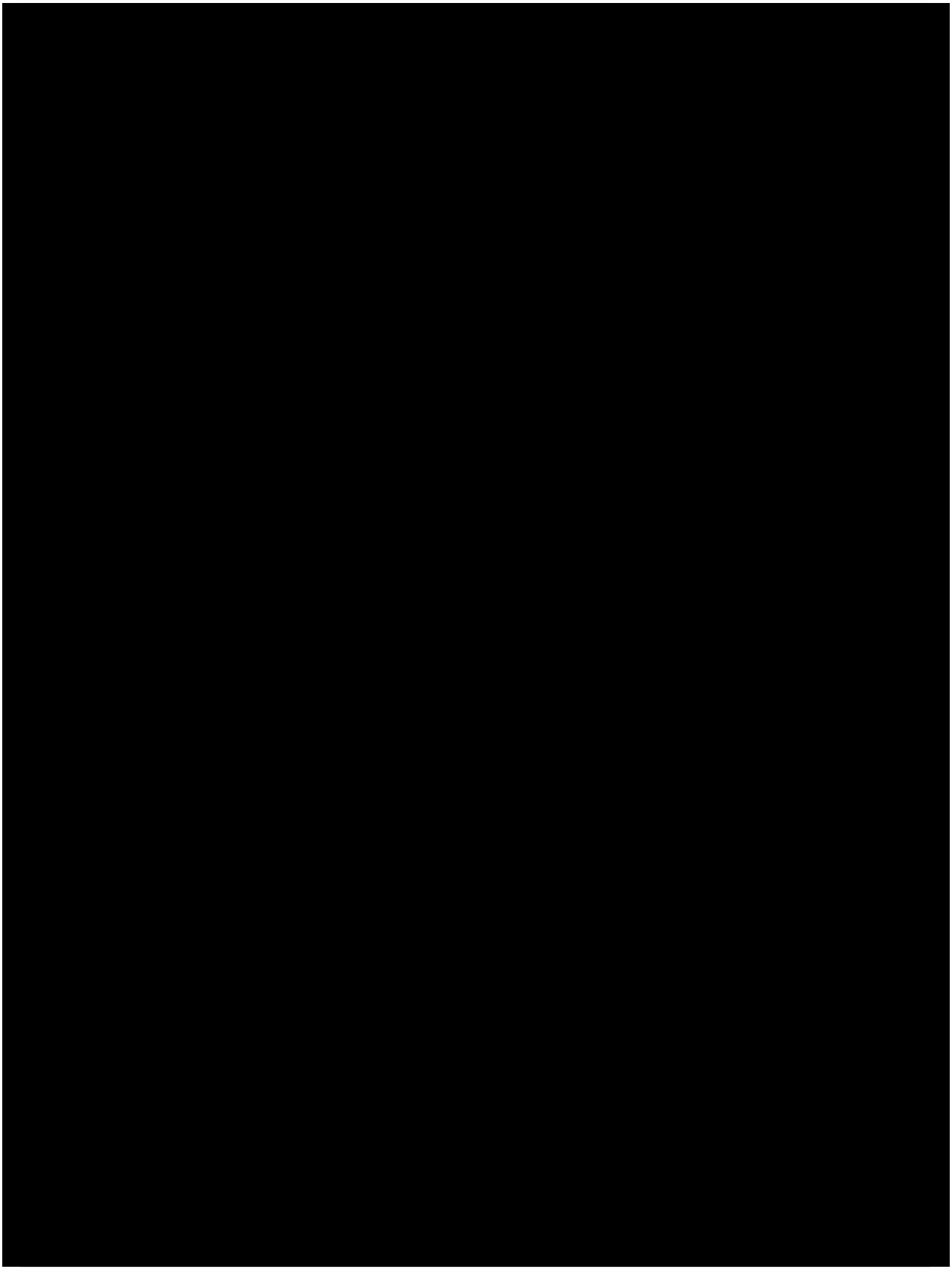
Appendix E Asthma Quality of Life Questionnaire

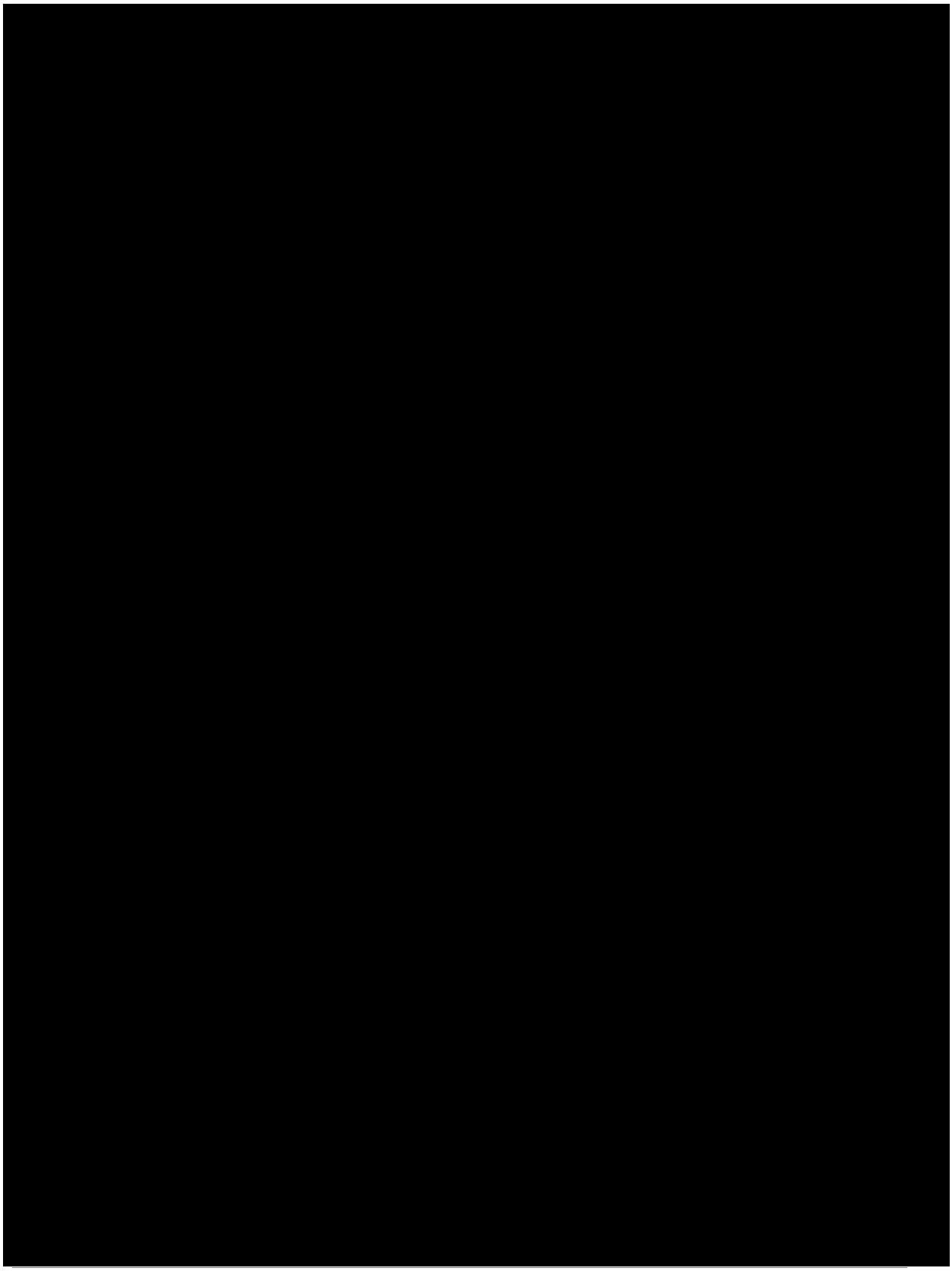
APRIL 2008

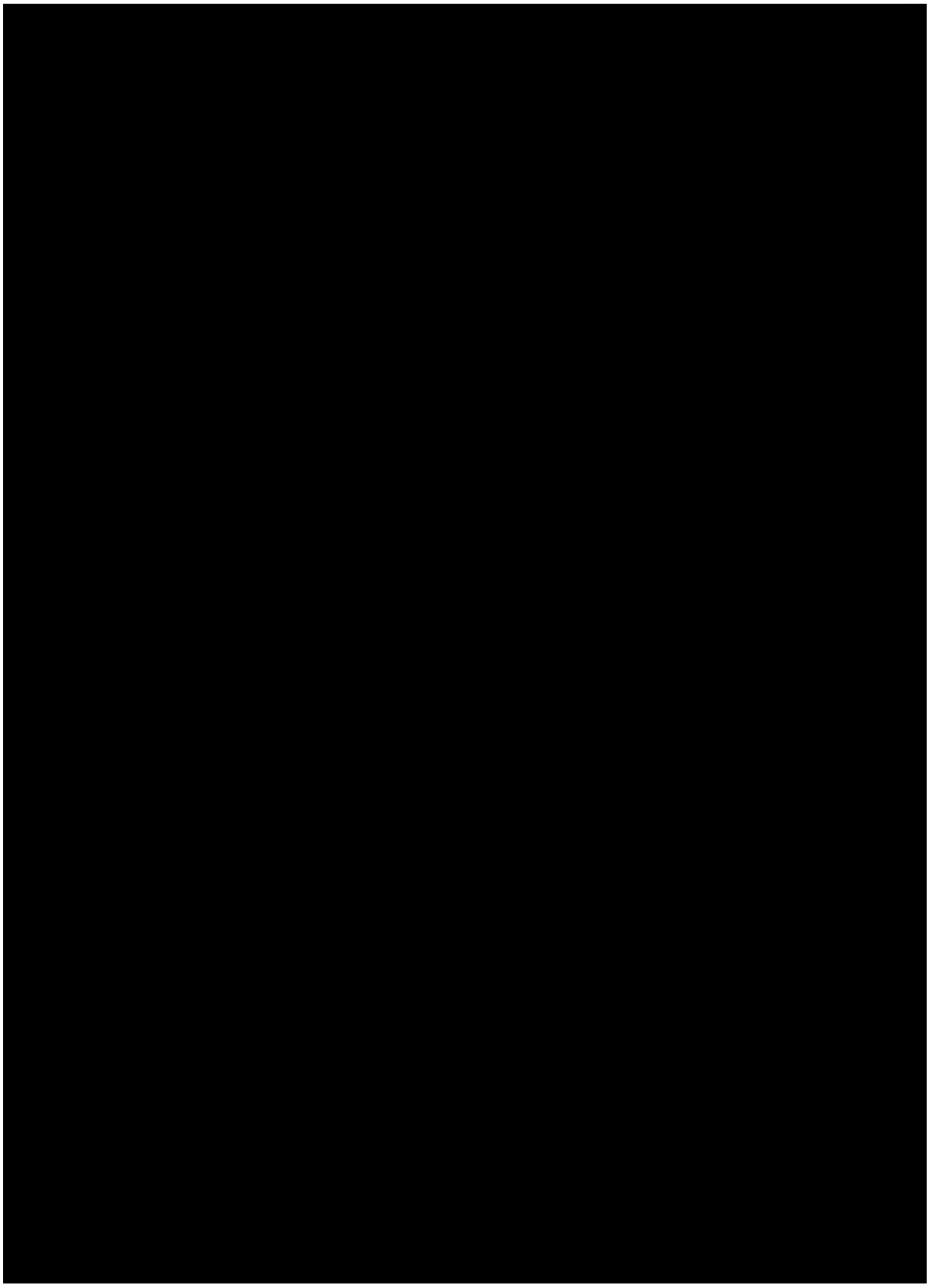
Modified September 2010
AQLQ(S)-SA North American English Version



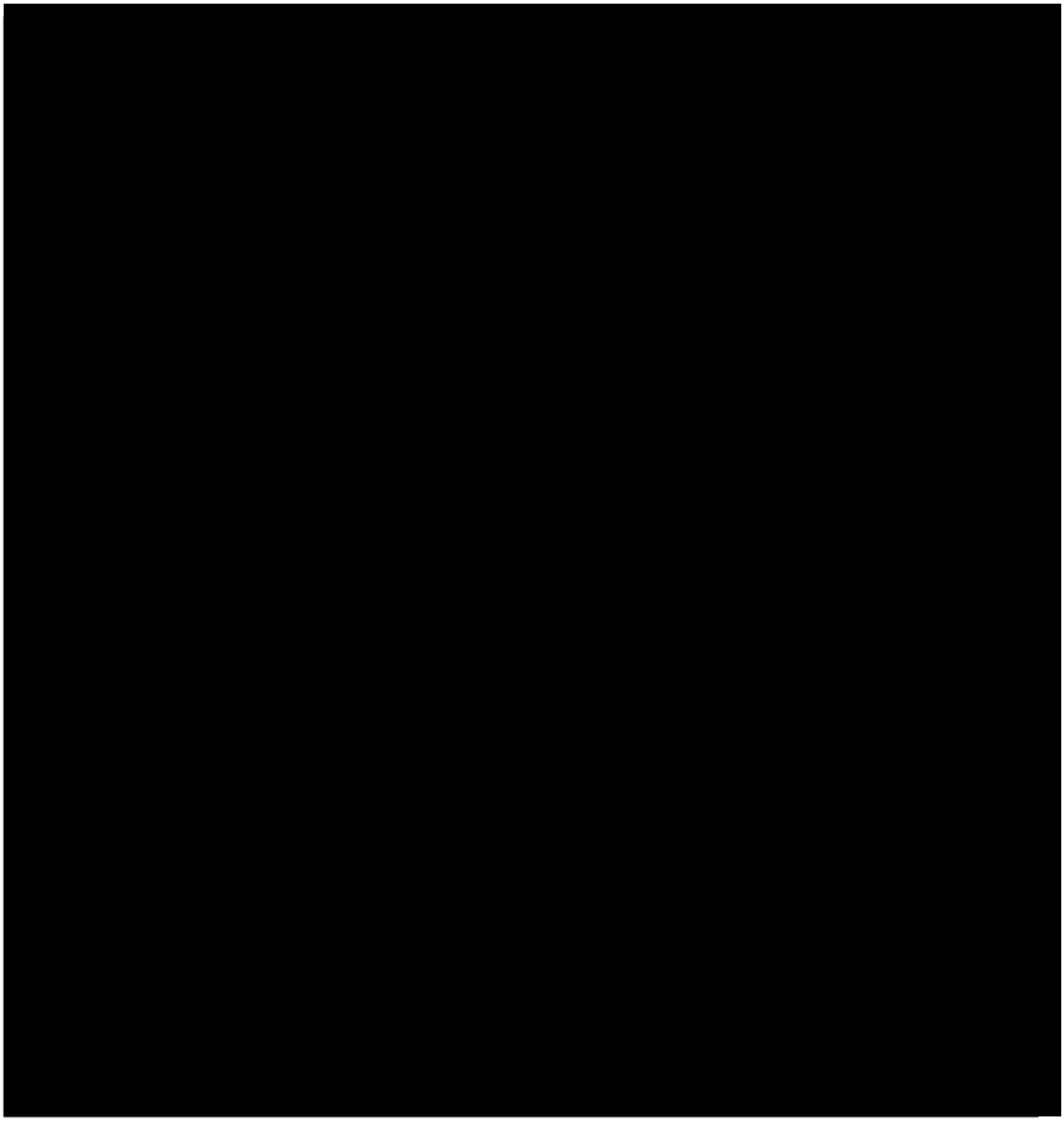








Appendix F Standardized Rhinoconjunctivitis Quality Of Life Questionnaire RQLQ(S)



NOVEMBER 2001

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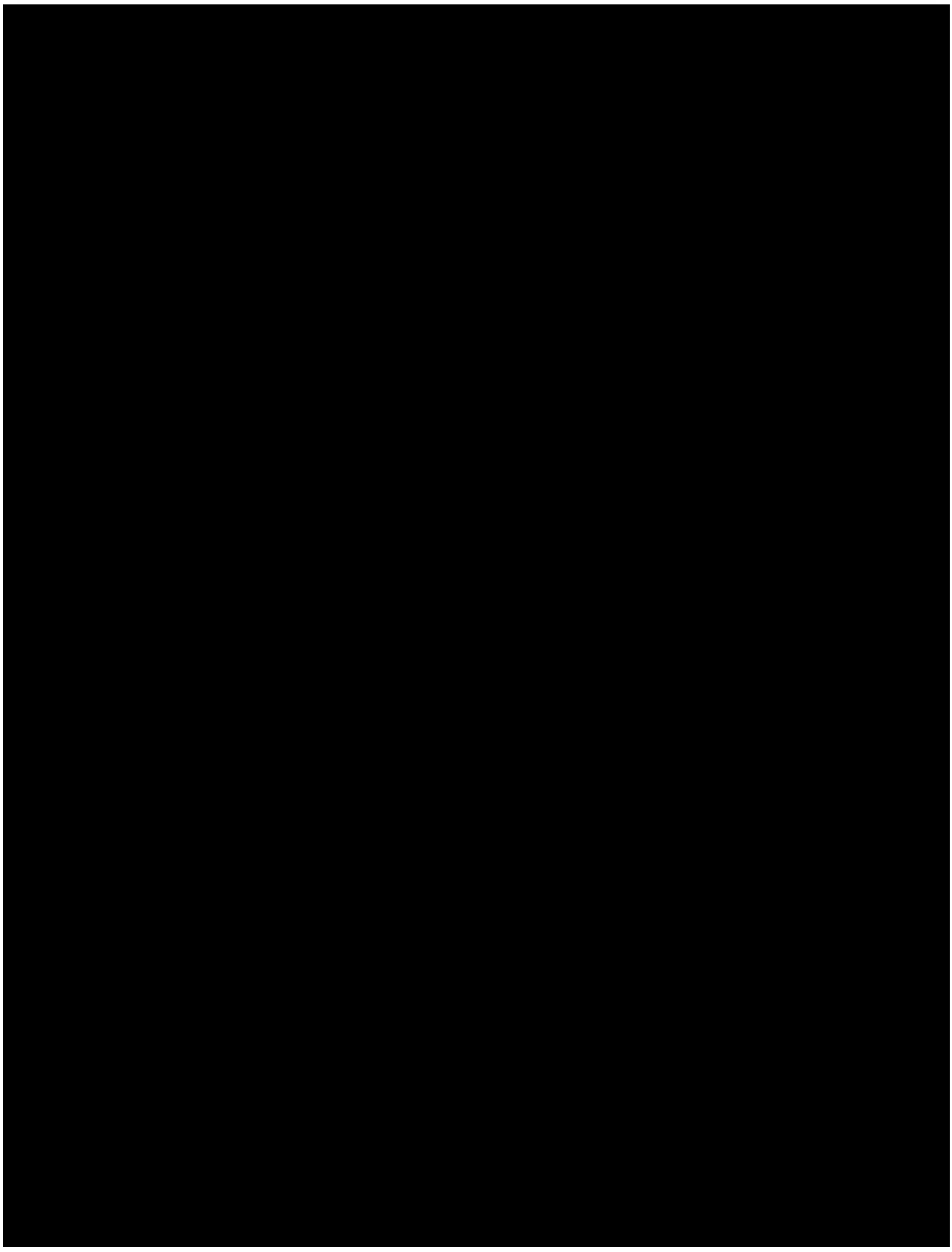
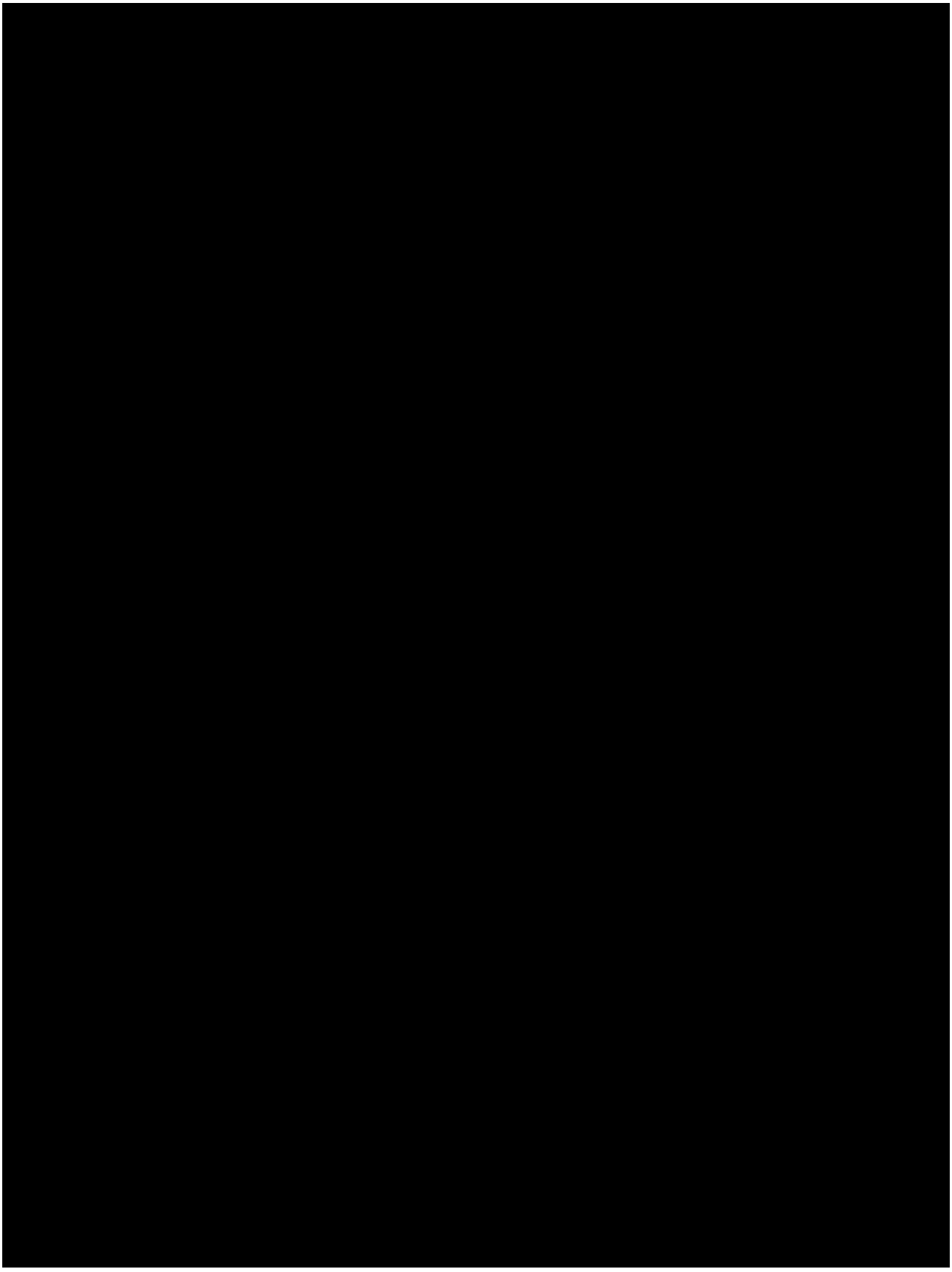
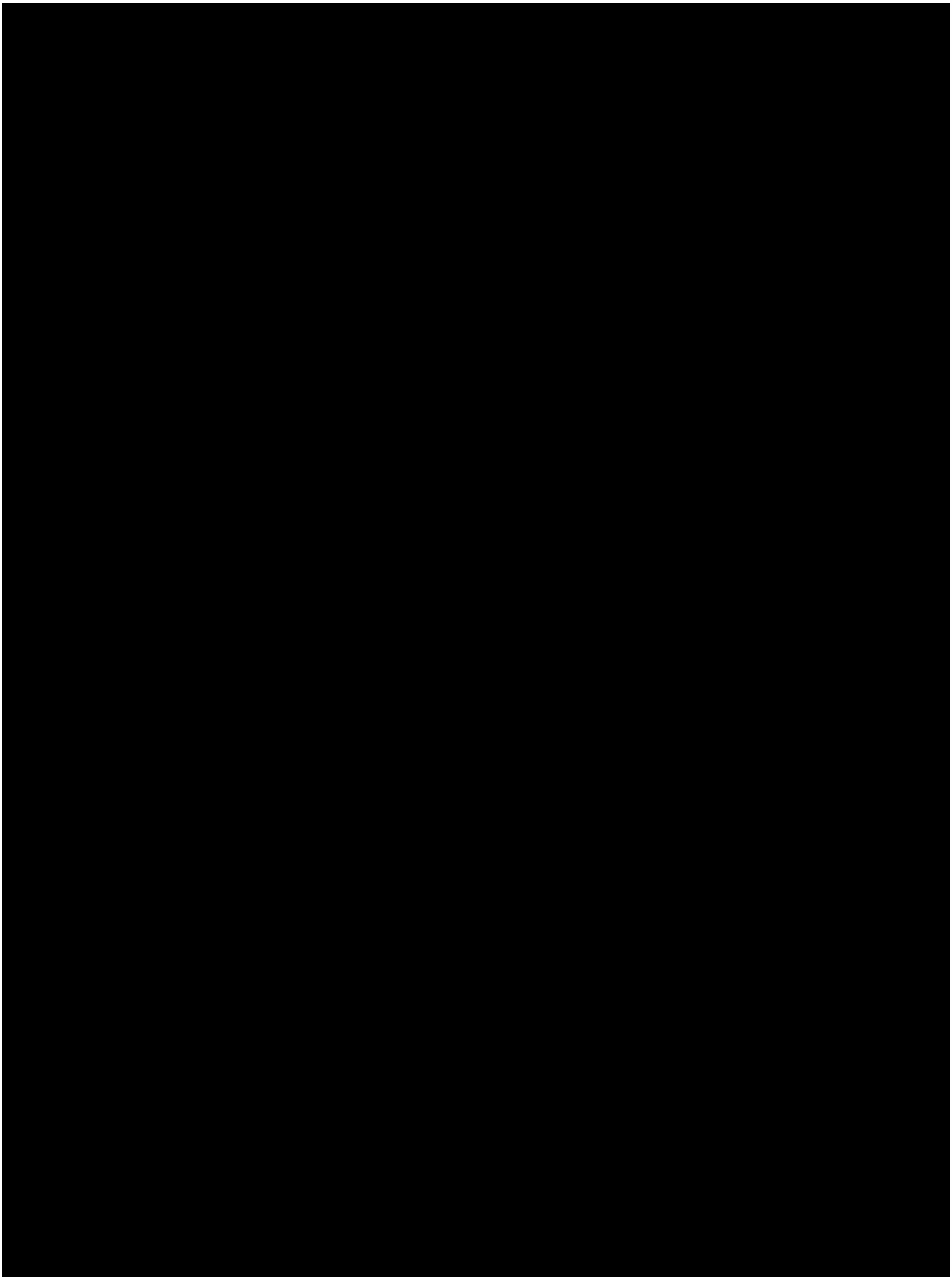
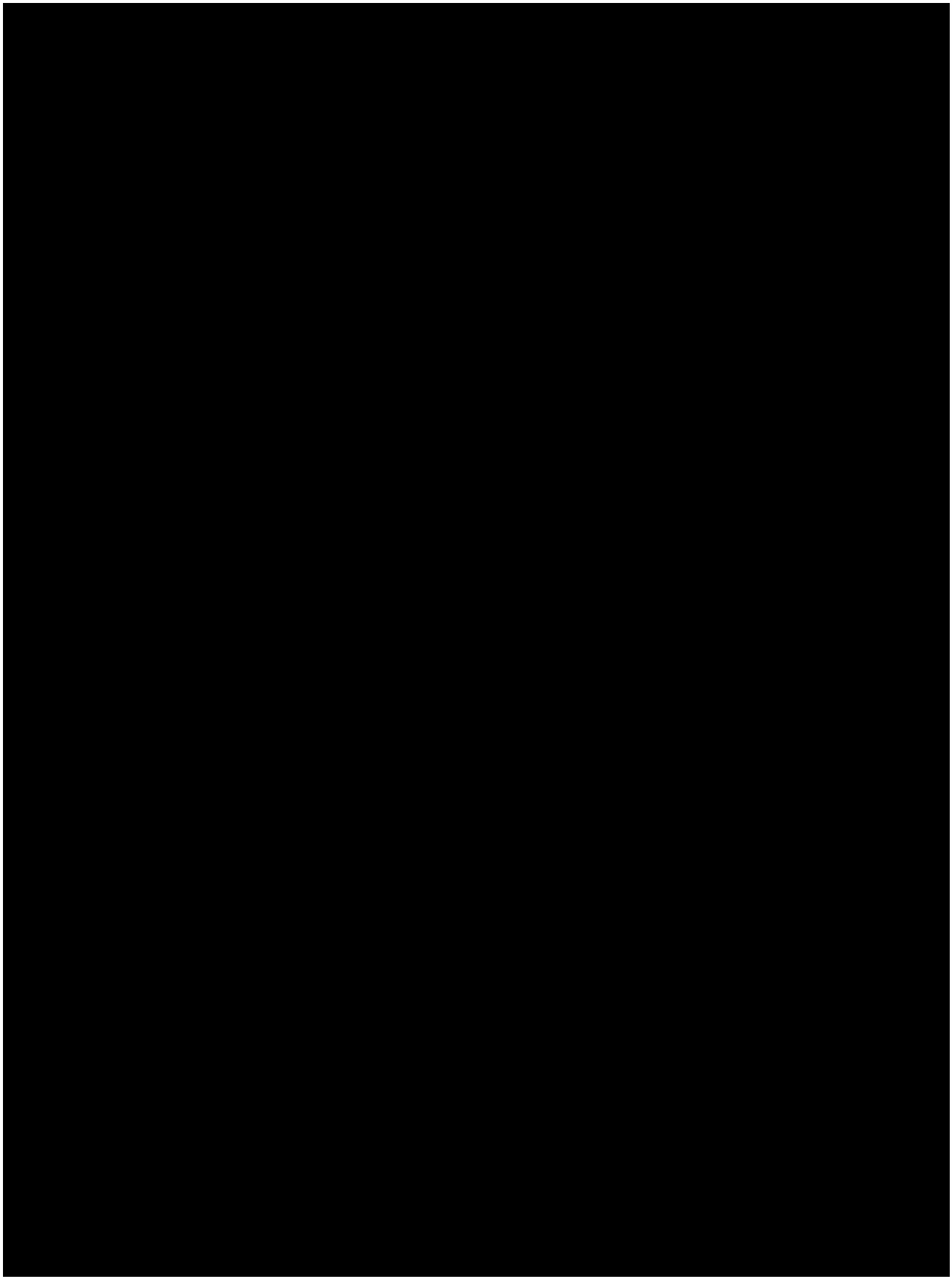








Appendix G Asthma Symptom Score Numerical Rating Scale (NRS)

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 H General guidance for the follow-up of laboratory abnormalities by Sanofi

NEUTROPENIA

Neutrophils < 1500/mm^3 or according to ethnic group

Repeat immediately a full blood count if value close to 1500/mm^3

Neutrophils < 1500/mm^3 confirmed with signs of infection	Neutrophils < 1500/mm^3 confirmed with no signs of infection
1. DISCONTINUE Investigational Medicinal Product, hospitalization should be considered **2. PERFORM** biological investigations for infection	**1. DISCONTINUE** Investigational Medicinal Product **2. INVESTIGATE** for infection

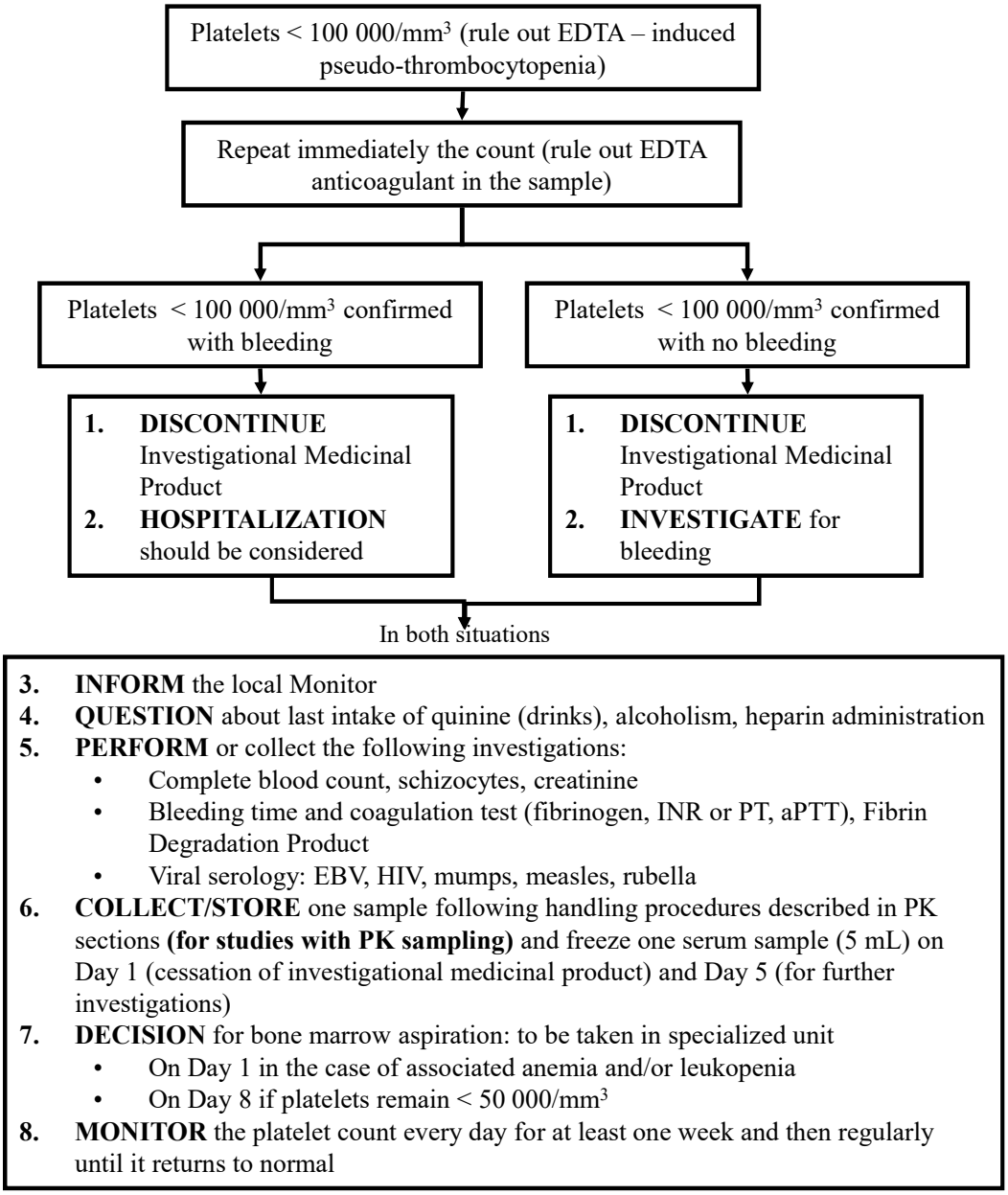
In both situations

3. **INFORM** the local monitor
4. **INVESTIGATE** previous treatments particularly long-term, even a long time ago, exposure to toxic agents, e.g., benzene, X-rays, etc.
5. **PERFORM** and collect the following investigations (results):
   - RBC and platelet counts
   - Serology: EBV, (HIV), mumps, measles, rubella
6. **DECISION** for bone marrow aspiration: to be taken in specialized unit
7. **COLLECT/STORE** one sample following handling procedures described in PK sections **(for studies with PK sampling)** and freeze one serum sample (5 mL) on Day 1 (cessation of investigational medicinal product) and Day 5 (for further investigations)
8. **MONITOR** the leukocyte count 3 times per week for at least one week, then twice a month until it returns to normal

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

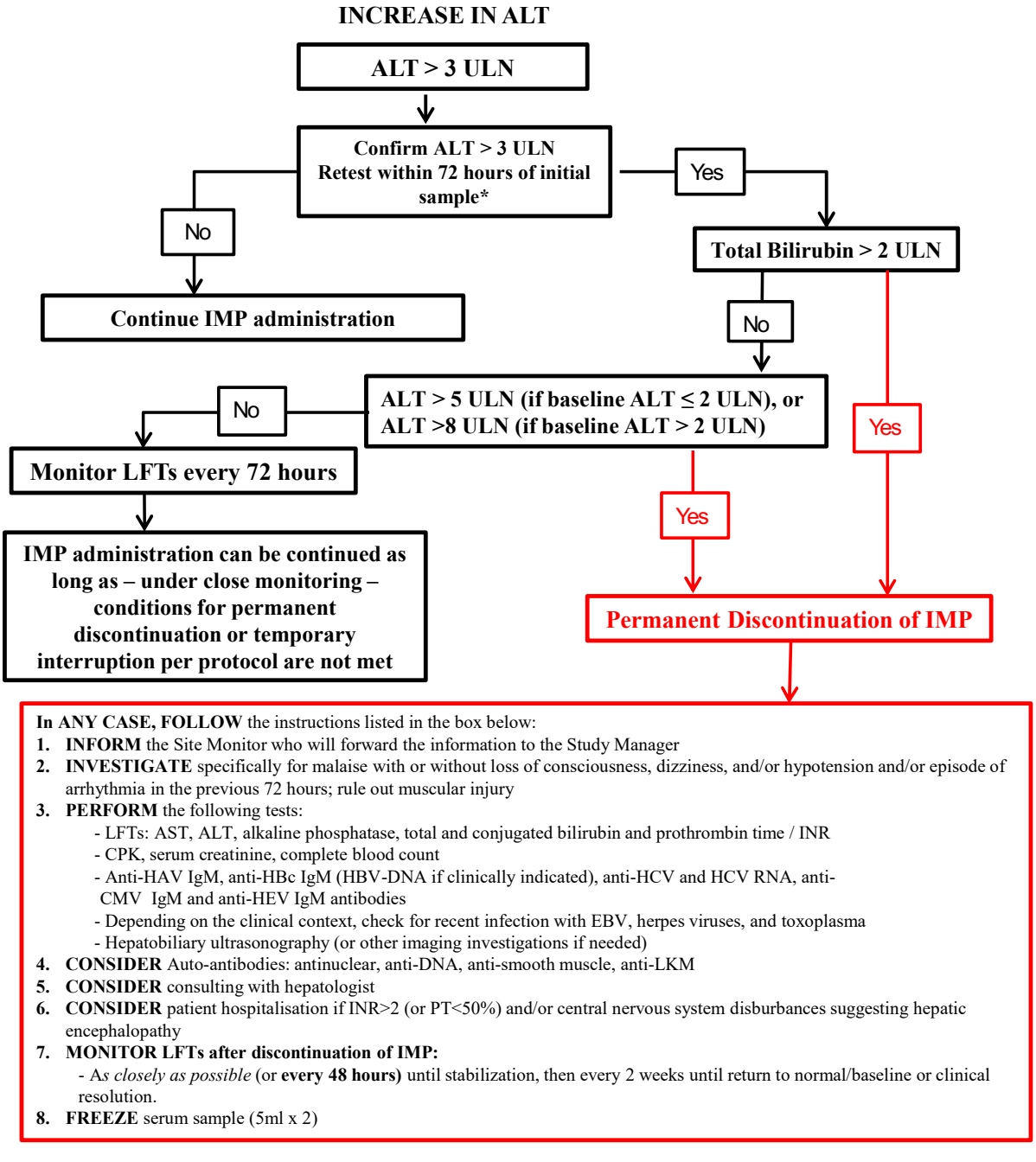
Neutropenia is to be recorded as an AE only if at least 1 of the criteria listed in the general guidelines for reporting AEs in Section 10.4.3 is met.

THROMBOCYTOPENIA



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

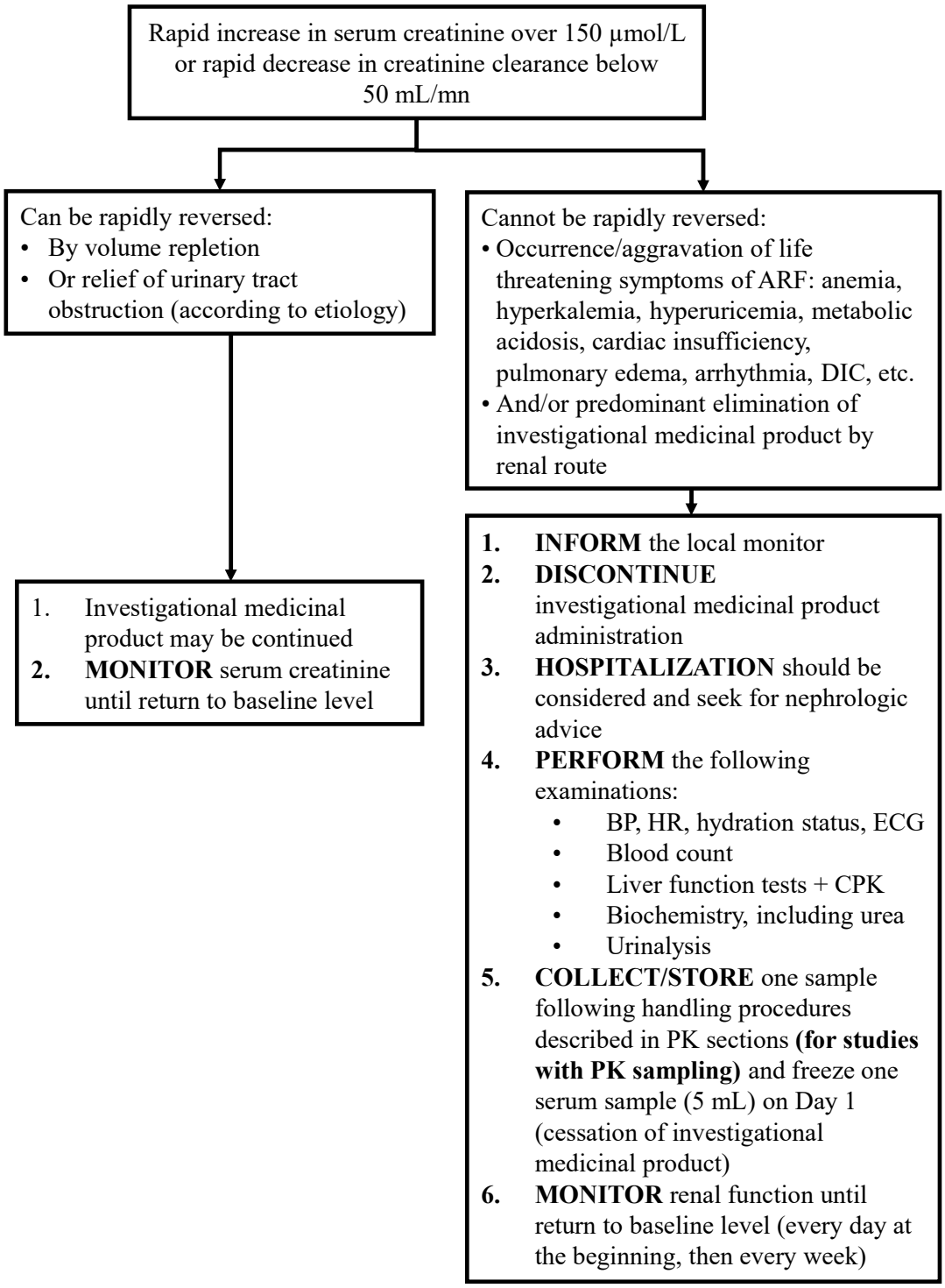
Thrombocytopenia is to be recorded as an AE only if at least 1 of the criteria listed in the general guidelines for reporting AEs in Section 10.4.3 is met.



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

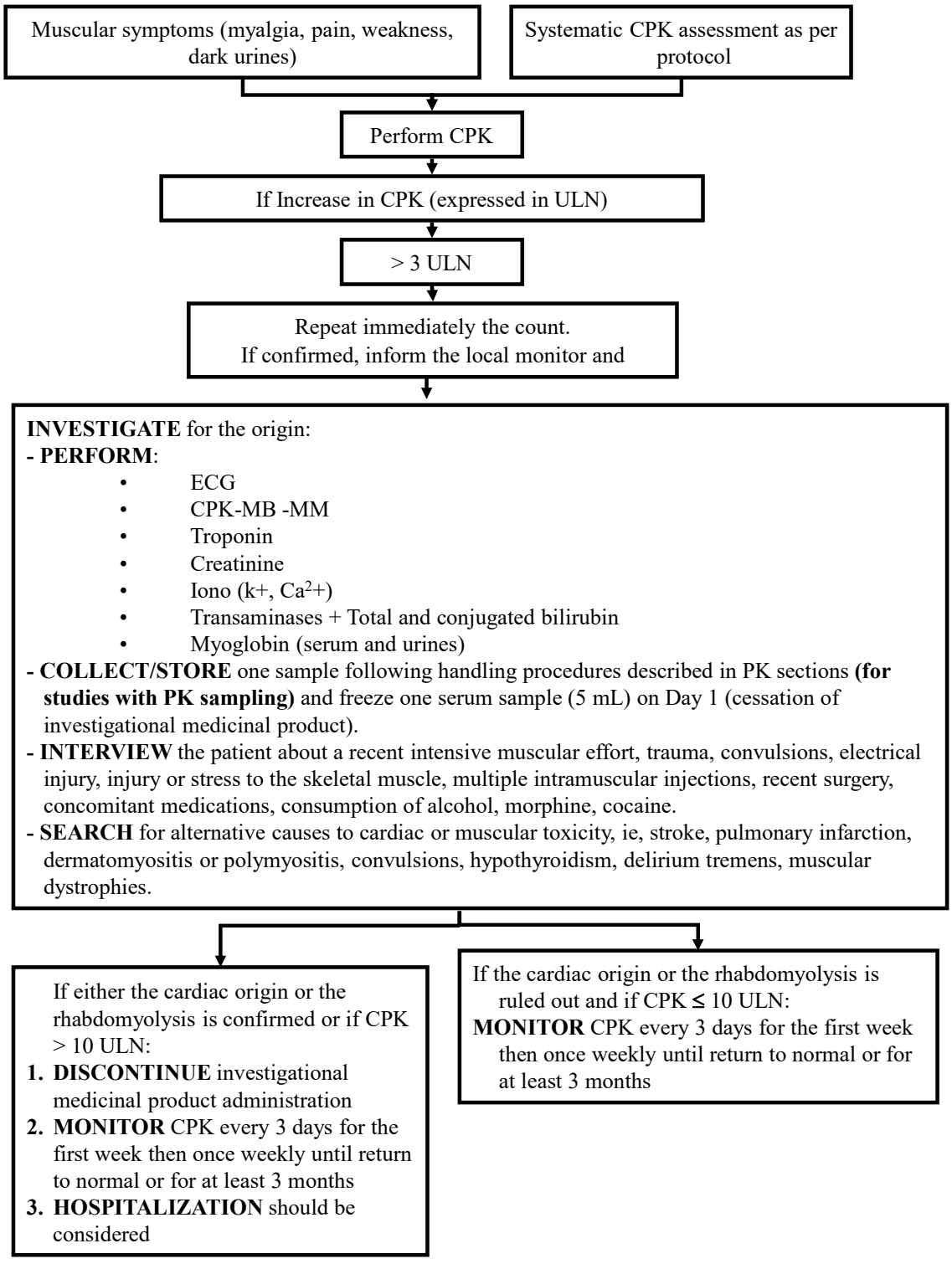
- "Baseline" refers to ALT sampled at baseline visit; or if baseline value unavailable, to the latest ALT sampled before the baseline visit. The algorithm does not apply to the instances of increase in ALT during screening.
- See Section 10.4.6 for guidance on safety reporting.
- Normalization is defined as ≤ ULN or baseline value, if baseline value is >ULN.

INCREASE IN SERUM CREATININE



Increase in serum creatinine is to be recorded as an AE only if at least 1 of the criteria listed in the general guidelines for reporting AEs in Section 10.4.3 is met.

INCREASE IN CPK SUSPECTED TO BE OF NON-CARDIAC ORIGIN AND NOT RELATED TO INTENSIVE PHYSICAL ACTIVITY



Increase in CPK is to be recorded as an AE only if at least 1 of the criteria in the general guidelines for reporting AEs in Section 10.4.3 is met.

Appendix I List of opportunistic infections

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

Not applicable

Appendix L Protocol Amendment History

The changes for this amended protocol are described in the Protocol Amendment Summary of Changes section.

ACT15102 Amended Protocol 01

ELECTRONIC SIGNATURES

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