AstraZeneca

Clinical Study Protocol

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A Phase 2 Placebo-Controlled, Randomized, Double Blind, Adaptive Dose Trial of the Safety and Efficacy of Inhaled AZD1419 in Adults With Eosinophilic, Moderate to Severe Asthma

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VERSION HISTORY

Version 2.0, Initial creation

Updates done in Sect. 1.2 (2 typos corrected), Sect 1.3 (paragraph added), Figure 1 (Visit windows), Sect 3.1 (Incl crit 3), Sect 3.2 (typo corrected and Excl crit 2 & 9), Sect 3.8 (restriction added), Table 1 (typo corrected and clarification of FEV1), Sect 4.2.2 (clarification re vaccination), Sect 5.1.5 (clarification of FEV1) and Table 3 (typo corrected).

This Clinical Study Protocol has been subject to a peer review according to AstraZeneca Standard procedures. The clinical study protocol is publicly registered and the results are disclosed and/or published according to the AstraZeneca Global Policy on Bioethics and in compliance with prevailing laws and regulations.

AstraZeneca

PROTOCOL SYNOPSIS

A Phase 2 Placebo-Controlled, Randomized, Double Blind, Adaptive Dose Trial of the Safety and Efficacy of Inhaled AZD1419 in Adults With Eosinophilic, Moderate to Severe Asthma

[redacted]

Study site(s) and number of patients planned

This study will be a multi-centre study conducted at approximately 20 centres in 4-5 countries. Approximately 170 patients will be enrolled to achieve 70 randomised patients.

Study period		Phase of development
Estimated date of first patient enrolled	Q4 2016	II
Estimated date of last patient completed	Q4 2018	II

Study design

This phase 2a study is a randomized, double-blind, placebo-controlled trial designed to assess the efficacy and safety of 13 once weekly doses of inhaled AZD1419 administered to patients with eosinophilic asthma controlled on a maintenance treatment of inhaled corticosteroids (ICS) and a long-acting β2 agonist (LABA), but no other controller medication.

Prior to randomization patients will undergo an approximately 2-4 week screening period. Eligible patients will be prescribed their usual controller medication (i.e. ICS + LABA in separate inhalers, in addition to a rescue medication inhaler (short-acting β2 agonist [SABA]), and issued electronic diaries, peak flow and FeNO meters to record asthma symptoms and lung function during each morning and evening at home. Asthma control will be assessed using the 5-item asthma control questionnaire (ACQ-5) and when patients have shown to be controlled (ACQ-5 $\leq$0.75) they are randomized to receive AZD1419 or placebo administered as an inhalation at the clinic once per week.

A withdrawal design will be used where the first 6 doses of IMP will be administered as add-on to the patient's regular ICS + LABA. The controller treatment will then be tapered down during the next 3 doses of AZD1419/placebo and the last 4 doses will be administered during a period of complete withdrawal of maintenance treatment. SABA will be allowed and used as

reliever medication during the whole study. The first 4 doses of IMP will be given as 4mg per week after which the dose is potentially adjusted to 1 mg or 8 mg per week based on frequency and severity of flu-like adverse events (arthralgia, chills, pyrexia, myalgia) occurring within 24h of inhalation in the individual patient.

The patients will be monitored closely with regards to asthma symptoms, reliever use and lung function and upon loss of control of their asthma they will resume their ICS + LABA controller medication and are considered to have met the primary endpoint. The patients are then followed for an additional 4 weeks.

Objectives

Primary Objective:	**Outcome Measure:**
To assess the efficacy of inhaled AZD1419 in eosinophilic asthma patients after withdrawal of controller treatment of ICS + LABA	Time to loss of asthma control

For the purpose of the study loss of asthma control is defined as any of the following:

(a) An increase of ACQ-5 to 1.5 or more

(b) A reduction of 30% or more in morning peak expiratory flow (PEF) from baseline on 2 consecutive days

(c) At least six additional reliever inhalations of SABA in a 24-hour period relative to baseline on 2 consecutive days

(d) An exacerbation requiring systemic corticosteroids

Secondary Objective:	**Outcome Measure:**
To further assess the efficacy of inhaled AZD1419 in eosinophilic asthma patients after withdrawal of controller treatment of ICS + LABA	Proportion of patients who experience loss of asthma control Changes over the course of the study in ACQ-5 Changes over the course of the study in asthma daily diary score Changes over the course of the study in number of moderate and severe exacerbations Changes over the course of the study in the use of reliever bronchodilator (short-acting beta-agonist SABA) Changes over the course of the study in pre- and post-bronchodilator FEV1 Changes over the course of the study in PEF Changes over the course of the study in fractional exhaled nitric oxide (FeNO)

Safety Objective:	**Outcome Measure:**
To evaluate the safety and tolerability of inhaled AZD1419 in eosinophilic asthma patients after withdrawal of controller treatment of ICS + LABA	Adverse events, vital signs, ECG and laboratory parameters Weekly peak expiratory flow rate (PEFR) Lung diffusion capacity (DLco)
Exploratory objective:	**Outcome Measure:**
• To assess the responses of selected systemic peripheral blood and sputum biomarkers to inhaled AZD1419 in eosinophilic asthma patients after withdrawal of controller treatment of ICS + LABA	• Peripheral blood and sputum biomarkers (to be specified)
• To assess the composite endpoint for exacerbations, CompEx	• Time to first CompEx event • Changes over the course of the study in CompEx
• To investigate the genes and genetic variation that may influence response to AZD1419	• DNA from whole blood
• To assess the expression of selected genes in cells from whole blood and sputum	• RNA from whole blood and sputum
• To assess the effects on DNA methylation	• DNA from whole blood
• To assess the immune function of PBMC	• PBMCs

Target patient population

The study population will comprise adult eosinophilic asthma patients on a background treatment of ICS + LABA.

Duration of treatment

The total duration of patient participation will be up to 56 weeks. This includes an approximately 2-4 week screening period prior to the first trial treatment, a 12 week dosing period with AZD1419 or placebo and an up to 40-week observation/follow up period following the last trial treatment.

Investigational product, dosage and mode of administration

The investigational product, AZD1419 or matching placebo, will be administered once weekly using the commercially available and CE marked I-neb® Adaptive Aerosol Delivery [ADD] System from Philips Respironics.

AZD1419/placebo is supplied as a solution at a concentration of 2 mg/mL, 8 mg/mL and 16 mg/mL in phosphate-buffered saline.

Three inhaled dose levels of AZD1419/placebo, 1 mg, 4 mg and 8 mg may be investigated in a 12 week regimen consisting of 4 once weekly inhaled doses of 4 mg followed by 8 weeks of

inhaled doses of 1 mg, 4 mg, or 8 mg. The maximum possible dose that any patient will receive during the study is 8 mg.

The placebo for this trial is phosphate-buffered saline, pH 7.2.

Statistical methods and sample size

The primary efficacy variable is the time to loss of asthma control, and the primary analysis is to compare the time to loss of asthma control for AZD1419 with placebo. The time to loss of control in the AZD1419 group will be compared to that of the placebo group using a log rank test (with accompanying Kaplan-Meier plot). The hypothesis test will be one-sided, with alpha=0.05.

The secondary outcome variables listed above will be analysed longitudinally using all measurements taken over the course of the study. Continuous variables will be modelled using mixed effects models; categorical outcomes will be modelled using generalized estimating equations. Additionally, all outcomes will be summarized by treatment group at each measurement time point.

This trial has about 90% power to yield a statistically significant (alpha = 0.05, 2-sided) difference between the pooled active and placebo groups in time to loss of asthma control given that the cumulative number of controlled subjects at week 52 is 20% and 60% for control versus active respectively. Assuming a drop-out of about 10-15%, this will require about 70 patients in total (32 events).

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study Clinical Study Protocol.

Abbreviation or special term	Explanation
AAD	Adaptive Aerosol Delivery
AE	Adverse event
ANA	Antinuclear antibody
AZ	AstraZeneca
CBC	Complete blood count
CO	Carbon monoxide
CpG	Cytidine-phospho-guanosine
CRF	Case Report Form (electronic/paper)
CRP	C-reactive protein
CSA	Clinical Study Agreement
CSR	Clinical Study Report
CXCL-10	C-X-C motif chemokine 10 (Formerly known as IP-10 - Interferon inducible protein 10)
DAE	Discontinuation of Investigational Product due to Adverse Event
DBP	Diastolic blood pressure
DLco	Diffusing capacity of the lung for carbon monoxide
DNA	Deoxyribonucleic acid
dsDNA	Double-stranded DNA
DSMB	Data and safety monitoring board
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
ECG	Electrocardiogram
FAS	Full analysis set
FEV1	Forced expiratory volume in 1 second
FEF25-75	Forced expiratory flow 25% to 75%
FeNO	Fractional exhaled nitric oxide
GCP	Good Clinical Practice
GINA	Global Initiative for Asthma
HCV	hepatitis C virus
HIV	Human immunodeficiency virus
HR	Heart rate
HV	Healthy volunteer
IC	Inspiratory capacity

Abbreviation or special term	Explanation
ICF	Informed consent form
ICH	International Conference on Harmonisation
ICS	Inhaled corticosteroids
ICI	If a study is conducted in several countries the International Co-ordinating Investigator is the Investigator co-ordinating the investigators and/or activities internationally.
IFN-α	Interferon alpha
Ig, IgE, IgG	Immunoglobulin, Immunoglobulin E, Immunoglobulin G
IL	Interleukin
IP/IMP	Investigational (Medicinal) Product
IP-10	Interferon inducible protein 10 (see CXCL-10)
IXRS	IVRS or IWRS Interactive Voice or Web Response System
ISS	Immunostimulatory sequence
LABA	Long-acting beta agonist(s)
LDH	Lactate dehydrogenase
LSLV	Last Subject Last Visit
MTD	Maximum tolerated dose
NICE	National Institute for Health and Care Excellence
OAE	Other Significant Adverse Event
OCS	Oral corticosteroids
ODN	Oligodeoxynucleotide
PBMC	Peripheral blood mononuclear cell
PC20	Provocative concentration of methacholine or histamine causing a 20% fall in FEV1
PD	Pharmacodynamics
PD15	Provocative Dose of mannitol causing a 15% fall in FEV1
PEF	Peak expiratory flow
PGx	Pharmacogenetic research
PS ODN	Phosphorothioate oligodeoxynucleotide
RNA	Ribonucleic acid
SABA	Short-acting beta agonists
SAD	Single ascending dose
SADR	Serious adverse drug reaction
SAE	Serious adverse event
SAP	Statistical analysis plan
SBP	Systolic blood pressure

Abbreviation or special term	Explanation
SUSAR	Suspected Unexpected Serious Adverse Reaction
Th1, Th2	T helper 1, T helper 2
TLR	Toll-like receptor
VC	Vital capacity
WBDC	Web Based Data Capture
WOCBP	Women of childbearing potential

1. INTRODUCTION

1.1 Background and rationale for conducting this study

Asthma is a common, chronic respiratory disease affecting up to 18% of the population in different countries, and with a global prevalence of approximately 300 million patients (GINA 2015). Asthma is characterized by wheeze, shortness of breath, chest tightness and/or cough, and by expiratory airflow limitation. Both symptoms and airflow limitation characteristically vary over time and in intensity. Worsening is often triggered by factors such as exercise, allergen or irritant exposure, change in weather, or viral respiratory infections.

In many patients the underlying immunological basis for asthma is a preponderant T-helper cell Type 2 (Th2) differentiation of T cells specific for environmental allergens (Holgate 2012) and an immune response polarized towards Th2 responses. This results in the production of cytokines such as IL-4, IL-5, and IL-13, leading to eosinophilic pulmonary inflammation and bronchial hyperresponsiveness. The current approach to anti-inflammatory controller therapy in asthma is based on a step-wise intensification of maintenance treatment primarily centered on daily inhaled corticosteroids (ICS) with the addition of long-acting β2 agonists (LABA).

Human Toll-like receptors (TLRs) are a key family of pattern-recognition receptors expressed in cells of the innate immune system. Recognition of invading pathogens by a TLR triggers innate immune responses that promote adaptive immune response and enhance development of long term acquired immunity (O'Neill et al 2009). Stimulation of specific TLRs can also elicit patterns of cytokine and chemokine production that orients the adaptive response towards a particular helper T cell subset. In humans, the TLR family is composed of 10 different receptors. One sub-family of TLRs, comprising TLR3, TLR7, TLR8 and TLR9, is located on the endosomal membrane of cells of the innate immune system and detects nucleic acids from invading pathogens. TLR9, the target of AZD1419, recognizes unmethylated CpG motifs in bacterial, viral, and fungal DNA.

Activation of TLR9 by CpG-containing DNA from an invading pathogen leads to maturation of plasmacytoid dendritic cells (pDCs) and subsequent production of T-helper type-1 (Th1) cytokines, including IFN-α, and chemokines such as CXCL-10. Stimulation of the innate immune response through TLR9 has the potential to alter T cell responses to environmental antigens from a Th2-dominant allergic response toward a more balanced Th2/Th1 response. This immune modification may have the effect of reducing the asthmatic response to e.g. allergic triggers, potentially inducing a sustained clinical improvement in airway function and asthma symptoms after a relatively short course of treatment.

Stimulation of the innate immune response in asthma via TLR9 has been investigated with the compound CYT003-QbG10 (Cytos Biotechnology AG), a virus-like particle containing the oligonucleotide TLR9 agonist G10, delivered as a subcutaneous injection. In a phase 2 trial this was shown to reduce asthma symptoms and allowed patients to maintain both lung function (forced expiratory volume in 1 second [FEV1]) and asthma control as measured by

the Asthma Control Questionnaire, also after removing the patients' controller medication (Beeh et al 2013).

AZD1419 is planned to be developed as a potential disease-modifying therapy for asthma. AstraZeneca considers that a course of inhaled AZD1419 administered once weekly for a limited period may confer disease remission for a period of time after the course, and potentially remove the need for asthma controller medication. The proposed clinical trial of AZD1419 in patients with moderate to severe asthma is designed to further characterize the safety and efficacy of AZD1419 treatment, and to determine whether AZD1419 provides sustained asthma control in patients when removing their controller ICS + LABA medication.

1.2 Rationale for study design, doses and control groups

This study is designed as a withdrawal trial, i.e. the asthma controller (maintenance) medication will be reduced and discontinued during the treatment period and the patients are followed for up to one year with regards to loss of asthma control (as defined in 2.1.1).

In addition to the study by Beeh et al 2013, described above, similar withdrawal designs have been shown to be valuable in asthma trials evaluating the monoclonal IL-4 receptor antibody dupilumab (Wenzel et al 2013) and House Dust Mite Sublingual Allergen Immunotherapy (Virchow JC et al 2016), respectively. Controller medication was withdrawn from patients with not fully controlled asthma (ACQ-5 between 1.5-3 and 1 to 1.5, respectively, at randomization) and followed until need to resume the maintenance medication. A withdrawal design is considered appropriate for evaluating the potential for AZD1419 to re-balance the immune system with a subsequent disease remission allowing the patients to retain asthma control despite having their controller medication reduced and discontinued. There is currently no marketed TLR9 agonist, and placebo will be used as comparator to AZD1419. Use of SABA is allowed as reliever medication throughout the study.

Asthma patients with Th2 polarized airway inflammation is the target population for AZD1419 in this study. Peters et al (Peters et al 2013) have suggested that peripheral blood eosinophil counts of 230 cells/mL or above, a value that had similar sensitivity and specificity as sputum eosinophilia, is indicative of airway Th2-high driven asthma. For the present study we have chosen to allow historical data for blood eosinophils - up to 2 years old - setting the cut-off at 250 cells/μL, and $\geq$150 cells/μL at screening.

A combined single ascending dose (SAD), multiple ascending dose (MAD) trial in healthy adult volunteers (men and women) has been performed with AZD1419 administered once weekly for 4 weeks in doses up to 23.1 mg. The dose levels and the weekly dosing regimen used in the SAD/MAD was based on results from pharmacodynamics studies and nonclinical efficacy (in the ragweed and ovalbumin [OVA] mouse models of allergic pulmonary inflammation) and pre-clinical safety studies. Data from the SAD/MAD study suggested target engagement at all dose levels. Flu-like symptoms emerged at the 2 highest doses (15.4 and 23.1 mg), with the 15.4 mg dose regarded as the maximum tolerated dose. Dose levels of 0.8, 2.3, and 7.7 mg were considered well tolerated. In the proposed study the highest dose given will be 8.0 mg/week. However, the dose of IMP (AZD1419 or placebo) will be adapted

during the study based on the occurrence and severity of flu-like symptoms in the individual patient, to maintain safety and tolerability while testing efficacy in controlling asthma symptoms. Patients will start with 4 weeks of 4.0 mg/week inhaled AZD1419, then dosing will be adapted for each patient individually, see Section 4.2.2. Pre-clinical data have suggested that 12 weekly treatments with the TLR9 agonist ISS 1018 induce suppression of allergic airway inflammation lasting for 15 weeks post treatment when the last evaluation was performed (Campbell et al 2014). In the present study 13 doses will be administered once weekly. This will allow for dosing of IMP on top of controller medication and then allow time for safe withdrawal of ICS+LABA as well as dosing in the absence of controller medication.

1.3 Benefit/risk and ethical assessment

Asthma is a chronic inflammatory disorder of the airways associated with substantial morbidity. There are currently no available treatments shown to provide remission in asthma, but based on data gathered to date AstraZeneca considers AZD1419 to have the potential to induce long-term remission and disease control in asthmatics, removing the need for controller (maintenance) medication.

TLR9 agonists delivered as subcutaneous, intramuscular or intratumoral injection have been widely investigated in clinical studies, mainly for treatment of malignancies and as vaccine adjuvants, but also evaluated for treatment of asthma and allergic rhinitis. The most commonly reported adverse events are injection site reactions, flu-like symptoms (including headache, chills, fatigue, headache, myalgia and pyrexia) and in some cases hematological effects such as transient lymphopenia (Scheiermann J and Klinman DM 2014, Qin M et al 2014).

AZD1419 was not detected in any plasma sample from patients in the highest dose cohort (23.1 mg) in the previous trial and the systemic exposure in the proposed study, where the maximum given dose will be 8 mg, is expected to be low. The aim is to keep the sensitive parameter flu-like AEs at a low or absent level. Patients will start at 4 mg/week and based on occurrence of the flu-like symptoms in the individual patient, the dose will be maintained or adapted up or down. Should symptoms occur, they should be treated per standard medical practice (e.g. paracetamol) based on the judgment of the investigator.

TLR9 agonists could potentially, by inducing type 1 interferon production, aggravate or contribute to the development of autoimmune disease. To mitigate the potential risk for subsequent autoimmune reactions patients with a history of autoimmune disease will be excluded from taking part in the study. Transient increases in antinuclear antibodies (ANA) and anti-doublestranded DNA (anti-dsDNA) without clinical relevance have been seen upon CpG oligodeoxynucleotide (CpG ODN) (TLR9 agonist) and Interferon α (IFN-α) exposure. To increase our knowledge for the future clinical program patients will donate blood samples during the study for later analysis of selected auto-antibodies.

The nonclinical data support the administration of AZD1419 in human repeat-dose inhalation studies of up to 13 weeks duration with the proposed doses. Toxicology safety studies performed in monkey indicate that AZD1419 induces a dose dependent and transient

activation and recruitment of immune cells in the lungs that persists for at least 2 weeks after cessation of dosing, but fully resolves after 8 to 12 weeks after the last dose. The data from the previous clinical trial with AZD1419 does not indicate risk for local adverse effects in the lungs when administered to healthy volunteers. However, patients with asthma or other lung diseases may react differently. In the proposed study, patients with lung disease other than asthma or clinically relevant chest x-ray changes will be excluded. All doses of study drug will be administered at the clinic and the patients will be observed at the clinic for at least 6 hours after the first dose and for at least 2 hours after the remainder of doses. Patients will be followed from start of treatment with standard Adverse Event (AE) monitoring and daily lung function tests using home spirometry (peak expiratory flow [PEF]), and in addition spirometry performed at the clinic during scheduled visits. Patients will be encouraged to contact the study site if they have any concerns about their lung function during the study.

A sentinel dosing period will precede open enrollment into the trial. Four patients will be randomly assigned 1:1 either to placebo or AZD1419 at 4 mg/week and observed at the clinic for 24 hours after the first 2 doses for significant safety concerns, including bronchospasm and allergic reactions. These patients will then continue in the study in accordance with the study protocol. After the last of the 4 sentinel patients has received 4 doses, a Data Safety Monitoring Board (DSMB) will review safety data and approve enrollment of additional patients in the study.

During the dosing period the patients' controller medication (ICS + LABA) will be gradually reduced and discontinued. There is a risk of asthma worsening during the study due to this withdrawal design. SABA will be allowed and should be used as needed during the whole study. Patients are required to be well controlled in their asthma (ACQ-5 $\leq$0.75) at time of randomization and are closely monitored on a daily basis with regards to asthma symptoms, reliever use and lung function (PEF), captured in an ePRO device, during and after the withdrawal period. An automatic asthma action plan will be embedded in the ePRO device and upon worsening of asthma control, i.e. not being adequately controlled as indicated by ACQ-5 $\geq$1.5, or reduction in PEF and/or increase in rescue medication beyond the set limits the patient will be prompted to resume his/her regular ICS+ LABA controller medication and an alert will be sent to the site (see Section 5.3). With these precautions a gradual worsening of asthma will be detected and the endpoint criteria for reduced asthma control are set so that ICS+LABA can be resumed without undue delay and without risk for patients.

No reproductive toxicology data are available for AZD1419. However, in multiple dose toxicity studies no effects on reproductive organs were observed in either mice or cynomolgus monkeys. Women of childbearing potential will be allowed in the present study provided that contraceptive methods are used as described in this Clinical Study Protocol.

Although the systemic exposure of AZD1419 is expected to be low, systemic Type 1 cytokines (e.g. IFN-α) produced as a result of target engagement may be harmful for an unborn child or lead to spontaneous abortion and the Investigator needs to stress the importance of complying with the contraceptive requirements to Women of Child Bearing Potential.

Women who are breastfeeding, pregnant (verified by urine dipstick pregnancy test) or intends to become pregnant during the study are not allowed to be included.

Pregnancy tests and check of contraceptive compliance will be performed during the treatment. Use of CYP3A4 inducing drugs that may reduce effect of hormonal contraceptives are not allowed.

Patients with asthma may have a potential benefit from treatment as described in the introductions section. With the mitigations and monitoring implemented in the study the overall benefit/risk for the trial patients is judged acceptable.

A detailed assessment of the overall risk/benefit of AZD1419 is given in Section 6 of the Investigator's Brochure.

1.4 Study Design

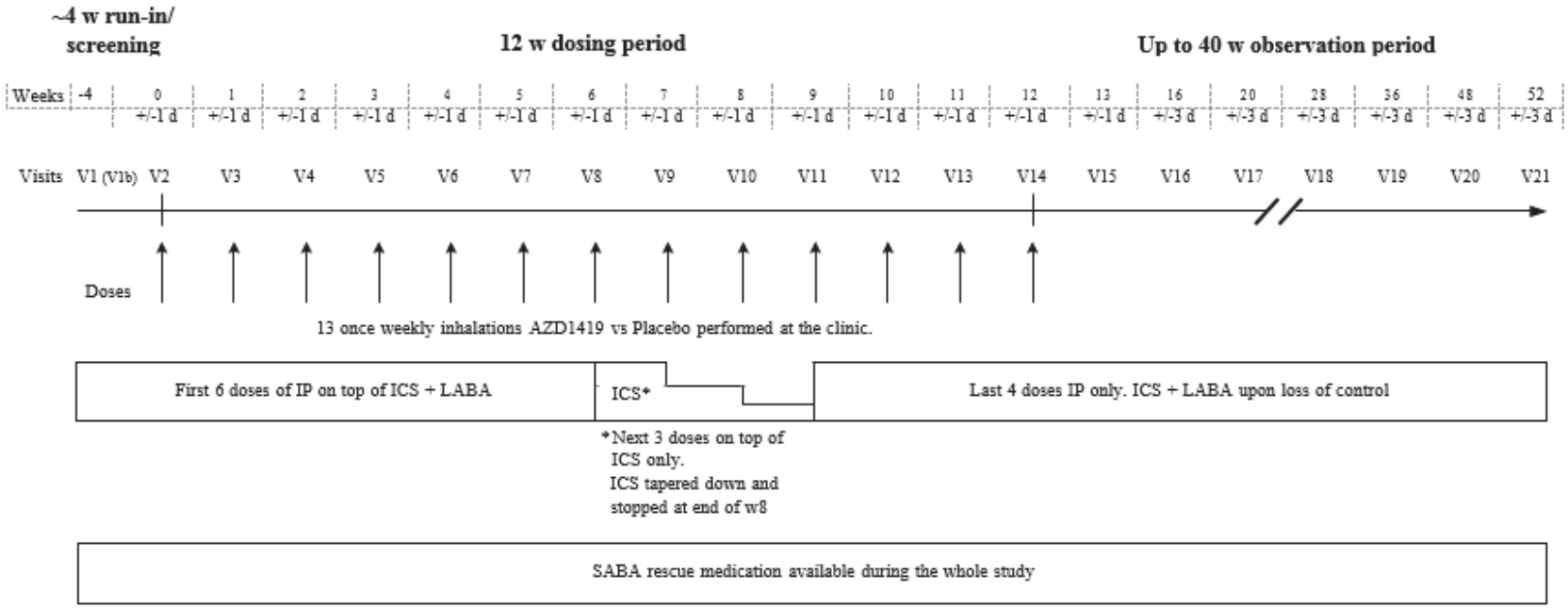
This phase 2a study is a randomized, double-blind, placebo-controlled trial designed to assess the efficacy and safety of 13 once weekly doses of inhaled AZD1419 administered to patients with eosinophilic asthma controlled on a maintenance treatment of ICS plus a LABA but no other controller medication.

A withdrawal design will be used where the first 6 doses of IMP will be administered as add-on to the patient's regular ICS + LABA medication. The controller medication will then be tapered down and discontinued during the next 3 doses of IMP, and the last 4 doses will be administered during a period of complete ICS and LABA withdrawal (see Figure 1). In addition the study drug dose level will be adjusted using an adaptive dosing scheme (defined in Section 4.2.2) based on appearance of flu-like symptoms. The primary endpoint is loss of asthma control, defined in Section 2.1.1. When a patient meets the primary endpoint the patient will resume ICS + LABA and will be followed for an additional 4 weeks before discontinuing the study.

The total duration of patient participation will be up to 56 weeks. This includes a screening period of approximately 2-4 weeks, a 12 week dosing period and an up to 40-week observation period following the last dose, further outlined in Section 4. The schedule of trial procedures is presented in Table 1.

The study will start with a sentinel dosing period to be conducted at 1 or 2 selected study centers, during which 4 patients will be randomly assigned 1:1 either to placebo or AZD1419 at 4 mg, dosed once weekly. Sentinel patients will be observed at the clinic for 24 hours after each of the first two doses, for details see Section 4.2.1. A Data Safety Monitoring Board (DSMB) will review safety data from these patients and approve enrollment of additional patients in the study (details in Section 6.8.1).

Figure 1 Phase 2a Study Design



2. STUDY OBJECTIVES

2.1 Primary objective

Primary Objective:	Outcome Measure:
To assess the efficacy of inhaled AZD1419 in eosinophilic asthma patients after withdrawal of controller treatment of ICS + LABA	Time to loss of asthma control.

2.1.1 Definition of Loss of asthma control

For the purpose of the study Loss of asthma control is defined as any of the following:

a) An increase of ACQ-5 to 1.5 or more

b) A reduction of 30% or more in morning peak expiratory flow (PEF) from baseline on 2 consecutive days

c) At least six additional reliever inhalations of SABA in a 24-hour period relative to baseline on 2 consecutive days

d) An exacerbation requiring systemic corticosteroids

2.2 Secondary objectives

Secondary Objective:	Outcome Measure:
To further assess the efficacy of inhaled AZD1419 in eosinophilic asthma patients after withdrawal of controller treatment of ICS + LABA	Proportion of patients who experience loss of asthma control Changes over the course of the study in ACQ-5 Changes over the course of the study in asthma daily diary score Changes over the course of the study in number of moderate and severe exacerbations Changes over the course of the study in the use of reliever bronchodilator (short-acting beta-agonist SABA) Changes over the course of the study in pre- and post-bronchodilator FEV1 Changes over the course of the study in PEF Changes over the course of the study in fractional exhaled nitric oxide (FeNO)

2.3 Safety objectives

Safety Objective:	Outcome Measure :
To evaluate the safety and tolerability of AZD1419 in eosinophilic asthma patients after withdrawal of controller treatment of ICS + LABA	Adverse events, vital signs, ECG and laboratory parameters Weekly peak expiratory flow rate (PEFR) Lung diffusion capacity (DLco)

2.4 Exploratory objectives

Exploratory objective:	Outcome Measure:
• To assess the responses of selected systemic peripheral blood and sputum biomarkers to inhaled AZD1419 in eosinophilic asthma patients after withdrawal of controller treatment of ICS + LABA	• Peripheral blood and sputum biomarkers (to be specified)
• To assess the composite endpoint for exacerbations, CompEx	• Time to first CompEx event • Changes over the course of the study in number of CompEx events
• To investigate the genes and genetic variation that may influence response to AZD1419	• DNA
• To assess the expression of selected genes in cells from whole blood and sputum	• RNA from whole blood and sputum
• To assess the effects on DNA methylation	• DNA from whole blood
• To assess the immune function of PBMC	• PBMCs

3. PATIENT SELECTION, ENROLMENT, RANDOMISATION, RESTRICTIONS, DISCONTINUATION AND WITHDRAWAL

Each patient should meet all of the inclusion criteria and none of the exclusion criteria for this study. Under no circumstances can there be exceptions to this rule.

3.1 Inclusion criteria

For inclusion in the study patients should fulfil the following criteria:

1. Provision of informed consent prior to any study specific procedures
2. Male and female patients 18 years and above
3. Physician-diagnosed asthma requiring treatment with ICS and a long-acting beta agonist (LABA), but no other controller medication. The ICS plus LABA can be

any combination inhaler or 2 separate inhalers. Patients must have taken ICS plus LABA controller medication for at least 3 months prior to screening

4. Pre-bronchodilator forced expiratory volume in 1 second (FEV1) ≥50% predicted
5. Female patients must be 1 year post-menopausal, surgically sterile, or using an acceptable method of contraception, refer to Section 3.1.1.
6. Negative pregnancy test (urine) and a date of last menstruation consistent with non-pregnancy for female patients of childbearing potential.
7. Male patients must be surgically sterile or using an acceptable method of contraception (defined as barrier methods in conjunction with spermicides) from the first dose of the IMP and until 1 month after the last dose of the IMP to prevent pregnancy in a partner.
8. Blood eosinophil levels ≥ 250 cells/μL at screening OR a history of blood eosinophil levels ≥ 250 cells/μL at any time in the preceding 2 years AND blood eosinophil levels ≥ 150 cells /μL at screening. The eosinophilia must be believed to be due to asthma and not have other known causes, e.g. helminth infection
9. ACQ-5 score ≤1.5 at screening
10. ACQ-5 score ≤0.75 at randomization
11. Documentation of any of the following within 5 years prior to Visit 1:
    - Proof of post-bronchodilator reversibility in FEV1 of ≥12% and ≥200 mL (Pellegrino et al 2005)
    - Proof of a positive response to a methacholine or histamine challenge (a decrease in FEV1 by 20% [PC20] at ≤8 mg/mL) performed according to ATS/ERS guidelines (American Thoracic Society 2000)
    - Proof of positive response to mannitol challenge (a decrease in FEV1 by 15% [PD15] at ≤635 mg or a >10% decrease in FEV1 between consecutive doses) (Anderson et al 2009)
    - Proof of diurnal variability in PEF >20% over the course of 24 hours in at least 4 out of 7 consecutive days

    If historical documentation is not available, proof of reversibility or a positive response to a methacholine, histamine or mannitol challenge or diurnal variation must be demonstrated according to above and documented during Visit 1
12. In the judgment of the investigator: able to adhere to study procedures including correct twice-daily use of the electronic symptom diary, home monitoring of peak flow, ability to perform spirometry and FeNO measurements
13. Patients should be willing to switch to fixed dose morning and evening ICS+LABA in separate inhalers, together with SABA as rescue medication.

14. Patients who are blood donors should not donate blood during the study and for 3 months following their last dose of the IMP

In addition to the above, the following additional inclusion criterion will be applied to the Sputum Subset (approximately 20% of patients in selected sites)

15. Able to produce an adequate sputum sample at screening following induction with inhaled hypertonic saline

For inclusion in the genetic research, patients must fulfil all of the inclusion criteria above **and**:

16. Provide informed consent for the genetic sampling and analyses.

3.1.1 Acceptable birth control methods

Acceptable birth control methods are tubal occlusion, intrauterine device (provided coils are copper-banded), levonorgestrel intrauterine system (eg, Mirena™), medroxyprogesterone injections (eg, Depo-Provera™), etonogestrel implants (eg, Implanon™, Norplan™), normal and low dose combined oral pills, norelgestromin / ethinylestradiol transdermal system, intravaginal device (eg, ethinylestradiol and etonogestrel), desogestrel (eg, Cerazette™), total sexual abstinence and vasectomised sexual partner.

Women should have been stable on their chosen method of birth control for a minimum of 3 months before entering the trial and should continue with birth control for 1 month after the last dose of inhaled IMP. In addition to the acceptable birth control method (except for the practice of total sexual abstinence), condom should be used by male partner for sexual intercourse from randomization (Visit 2) and for 1 month after the last dose of inhaled AZD1419/matching placebo to prevent pregnancy.

The birth control method will be verified in the medical records prior to study start (contraceptive history) and women of childbearing potential will be asked to verify compliance at each visit up to 1 months after the last investigational product administration.

Patients should be made aware of the availability of emergency “post-coital” contraception if there is an indication for it (eg, missing IUD threads or a late injection). Acceptable emergency methods of contraception to be used should only include those approved by a regulatory agency in the patient’s region.

Women not of childbearing potential are defined as women who are either permanently sterilized (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy), or who are postmenopausal. Women will be considered postmenopausal if they have been amenorrheic for 12 months prior to the planned date of randomization without an alternative medical cause. The following age specific requirements apply:

Women <50 years old would be considered postmenopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatment and follicle stimulating hormone (FSH) levels in the postmenopausal range.

Women ≥50 years old would be considered postmenopausal if they have been amenorrheic for 12 months or more following cessation of all exogenous hormonal treatment

3.2 Exclusion criteria

Patients should not enter the study if any of the following exclusion criteria are fulfilled:

1. Clinically significant lung disease other than asthma (eg, chronic obstructive pulmonary disease, cystic fibrosis, allergic bronchopulmonary aspergillosis, active tuberculosis). Patients with CT or chest X-ray findings indicating bronchiectasis which in the opinion of the Investigator are not clinically significant may be enrolled at the discretion of the Investigator
2. Current tobacco smoking (smoking must have stopped for ≥6 months prior to enrolment) or a history of tobacco smoking for ≥10 pack-years (one pack year = 20 cigarettes smoked per day for 1 year)
3. Receipt of any marketed or investigational biologic within 4 months or 5 half-lives prior to enrolment (whichever is longer) or receipt of any investigational non-biologic agent within 30 days or 5 half-lives prior to enrolment (whichever is longer)
4. Known history of allergy or reaction to any component of the IMP formulation
5. Use of immunosuppressive medication (including but not limited to: methotrexate, troleandomycin, cyclosporine, azathioprine, systemic corticosteroids including regular treatment with OCS or intramuscular long-acting depot corticosteroids, or any experimental anti-inflammatory therapy) within 3 months prior to enrolment (Visit 1)
6. Receipt of immunoglobulin or blood products within 30 days prior to enrolment (Visit 1)
7. Positive HIV, hepatitis B surface antigen or hepatitis C virus antibody serology. Patients with a history of hepatitis B vaccination without a history of hepatitis B are allowed to be enrolled
8. History of autoimmune disease including but not limited to Wegener's granulomatosis, system lupus erythematosus, rheumatoid arthritis, Sjögren's syndrome, multiple sclerosis, autoimmune thrombocytopenia, primary biliary cirrhosis or any other autoimmune disease considered clinically relevant by the investigator
9. Ongoing allergen immunotherapy or plans to begin such therapy during the study period. The last dose of immunotherapy must have been taken at least 6 months prior to inclusion

10. History of chronic alcohol or drug abuse within 12 months of the enrolment visit
11. Perturbation of usual sleep pattern except due to asthma symptoms (eg, night shift workers)
12. Breast feeding, pregnancy or intention to become pregnant during the course of the study
13. DLco ≤ 60% of the lower limit of normal
14. Changes in chest X-ray suggesting clinically significant parenchymal disease other than asthma (further on X-ray in Section 5.2.6)
15. Any clinically significant abnormal findings in physical examination, vital signs, dECG, haematology, clinical chemistry, or urinalysis, which in the opinion of the Investigator, may put the patient at risk because of his/her participation in the study, or may influence the results of the study, or the patient's ability to complete entire duration of the study
16. Receipt of live attenuated vaccines within 30 days prior to the date of randomization and during the study including the follow-up period (Receipt of inactive/killed vaccinations (e.g., inactive influenza) is allowed)
17. Major surgery within 8 weeks prior to the enrolment visit, or planned in-patient surgery or hospitalization during the study period
18. Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site)
19. Previous randomisation in the present study

    In addition, any of the following is regarded as criteria for exclusion from the genetic research:
20. Previous bone marrow transplant
21. Whole blood transfusion within 120 days of the date of genetic sample collection

Procedures for withdrawal of incorrectly enrolled patients see Section 3.4.

3.3 Enrolment and randomization

Investigator(s) should keep a record, the patient screening log, of patients who entered pre-study screening.

The Investigator(s) will:

1. Obtain signed informed consent from the potential patient before any study specific procedures are performed.
2. Assign potential patient a unique enrolment number, beginning with 'E#'.
3. Determine patient eligibility. See Section 3.4.
4. Assign eligible patient unique randomisation code (obtained via the IxRS)

If a patient withdraws from participation in the study, then his/her enrolment/randomisation code cannot be reused. Patients can only be randomized into the study once.

Randomisation codes will be assigned strictly sequentially as patients become eligible for randomisation.

3.4 Procedures for handling incorrectly enrolled or randomized patients

Patients who fail to meet the eligibility criteria should not, under any circumstances, be enrolled or receive study medication. There can be no exceptions to this rule. Patients who are enrolled, but subsequently found not to meet all the eligibility criteria must not be randomized or initiated on treatment, and must be withdrawn from the study.

Where a patient does not meet all the eligibility criteria but is randomized in error, or incorrectly started on treatment, the Investigator should inform the AstraZeneca study physician immediately, and a discussion should occur between the AstraZeneca study physician and the investigator regarding whether to continue or discontinue the patient from treatment. The AstraZeneca study physician must ensure all decisions are appropriately documented.

3.5 Methods for assigning treatment groups

The randomization scheme for this study will be generated by the biostatistics group at AstraZeneca or designee. This will be done using AZRand system. Randomization will be performed through a centralized interactive voice and web response system (IxRS). Patients will be block randomized 1:1 to either placebo or AZD1419, with no stratification.

3.6 Methods for ensuring blinding

The study is double-blind; patients, study site personnel and AZ personnel involved in the evaluation of the data must be kept blinded.

Packaging and labelling of study drug will be performed in a way that ensures blinding.

The following personnel will have access to the randomisation list:

- AstraZeneca Supply Chain
- IxRS vendor
- CRO for drug distribution (Fisher)

Randomization will occur after eligibility has been confirmed based on all study inclusion and exclusion criteria.

If all eligibility criteria are met, blinded personnel will contact the centralized interactive voice and web response system (IxRS) to receive a randomization number and treatment assignment.

3.7 Methods for unblinding

Individual treatment codes, indicating the treatment randomisation for each randomised patient, will be available to the Investigator(s) or pharmacists from the IxRS. Routines for this will be described in the IxRS user manual that will be provided to each centre.

The treatment code should not be broken except in medical emergencies when the appropriate management of the patient requires knowledge of the treatment randomisation. The Investigator documents and reports the action to AstraZeneca, without revealing the treatment given to patient to the AstraZeneca staff.

AstraZeneca retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to an investigational product and that potentially require expedited reporting to regulatory authorities. Treatment codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual patient have been made and documented.

3.8 Restrictions

The following restrictions are applied during the trial or as indicated below:

- Patients should abstain from donating blood and plasma during the study
- Anti-IgE therapy
- Allergen immunotherapy
- Male patients should refrain from fathering a child or donating sperm during the treatment and until 3 weeks following the last dose
- WOCBP using hormonal contraceptives should abstain from use of any medication with CYP3A4 enzyme inducing properties, (eg, fenytoin, fenobarbital, primidon, karbamazepin, oxkarbazepin, rifampicin, rifabutin, ritonavir, topiramat, felbamat and herbal medicines such as St John's Wort) from Visit 1 until 1 months after last dose of IMP.
- ICS, LABA and SABA are the only asthma medications allowed in the study

3.9 Discontinuation of investigational product

Patients may be discontinued from investigational product (IMP) in the following situations:

- Patient decision. The patient is at any time free to discontinue treatment, without prejudice to further treatment
- Adverse Event
- Severe non-compliance with the study protocol
- Risk to the patient as judged by the Investigator and/or AstraZeneca.
- Eligibility criteria not fulfilled (see Section 3.1)
- Patient lost to follow-up
- Pregnancy
- Other (reason to be specified by the Investigator in the electronic Case Report Form)

3.10 Criteria for withdrawal

3.10.1 Screen failures

Screen failures are patients who do not fulfil the eligibility criteria for the study, and therefore must not be randomized. These patients should have the reason for study withdrawal recorded as 'Incorrect Enrolment' (i.e., patient does not meet the required inclusion/exclusion criteria). This reason for study withdrawal is only valid for screen failures (not randomized patients).

3.10.2 Rescreening

Patients who fail screening because of negative reversibility or challenge tests, or patients that are not controlled (i.e. ACQ-5 >0.75) at time for randomization, may be re-screened once. Patients who fail screening because of clinically significant vital signs and/or lab abnormalities without identified reversible etiology may not re-screen. Patients that screen fail for other reasons may potentially re-screen on a case-by-case basis after discussion with AstraZeneca study team physician. Any re-screened patients will keep their original enrolment number but will re-sign their Informed Consent Form (ICF). Re-screening is only allowed once for any patients.

3.10.3 Withdrawal of the informed consent

Patients are free to withdraw from the study at any time (investigational product and assessments), without prejudice to further treatment.

A patient who withdraws consent will always be asked about the reason(s) and the presence of any adverse events (AE). Provided the patient consents to do a follow-up visit, it is recommended that such a visit is scheduled after two weeks. Otherwise the Investigator will follow up AEs outside of the clinical study.

If a patient withdraws from participation in the study, then his/her enrolment/randomisation code cannot be reused. Withdrawn patients will not be replaced.

3.11 Discontinuation of the study

The study may be stopped if, in the judgment of AstraZeneca, trial patients are placed at undue risk because of clinically significant findings that:

- meet individual stopping criteria or are otherwise considered significant
- are assessed as causally related to study drug,
- are not considered to be consistent with continuation of the study

Regardless of the reason for termination, all data available for the patient at the time of discontinuation of follow-up must be recorded in the CRF. All reasons for discontinuation of treatment must be documented.

In terminating the study, the Sponsor will ensure that adequate consideration is given to the protection of the patients' interests.

However, the sponsor reserves the right to terminate the study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- Inability to enroll sufficient patients into study
- Good Clinical Practice (GCP) compliance issues that compromise the validity of the study
- Determination by the DSMB that patient safety is at risk

Guidelines for termination and withdrawal of individual patients are described in Section 3.10.

4. STUDY PLAN AND TIMING OF PROCEDURES

Table 1 Schedule of events

Trial Period		Screening	Dosing period													Observation period						EOT/ED[b]	UNS
Procedure	**Week**	-4	0	1	2	3	4	5	6	7	8	9	10	11	12	13	16	20	28	36	48	52	
	Dose		1	2	3	4	5	6	7	8	9	10	11	12	13								
	Visit	1[a]	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	
Informed consent		X																					
Inclusion/Exclusion criteria		X																					
Demographics/Medical & Surgical history/Prior medications		X																					
Height and weight		X																					
Urine drug screen[c]		X																					
12-Lead ECG		X																				X	
Chest X-ray[d]		X																					
Serum chemistry[e]		X	X[g]				X[g]									X						X	
Hematology[e]		X	X[g]				X[g]									X						X	
Urinalysis[e]		X																					
LH/FSH		X																					
Pregnancy testing[f]		X	X		X		X		X		X		X		X		X						
Serology (HIV, hepatitis B and C tests)		X																					
Contraceptive history and compliance (WoCBP only)		X	X	X	X	X	X	X	X	X	X	X	X	X	X		X						
Serum for Ig, IgG and IgE		X																					
Serum for e.g. ANA, anti-ds DNA, anti-thyroid antibodies		X					X									X						X	
Randomization			X																				
Inhalation/iNeb technique training			X																				
AZD1419/placebo treatment			X	X	X	X	X	X	X	X	X	X	X	X	X									
LABA therapy		X	→	→	→	→	→	→															
ICS therapy		X	→	→	→	→	→	→	→	→	→												

Table 1 Schedule of events

Trial Period		Screening	Dosing period													Observation period						EOT/ED[b]	UNS
Procedure	**Week**	-4	0	1	2	3	4	5	6	7	8	9	10	11	12	13	16	20	28	36	48	52	
	Dose		1	2	3	4	5	6	7	8	9	10	11	12	13								
	Visit	1[a]	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	
SABA rescue therapy (as needed)		X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	
Whole blood for gene expression			X[g]				X[g]			X			X		X[g]	X	X	X	X	X	X	X	
Whole blood for DNA methylation		X													X							X	
Induced sputum (PD)[h]		X	X[n]				X[n]								X[n]			X					
Exploratory biomarkers (including CXCL-10 (plasma)[i]			X[g]				X[g]			X			X		X[g]	X	X	X	X	X	X	X	
Single urine samples for exploratory biomarkers			X[g]				X[g]			X			X		X[g]	X	X	X	X	X	X	X	
Frozen PBMC sample[h]			X[g]				X[g]			X			X		X[g]	X	X	X	X	X	X	X	
Pharmacogenomic sample[j]			X																				
Concomitant medications		X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	
Adverse event assessment			X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	
Serious adverse event assessment		X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	
eDiary and PEF meter distribution, training, and collection		X[l]																				X	
eDiary and PEF recording[k]		X[l]	X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	X	
Compliance check (by site staff) of the patients' eDiary, PEF and FeNO recording				X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	X	
Asthma symptom score and reliever use (eDiary)			X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	X	
Asthma control questionnaire (ACQ-5)[m]			X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	X	
Spirometry (Pre- & post bronchodilator FEV1 at the clinic)		X	X				X			X					X	X	X	X	X	X		X	
Lung diffusion capacity testing (DLco)		X	X				X			X						X		X				X	
Full physical examination		X					X			X						X						X	
Vital signs		X	X				X			X						X						X	
Fractional excretion of nitric oxide (FeNO) measurement at the clinic		X	X				X			X					X	X	X	X	X	X		X	
Niox Vero FeNO@Home (measurements			X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	X	

Table 1 Schedule of events

Trial Period		Screening	Dosing period													Observation period						EOT/ED[b]	UNS
Procedure	**Week**	-4	0	1	2	3	4	5	6	7	8	9	10	11	12	13	16	20	28	36	48	52	
	Dose		1	2	3	4	5	6	7	8	9	10	11	12	13								
	Visit	1[a]	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	
done by the patient every other day)																							

EOT = end of trial; UNS = unscheduled visit. For any efficacy/safety or exploratory assessments as indicated.

a. Can be done on several/different days within the up to 4 weeks screening period
b. Patients who discontinue trial participation prior to completion of all scheduled visits will be required to complete an Early Discontinuation (ED) visit.
c. According to local practice.
d. At screening and on other visits if indicated, see Section 5.2.6
e. For details see Table 3.
f. Urine pregnancy testing will be conducted in WOCBP. The test must be negative prior to trial treatment. Dipstick may be used.
g. Prior to and 24 h after dose.
h. At selected sites.
i. To be stored frozen for future testing.
j. DNA for pharmacogenomic analysis will only be collected from those patients who consent.
k. Morning and evening recording.
l. Training and distribution of the eDiary and PEF devices will be done on a V1b scheduled approximately one week prior to randomization to ensure sufficient number of baseline recordings (at least 5 days, twice daily).
m. Recorded weekly in the eDiary.
n. Only taken at 24h after dose

4.1 Enrolment/screening period

At screening, Visit 1, consenting patients are assessed to ensure that they meet eligibility criteria. The screening period will be approximately 2-4 weeks. The screening procedures will be performed according to the Schedule of Events, Table 1, and can be performed over several days if needed.

All eligible patients will be taking ICS and LABA during the screening period, with SABA rescue therapy as needed. Patients will be prescribed their usual controller medication (i.e. ICS + LABA) in separate inhalers, in addition to a rescue medication inhaler (SABA). To facilitate the tapering down during the treatment period, the ICS will be prescribed in a dose that will allow stepwise reduction using the same inhaler.

If the patient does not have historical positive post-bronchodilator reversibility or challenge test (methacholine, histamine or mannitol) information fulfilling that inclusion criterion, a reversibility or challenge test can be performed at Visit 1. In case the patient does not meet the eligibility criterion at this occasion, e.g. suspected to be due to bronchodilator treatment taken prior to the visit, a second re-test may be performed (not earlier than the next calendar day) as part of Visit 1. To increase the chances for a positive reversibility or challenge test at the re-test, patients should withhold their usual bronchodilator medications on the morning of the test, e.g. SABA for at least 6 hours and LABA for at least 12 hours before the test.

4.2 Treatment period

When patients are comfortable using the prescribed inhalers and have gone through the inclusion/screening assessments the patients may be randomized. An ACQ-5 score of $\leq$0.75 is required for randomization. A total of 70 patients are planned to receive 13 weekly doses of IMP (1:1) during the conduct of the study. Study drug will be administered as a nebulized inhalation (using the I-neb® device (Philips Respironics)) at the clinic. The patients will be observed at the clinic for at least 6 hours after the first dose and for at least 2 hours after the remainder of doses.

Patients will receive placebo or AZD1419 at 4 mg/week for 4 weeks, after which each patient's dose will be maintained or adjusted up or down based on the individual patient's frequency and severity of flu-like AEs (defined in Section 6.1.1) appearing within 24 hours after dosing, see Figure 2. All decisions are subject to investigator judgment. If an investigator believes that a patient is not tolerating a dose for any reason, the next dose can be reduced independent of the rules described. Further instructions on Dose Adaptation are included in Section 4.2.2.

During the dosing period, patients will have ICS + LABA controller medications tapered down and discontinued. LABA will be stopped on the evening prior to receiving dose 7 (Visit 8), and ICS will then be gradually tapered down and discontinued during the next 3 weeks. The first week after LABA discontinuation, the patients will receive their usual full dose of ICS. The week thereafter the total daily ICS dose will be reduced by 50% and the week thereafter the total daily dose will be reduced to 25% of the patient's usual full dose of ICS. ICS is discontinued in the evening prior to receiving IMP dose 10 (Visit 11). The regimen for tapering down the ICS according to the above guidelines will be decided by the Investigator for the individual patient, i.e. as appropriate the Investigator will adjust the ICS dose down and

potentially change dosing regimen from BID to QD to achieve half and then a quarter of the daily dose of ICS. Patients will be able to use SABA reliever therapy as needed at all times during the study. Reliever use will be monitored on a daily basis in the ePRO device, as a component of asthma control throughout the trial.

For details of all assessments done during the treatment period refer to Section 5 and for timing of the procedures refer to Table 1.

4.2.1 Sentinel Dosing Procedure

The first 4 patients randomized in the study at one or two selected sites constitute the sentinel group and will be evaluated by a DSMB for safety before enrolment of additional patients can commence. The sentinel patients will be randomly assigned (1:1) to receive AZD1419 or placebo (4mg) once weekly. After the first 2 doses (i.e. Visits 2 and 3) the 4 sentinel patients will be observed for 24 hours at the clinic for safety (including allergic reactions or bronchospasm). In addition to the assessments outlined in Table 1, assessment of AEs, vital signs and FEV1 measurements will be carried out at the following time points after dose: 0.5, 1, 2, 6, 12, 24 hours, and in addition as needed as judged by the investigator. These patients will then continue in the study in accordance with the study protocol.

When the last of the 4 sentinel patients has received 4 doses, the DSMB will review safety data and approve enrolment of additional patients into the study. The DSMB may recommend further measures to ensure patient safety when administering first doses of IMP to additional patients.

4.2.2 Dose Adaptation Procedure

Given the well-known potential for flu-like symptoms from TLR9 agonism, dosing for each patient will be adapted based on the individual's flu-like AEs. The flu-like symptoms usually respond well to paracetamol (and otherwise resolve spontaneously within 24-48 hours following dosing), and the dose adaptation should be based on the assessment of flu-like symptoms after intake of paracetamol.

After the first 4 doses an assessment of the individual patient will be performed according to experiences of flu-like AEs (arthralgia, chills, pyrexia, myalgia) within 24h of inhalation, with adaptation of AZD1419 accordingly:

If no or only mild flu-like AEs occur after the first 4 doses, then the subsequent doses will be stepped up to 8 mg.

If any severe flu-like AEs occur after any of the first 4 doses, then the subsequent doses will be stepped down to 1 mg.

Otherwise, the subsequent doses will be maintained at 4 mg.

All patients will continue dosing with placebo or AZD1419 at the adjusted levels until they have received a total of 13 inhaled weekly doses.

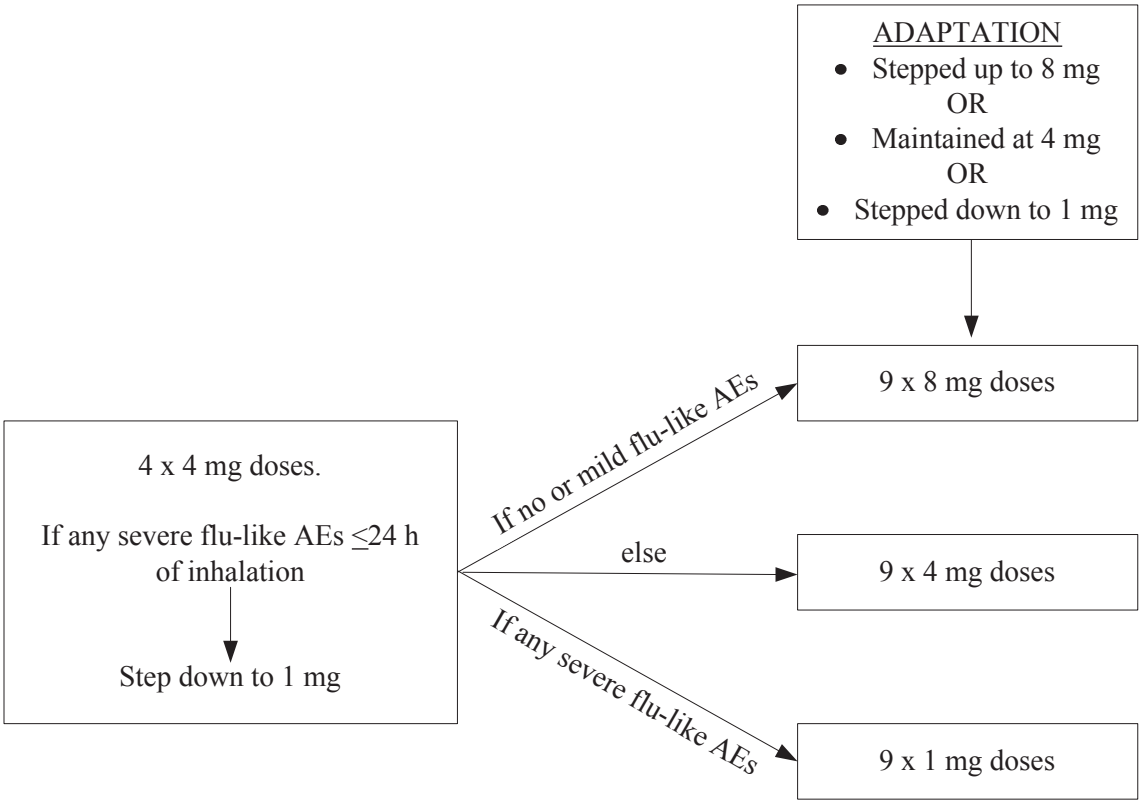
All dosing decisions are subject to investigator judgment. If an investigator believes that a patient is not tolerating a dose for any reason, the next dose can be reduced independent of the rules described above.

Dosing will be stopped in patients who do not tolerate a 1mg dose and they will be followed for an additional 4 weeks for safety before they discontinue the study.

Since e.g. side effects from influenza vaccination could potentially impact the interpretation of the flu-like symptoms after the dosing of study drug, it is suggested that such vaccination should be performed e.g. 2 days after a dose of IMP.

For definition of severity of AE (including flu-like symptoms), see Section 6.3.3.

Figure 2 Dosing



4.3 Follow-up period/Observation period

After the treatment period patients are followed until they experience loss of asthma control or for the whole period of up to 52 weeks (Visit 21). For details of the study assessments during the observation period refer to the Schedule of events, Table 1.

Patients will be monitored with regards to safety, tolerability and efficacy aspects during the whole study period. In addition to assessments performed at the clinical visits, an ePRO device coupled with a home spirometer will on a daily basis capture asthma symptoms, reliever use and lung function (PEF) and a FeNO meter measurements will be performed every second day.

At any time during the tapering period or after, when patients experience loss of asthma control as defined below, they will resume their usual ICS+LABA asthma controller therapy and will be considered to have reached the primary endpoint. They will then stop IMP administration and will be followed for an additional 4 weeks in the study.

For the purpose of the study Loss of asthma control is defined as any of the following:

a) An increase of ACQ-5 to 1.5 or more

b) A reduction of 30% or more in morning peak expiratory flow (PEF) from baseline on 2 consecutive days

c) At least six additional reliever inhalations of SABA in a 24-hour period relative to baseline on 2 consecutive days

d) An exacerbation requiring systemic corticosteroids

Upon a), b) or c) being fulfilled, an automatic asthma action plan will be triggered in the ePRO device prompting the patient to resume their usual ICS + LABA medication. In addition an alert will be sent to the site/Investigator. Upon receiving such an alert the Investigator should contact the patient and arrange a visit to the clinic for evaluation, see Section 5.1.3.1. Blood sampling for biomarkers should be part of this evaluation.

5. STUDY ASSESSMENTS

The Rave Web Based Data Capture (WBDC) system will be used for data collection and query handling. The investigator will ensure that data are recorded in the eCRFs as specified in the study protocol and in accordance with the instructions provided.

The investigator ensures the accuracy, completeness, and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement. The investigator will sign the completed eCRFs. A copy of the completed eCRFs will be archived at the study site.

5.1 Efficacy assessments

5.1.1 Asthma Control Questionnaire

The ACQ was developed by Professor Elizabeth Juniper (Juniper et al 1999a). The ACQ includes 7 items covering all the criteria deemed necessary by international guidelines committees for determining the adequacy of asthma control (symptoms, FEV1, and SABA used as reliever medication). The ACQ has undergone rigorous validation and has been shown to have strong evaluative and discriminative measurement properties (Juniper et al 1999a). In this study, the 5-item version, the ACQ-5, will be used, in which the FEV1 and SABA question is excluded since it will be collected outside the questionnaire. It has been shown that exclusion of these questions does not alter the validity and the measurement properties of the questionnaire (Juniper et al 2001). Linguistically validated translations of the ACQ-5 into the local languages will be used. The original North American English version is included in Appendix E.

The ACQ-5 will be self-administered within the ePRO once weekly during the study. The questions take approximately 2 to 3 minutes to complete.

5.1.2 The Asthma Daily Diary

The Asthma Daily Diary will be completed in the ePRO device each morning and evening and will include the following daily recordings: morning and evening home peak expiratory flow data (obtained from the home peak flow meter), asthma symptoms, inhalations of reliever medication, nights with awakenings due to asthma symptoms, asthma maintenance medication compliance, see Appendix F.

Home peak expiratory flow measurement
An electronic, hand-held home spirometer connected to an ePRO device will be dispensed to the patient prior to randomization to monitor their PEF at home. The PEF should be monitored morning and evening every day, and the measurements should be performed by the patient before intake of asthma maintenance treatment upon rising in the morning, and at bedtime in the evening. Patients should perform 3 successive peak flow manoeuvres while sitting or standing, but in the same position at every testing; the highest of the 3 values will be captured for the morning and for the evening manoeuvres. Note that FeNO measurements should be performed before the PEF measurements, see Section 5.1.4. Investigator/authorized delegate will check patient's adherence to correct use of the hand-held spirometer at each visit.

Asthma symptoms
Asthma symptoms during night time and daytime will be recorded by the patient twice daily in the Asthma Daily Diary, according to the following scoring system:

0 = no asthma symptoms
1 = you are aware of your asthma symptoms but you can easily tolerate the symptoms
2 = your asthma is causing you enough discomfort to cause problems with normal activities (or with sleep)
3 = you are unable to do your normal activities (or to sleep) because of your asthma

Daytime is defined as the time period between the morning lung function assessment (upon rising in the morning) and the evening lung function assessment. Night time is defined as the time period between the evening lung function assessment (at bedtime) and the morning lung function assessment.

Reliever medication
The number of reliever medication inhalations taken will be recorded by the patient in the Asthma Daily Diary twice daily. The number taken between the morning and evening lung function assessments will be recorded in the evening. The number of inhalations taken between the evening and morning lung function assessments will be recorded in the morning. Reliever medication usage is captured in the daily diary as the number of inhaler puffs.

Night-time awakenings
Night-time awakenings due to asthma symptoms will be recorded by the patient in the Asthma Daily Diary each morning by answering the question whether he/she woke up during the night due to asthma symptoms by a "yes" or "no" response.

Asthma maintenance medication

Asthma maintenance medication administration will be recorded in the Asthma Daily Diary in the morning and evening as "yes" or "no" response.

5.1.3 Composite endpoint for exacerbations (CompEx)

CompEx will be assessed as an exploratory variable. It consists of a mixture of severe asthma exacerbation and diary driven events. Several different definitions based on selection of ingoing variables exists, thus several variants of CompEx will be explored. The main outcome will be based on a definition including morning and evening PEF and day-time and night-time reliever medication. The Statistical Analysis Plan (SAP) will contain the details concerning this surrogate composite endpoint.

Exacerbations are defined as follows in this study:

Table 2 Exacerbation categories

Severe exacerbation	A worsening in asthma symptoms and: - Use of systemic corticosteroids for at least three days and/or - An unscheduled visit or emergency room visit due to asthma symptoms that requires at least one dose of systemic corticosteroids and/or - An in-patient hospitalization due to asthma requiring at least one dose of systemic corticosteroids
Moderate exacerbation	A temporary increase in maintenance therapy in order to prevent a severe event supported by a sustained (≥2d) worsening in at least one key control metric ie asthma score, reliever medication use, night time awakening or morning PEF
Duration of a severe exacerbation	The start of an exacerbation is defined as the start date of systemic corticosteroids or emergency room visit or hospital admission, whichever occurs first, and the end date is defined as the last day of systemic corticosteroids or hospital discharge, whichever occurs last.
Duration of a moderate exacerbation	For moderate exacerbations the start date is defined as the first day of increase in temporary maintenance therapy and the end date is defined as the last day of this treatment.

5.1.3.1 Evaluation of Loss of asthma control

Upon Loss of asthma control (as previously defined) the patient should be assessed by the Investigator and data recorded in the exacerbation module in the eCRF. Information regarding the circumstances for the loss of control, e.g. if there were any specific triggers, should be noted. Sampling for biomarkers should also be performed using the Loss of control Lab kit. Worsening of asthma symptoms leading to treatment with systemic corticosteroids, hospitalisation, or emergency room visits from Visit 1 until the End of Treatment Visit should

also be recorded in the exacerbation module in the eCRF. A copy of the medical record should be obtained for exacerbation evaluated and treated at non-study sites (e.g. by the primary care health care provider or at an ER/hospital) and details entered into the exacerbation eCRF module in a timely fashion. Changes in concomitant medication due to exacerbation must be recorded in the appropriate module of the eCRF.

5.1.4 Fractional Exhaled Nitric Oxide (FeNO)

The American Thoracic Society and NICE recommend the use of FeNO in the diagnosis of eosinophilic airway inflammation (Dweik et al 2011). Specific devices used for measuring the amount of FeNO in the breath of a patient will be provided by the sponsor. This sample is collected by having the patient breathe into the mouthpiece of the device that performs the measurement. At the clinic FeNO must be performed prior to spirometry assessment.

FeNO measurements will be done both at the clinic (for time points see Table 1) and by the patients at home using the NIOX Vero® device every second day. The home based FeNO measurement should be performed in the morning before morning PEF measurement and before morning maintenance treatment inhalation. Detailed instructions for use will be provided to the patients at Visit 2.

5.1.5 Spirometry

Spirometry, pre- and post bronchodilator, will be performed at the site at timepoints indicated in the Schedule of Events (Table 1) according to the joint ATS-ERS Task Force 2005 guidelines (Miller et al 2005). Results will be entered in the eCRF.

Spirometry will be performed to monitor different compartments of the lung and identify post-treatment trends in airway function. Vital Capacity (VC), FEV1, Forced Expiratory Flow 25% to 75% (FEF25-75), and Inspiratory Capacity (IC) will be used as composite measures of airways and parenchyma. Changes in airway function with increased hyperreactivity are expected to give a signal in the FEV and IC while changes in lung volume mainly will be detected in the VC.

5.2 Safety assessments

5.2.1 Laboratory safety assessments

Blood and urine samples for determination of clinical chemistry, haematology, and urinalysis will be taken at the times indicated in Table 1.

Additional safety samples may be collected if clinically indicated at the discretion of the Investigator. The date, time of collection and results (values, units and reference ranges) will be recorded on the appropriate eCRF.

Additional details for specific tests are provided in the Laboratory Manual.

The following laboratory variables will be measured:

Table 3 Laboratory Safety Variables

Haematology/Haemostasis (whole blood)	**Clinical Chemistry (serum or plasma)**
B-Haemoglobin (Hb)	S/P-Creatinine
B-Leukocyte count	S/P-Bilirubin, total
B-Leukocyte differential count (absolute count)	S/P-Alkaline phosphatise (ALP)
B-Platelet count	S/P-Aspartate transaminase (AST)
	S/P-Alanine transaminase (ALT)
	S/P-Albumin
	S/P-Potassium
	S/P-Calcium, total
	S/P-Sodium
	S/P-Creatine kinase (CK)
	S/P-CRP
	S/P-TSH
Viral Serology	**Urinalysis (dipstick)**
Hepatitis B surface antigen (HbsAg)	U-Hb/Erythrocytes/Blood[a]
Hepatitis C virus antibody	U-Protein/Albumin
HIV I and II	U-Glucose
	Urine pregnancy test
Endocrinology (female patients only)	
Follicle-stimulating hormone (FSH) [a]	
Luteinising hormone (LH)[a]	

a. FSH and LH for women under the age of 50 considered to be post-menopausal to determine that the hormones are in the post-menopausal range and that the women thereby not need any contraceptives

The Investigator should make an assessment of the available results with regard to clinically relevant abnormalities. The laboratory results should be signed and dated and retained at centre as source data for laboratory variables. For information on how AEs based on laboratory tests should be recorded and reported, see Section 6.3.

NB. In case a patient shows an AST **or** ALT ≥3xULN **or** total bilirubin ≥2xULN please refer to Appendix X ‘Actions required in cases of combined increase of Aminotransferase and Total Bilirubin - Hy’s Law’, for further instructions.

5.2.1.1 Volume of Blood.

The total volume of blood that will be drawn from each patient in this study is specified in Table 4.

Table 4 Volume of blood to be drawn from each patient

Assessment	No of samples[b]	Sample volume (mL)	Total volume (mL)[b]
Safety – Clinical Chemistry	8	5	40
Safety – Haematology	8	2	16
Serology (HIV, Hepatitis B & C)	1	4	4
Serum for Ig, IgG and IgE	1	3.5	3.5
Serum for e.g. ANA, anti-ds DNA, anti-thyroid antibodies	4	10	40
Endocrinology (LH, FSH)[a]	1	2.5	2.5
Exploratory Biomarkers including e g CXCL-10 biomarker (plasma)	15	10	150
Whole blood for gene expression	15	2.5	37.5
Whole blood for DNA methylation	4	8.5	34
Frozen PBMC sample	15	10	150
Pharmacogenetics	1	10	10
Total	73		487.5

a only females
b The number of samples may be changed due to additional sampling at unscheduled visits and the blood volume required may be altered to fit the assay requirements. The total volume of blood drawn from each patient will however not exceed 450 mL during a 3 month period.

5.2.2 Physical examination

A complete physical examination will be performed as indicated in Table 1, and include an assessment of the following: general appearance, respiratory, cardiovascular, abdomen skin, head and neck (including ears, eyes, nose and throat), lymph nodes, thyroid, abdomen, musculo-skeletal (including spine and extremities) and neurological systems.

The outcome of the examination is to be recorded as normal/abnormal in the eCRF, with any abnormalities specified. Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline measurement will be reported as an AE (see Section 6.1)

Height and weight are collected only at screening.

5.2.3 ECG

5.2.3.1 Resting 12-lead ECG

12-lead pECG recordings will be collected at screening and at the safety follow-up visit at the end of the trial. The investigator will make an overall evaluation of the pECG as normal or abnormal. If abnormal, it will be decided whether or not the abnormality is clinically significant or not clinically significant and the reason for the abnormality will be recorded on the eCRF.

Abnormal values shall not be recorded as AEs unless deemed clinically significant. The printout of the ECG is to be signed, dated and filed in the ISF along with a signed and dated copy (if the printouts are not on archive-quality paper).

5.2.4 Vital signs

Vital signs will include pulse, pulse oximetry, and systolic and diastolic blood pressure. Vital signs will be obtained at timepoints indicated in Table 1 (and ad-hoc as medically indicated).

5.2.4.1 Pulse, pulse oximetry and blood pressure

Pulse (beats/minute, radial artery, during 30 seconds) and pulse oximetry will be measured before blood pressure and in a lying position after 10 minutes of rest. Thereafter, systolic and diastolic blood pressure (mmHg, the cuff method on the arm opposite to the one used for blood sampling) will be measured using the same cuff, appropriate for arm circumference, and in the same position, throughout the study. During the treatment period it should be done 15 minutes post-dose. Patients should be in the same position for the vital signs measurements throughout the study.

5.2.5 Diffusing Capacity of the Lung for Carbon Monoxide (DLco).

DLco will be determined at visits as indicated in Table 1. DLco, with other measures of spirometry, will be used to assess the alveolar compartment, and is expected to be a sensitive technique for detection of alveolar inflammation. Measurement of DLco will be performed by single-breath carbon monoxide (CO) uptake according to the joint ATS-ERS Task Force 2005 guidelines (Macintyre et al 2005).

5.2.6 Chest X-ray of the Lung

Chest X-ray will be performed at screening. It needs not be repeated for patients that have performed a chest X-ray during the last 12 months and as long as it is released for use in the CRF. Chest X-ray can be repeated, if indicated, during the study e.g. upon clinically relevant adverse events.

5.3 Other assessments

5.3.1 Patient reported outcomes

Patients will be supplied with an ePRO device combined with a hand-held home spirometer, and a separate FeNO measurement device during the screening period prior to or at Visit 2.

All patients will be carefully instructed and trained in how to complete and how to handle the devices. Patients should be informed that the recordings made electronically cannot be retrospectively or prospectively entered and must be completed within a defined time window. The patients must understand and be willing to use the devices and be instructed in how and where to request help if problems occur.

At home, patients will complete the eDiary each day and the FeNO every other day from the morning after Visit 2 throughout the study, as described in Sections 5.1.1 to 5.1.4.

5.3.2 Sputum induction

Sputum induction should be performed in a subgroup of patients (approximately 20% of the patients) at selected sites according to local procedures. An FEV1 measurement will be performed after the each sputum induction cycle for safety reasons.

The method for processing of induced sputum will be described in the Laboratory Manual. The sputum collection is also summarized in Section 5.5.1.

5.4 Pharmacokinetics

AZD1419 was not detected in any plasma sample from patients in the highest dose cohort (23.1 mg) in the previous trial and is therefore expected to be below the limit of quantification in the present trial where the highest dose given will be 8 mg. Pharmacokinetics sampling will not be performed.

5.5 Pharmacodynamics

5.5.1 Collection of samples

The pharmacodynamics (PD) of inhaled AZD1419 will be assessed by effects on TLR9-mediated interferon (IFN), Th2, and airway-remodelling associated genes and gene products. Additionally, changes in peripheral blood mononuclear cells will also be assessed.

These assessments will be performed in serum, whole blood, induced sputum, urine and peripheral blood mononuclear cells:

- Serum collections should be taken at study time points indicated in the Schedule of Events, Table 1 and will be assayed for CXCL-10, and multiplex other biomarkers.
- Peripheral whole blood will be collected by standard venipuncture into appropriate collection tubes for subsequent RNA isolation gene expression profiling and DNA methylation analysis.
- Sputum will be induced by inhalation of nebulized hypertonic saline according to local procedures. On dosing days, at visits indicated in Table 1, samples will be collected 24 hours after dosing. Sputum will be analyzed for cytology, RNA, and protein. Sputum cytology preparation will be performed according to local laboratory procedures.

Notes: Sputum will be analyzed only in patients able to produce a specimen. Salbutamol may be used to prevent bronchospasm, which may ensue because of sputum collection.

- Urine will be collected and stored for future exploratory research.
- PBMCs will be collected (at selected sites) and assessed for immune function.

Additional details regarding specimen preparation, handling, and analysis will be provided in the Laboratory Manual.

5.5.2 Storage, re-use and destruction of pharmacodynamic samples

Samples will be stored for a maximum of 15 years from the date of the Last Patient's Last Visit, after which they will be destroyed. The results of any investigation will be reported either in the Clinical Study Report itself or as an addendum, or separately in a scientific report or publication.

5.6 Pharmacogenetics

5.6.1 Collection of pharmacogenetic samples

The patient's participation in the pharmacogenetic (PGx) research components of the study is optional. The DNA sample will only be collected from those patients who consent.

The blood sample for genetic research will be obtained from the patients after randomisation. Although genotype is a stable parameter, early sample collection is preferred to avoid introducing bias through excluding patients who may withdraw due to an adverse event (AE), such patients would be important to include in any genetic analysis. If for any reason the sample is not drawn at Visit 2 it may be taken at any visit until the last study visit. Only one sample should be collected per patient for genetics during the study.

Samples will be collected, labelled, stored and shipped as detailed in the Laboratory Manual.

Peripheral whole blood will be collected by standard venipuncture for investigating the genes and genetic variation that may influence response to AZD1419.

Additional details regarding sample preparation, handling, and analysis will be provided in the Laboratory Manual.

5.6.2 Storage, re-use and destruction of pharmacogenetic samples

The processes adopted for the coding and storage of samples for genetic analysis are important to maintain patient confidentiality. Samples will be stored for a maximum of 15 years from the date of the Last Patient's Last Visit, after which they will be destroyed. DNA is a finite resource that may be used up during analyses. The results of any further analyses will be reported either in the Clinical Study Report itself or as an addendum, or separately in a scientific report or publication.

For all samples irrespective of the type of coding used the DNA will be extracted from the blood sample. The DNA sample will be assigned a unique number replacing the information on the sample tube. Thereafter, the DNA sample will be identifiable by the unique DNA number only. The DNA number is used to identify the sample and corresponding data at the AstraZeneca genetics laboratories, or at the designated contract laboratory. No personal details identifying the individual will be available to any person (AstraZeneca employee or contract laboratory staff working with the DNA.)

The samples and data for genetic analysis in this study will be single coded. The link between the patient enrolment/randomisation code and the DNA number will be maintained and stored in a secure environment, with restricted access within the Clinical Genotyping Group Laboratory Information Management System (LIMS) at AstraZeneca. The link will be used to

identify the relevant DNA samples for analysis, facilitate correlation of genotypic results with clinical data, allow regulatory audit and to trace samples for destruction in the case of withdrawal of consent when the patient has requested disposal/destruction of collected samples not yet analysed.

5.7 Biomarker analysis

The patient's consent to the use of donated biological samples is mandatory.

Biological samples will be collected and may be analysed for exploratory biomarkers to assess correlations with disease activity, effects of study drug, clinical outcomes and toxicity.

Pharmacodynamics (PD) data will use descriptive statistics to assess and compare the up and downregulation of TLR9-mediated interferon (IFN), Th2, and airway-remodeling gene and gene products or changes in PBMC functional assessments. PD parameters will be analyzed using the PD population.

5.7.1 Storage, re-use and destruction of biological samples

Samples will be stored for a maximum of 15 years from the date of the Last Patient's Last Visit, after which they will be destroyed. The results of this biomarker research will be reported either in the Clinical Study Report itself or as an addendum, or separately in a scientific report or publication. The results of this biomarker research may be pooled with biomarker data from other studies with the study drug to generate hypotheses to be tested in future research.

5.7.2 Labelling and shipment of biological samples

The Principal Investigator ensures that samples are labelled and shipped in accordance with the Laboratory Manual.

Any samples identified as Infectious Category A materials are not shipped and no further samples will be taken from the patient unless agreed with AstraZeneca and appropriate labelling, shipment and containment provisions are approved.

5.7.3 Chain of custody of biological samples

A full chain of custody is maintained for all samples throughout their lifecycle.

The Principal Investigator at each centre keeps full traceability of collected biological samples from the patients while in storage at the centre until shipment or disposal (where appropriate) and keeps documentation of receipt of arrival.

The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment and keeps documentation of receipt of arrival.

AstraZeneca keeps oversight of the entire life cycle through internal procedures, monitoring of study sites and auditing of external laboratory providers.

Samples retained for further use are registered in the AstraZeneca biobank during the entire life cycle.

5.7.4 Withdrawal of Informed Consent for donated biological samples

If a patient withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed, and the action documented. If samples are already analysed, AstraZeneca is not obliged to destroy the results of this research.

As collection of the biological samples is an integral part of the study, then the patient is withdrawn from further study participation.

The Principal Investigator:

- Ensures patients' withdrawal of informed consent to the use of donated samples is notified immediately to AstraZeneca
- Ensures that biological samples from that patient, if stored at the study site, are immediately identified, disposed of /destroyed, and the action documented
- Ensures the laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed, the action documented and the signed document returned to the study site
- Ensures that the patient and AstraZeneca are informed about the sample disposal.

AstraZeneca ensures the central laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed and the action documented and returned to the study site.

6. SAFETY REPORTING AND MEDICAL MANAGEMENT

The Principal Investigator is responsible for ensuring that all staff involved in the study are familiar with the content of this section.

Patient safety will be the primary responsibility of the investigator. The investigator, in consultation with the sponsor's Medical Monitor, may withdraw further study treatment for safety reasons in an individual patient who experiences any of the following:

- Pregnancy (described in Section 6.6)
- Development of an exclusionary medical condition (described in Section 3.2)
- An AE or SAE that, in the judgment of the investigator, requires treatment withdrawal due to its nature, severity, or required treatment, regardless of the causal relationship to treatment

- A clinically significant change in laboratory results, vital signs, or general condition that, in the judgment of the investigator, requires treatment withdrawal
- Worsening of asthma signs or symptoms that, in the judgment of the investigator, place the patient at increased risk, such as:
  - Decrease in FEV1 of more than 20 percent compared to baseline FEV1 that is persisting, not effectively treatable with SABA, and clinically significant as judged by the investigator.
  - Decrease in oxygen saturation to less than 85 percent (on room air) that is persisting and requires treatment with supplemental oxygen
  - Emergency room treatment, hospitalization, or intubation for asthma

Treatment withdrawal may also occur due to voluntary withdrawal of consent by a patient.

The investigator or designee must notify the sponsor of all treatment withdrawals in a timely manner, before the patient's next scheduled dose. The reason for any treatment withdrawal will be recorded in the appropriate case report form (CRF).

Patients, who undergo treatment withdrawal for any reason, including withdrawal of consent, will be encouraged to complete safety follow-up assessments (ref EOT/ED visit in Table 1).

6.1 Definition of adverse events

An adverse event is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (e.g., nausea, chest pain), signs (e.g., tachycardia, enlarged liver) or the abnormal results of an investigation (e.g., laboratory findings, electrocardiogram). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

6.1.1 Definition of Flu-like Symptoms

For the dose adaptation in the present study flu-like symptoms are defined as events of arthralgia, chills, pyrexia (fever), or myalgia, any of which occur within 24 hours after treatment with IP. The severity of these flu-like symptoms are defined as mild, moderate and severe in accordance with the general AE definitions described below (Section 6.3.3), and should for the purpose of dose adaptation be graded with regards to severity after intake of e.g. paracetamol. The individual symptoms should be reported, i.e. not reported as the preferred term "Influenza-like illness".

6.2 Definitions of serious adverse event

A serious adverse event is an AE occurring during any study phase (i.e., run-in, treatment, follow-up), that fulfils one or more of the following criteria:

- Results in death

- Is immediately life-threatening
- Requires in-patient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardise the patient or may require medical intervention to prevent one of the outcomes listed above.

For further guidance on the definition of a SAE, see Appendix A.

6.3 Recording of adverse events

6.3.1 Time period for collection of adverse events

Adverse Events will be collected from *randomization,* throughout the treatment period and including the follow-up period.

SAEs will be recorded from the time of informed consent.

6.3.2 Follow-up of unresolved adverse events

Any AEs that are unresolved at the patient's last AE assessment or other assessment/visit as appropriate in the study are followed up by the Investigator for as long as medically indicated, but without further recording in the CRF. AstraZeneca retains the right to request additional information for any patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

6.3.3 Variables

The following variables will be collect for each AE;

- AE (verbatim)
- The date and time when the AE started and stopped
- Maximum intensity of the adverse event

  Intensity rating scale:

  1 mild (awareness of sign or symptom, but easily tolerated)

  2 moderate (discomfort sufficient to cause interference with normal activities)

  3 severe (incapacitating, with inability to perform normal activities)
- Whether the AE is serious or not
- Investigator causality rating against the Investigational Product (yes or no)
- Action taken with regard to investigational product
- Outcome.

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for serious AE
- Date Investigator became aware of serious AE
- AE is serious due to
- Date of hospitalization
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to Study procedure(s)
- Description of AE. It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 6.2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE unless it meets the criteria shown in Section 6.2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE when it satisfies the criteria shown in Section 6.2.

6.3.4 Causality collection

The Investigator will assess causal relationship between Investigational Product and each Adverse Event, and answer ‘yes’ or ‘no’ to the question ‘Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?’

For SAEs causal relationship will also be assessed for other medication and study procedures. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as ‘yes’.

A guide to the interpretation of the causality question is found in Appendix A

6.3.5 Adverse events based on signs and symptoms

All AEs spontaneously reported by the patient or reported in response to the open question from the study personnel: *‘Have you had any health problems since the previous visit/you were last asked?’*, or revealed by observation will be collected and recorded in the CRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

Adverse events will be reviewed with the patient before dosing at each visit.

- Adverse Events (AEs)

Adverse events, as defined in Section 6.1, will be evaluated from Visit 1 through the duration of trial participation.

Flu-like symptoms (defined in Section 6.1.1) are important in dose adaptation for each patient, and therefore will be tracked but not solicited by investigators and site staff.

Exacerbations of asthma symptoms, including need for SABA medication, and worsening of asthma control requiring the need for controlling medications (ICS/LABA) are important for the primary endpoint of the trial and should be closely monitored.

- Serious Adverse Events

Serious Adverse Events (SAEs), as defined in Section 6.2, will be evaluated from the time the consent is signed through the duration of trial participation. Any SAE occurring from the time the consent is signed through completion, whether or not related to the investigational medicinal product, must be reported to AstraZeneca or its designee within 24 hours of the knowledge of the event.

The investigator will assess all SAEs occurring after consent and prior to enrolment for their potential effect on patients' continued eligibility to enrol.

6.3.6 Adverse events based on examinations and tests

The results from protocol mandated laboratory tests and vital signs will be summarised in the clinical study report. Deterioration as compared to baseline in protocol-mandated laboratory values and vital signs should therefore only be reported as AEs if they fulfil any of the SAE criteria or are the reason for discontinuation of treatment with the investigational product.

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting Investigator uses the clinical, rather than the laboratory term (e.g., anaemia versus low haemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE.

6.3.7 Hy's Law

Cases where a patient shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT $\geq$ 3xULN together with total bilirubin $\geq$ 2xULN may need to be reported as SAEs. Please refer to Appendix D for further instruction on cases of increases in liver biochemistry and evaluation of Hy's Law.

6.4 Reporting of serious adverse events

All SAEs have to be reported, whether or not considered causally related to the investigational product, or to the study procedure(s). All SAEs will be recorded in the CRF.

If any SAE occurs in the course of the study, then Investigators or other site personnel inform the appropriate AstraZeneca representatives within one day i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within 1 calendar day** of initial receipt for fatal and life threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening adverse events where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform AstraZeneca representatives of any follow-up information on a previously reported SAE within one calendar day i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

Once the Investigators or other site personnel indicate an AE is serious in the WBDC system, an automated email alert is sent to the designated AstraZeneca representative.

If the WBDC system is not available, then the Investigator or other study site personnel reports a SAE to the appropriate AstraZeneca representative by telephone.

The AstraZeneca representative will advise the Investigator/study site personnel how to proceed.

The reference document for definition of expectedness/listedness is the IB for the AstraZeneca study drug and the EU Summary of Product Characteristics (SPC) for the maintenance treatment products.

6.5 Overdose

The IMP in this study is administered at the study site under oversight by the site staff. Hence the risk for an overdose is considered low. There is no experience of overdose and no antidote to AZD1419. In cases of known or suspected overdose, symptomatic treatment and monitoring of vital functions and e.g. haematology parameters should be performed according to routine clinical practice based on the judgment of the investigator. In addition, should an overdose occur the following procedures should be followed:

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the CRF and on the Overdose CRF module.
- An overdose without associated symptoms is only reported on the Overdose CRF module.

If an overdose on an AstraZeneca study drug occurs in the course of the study, then the Investigator or other site personnel inform appropriate AstraZeneca representatives immediately, or **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site.

For overdoses associated with a SAE, the standard reporting timelines apply, see Section 6.4. For other overdoses, reporting must occur within 30 days.

6.6 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca.

6.6.1 Maternal exposure

If a patient becomes pregnant during the course of the study investigational product should be discontinued immediately.

Pregnancy itself is not regarded as an adverse event unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be followed up and documented even if the patient was discontinued from the study.

If any pregnancy occurs in the course of the study, then the Investigator or other site personnel informs the appropriate AstraZeneca representatives within 1day i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 or 5 calendar days for SAEs (see Section 6.4) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

The PREGREP module in the CRF is used to report the pregnancy and the PREGOUT is used to report the outcome of the pregnancy.

6.6.2 Paternal exposure

Male patients should refrain from fathering a child or donating sperm during the treatment and until 1 month following the last dose of IMP.

Pregnancy of the patient's partners is not considered to be an adverse event. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should if possible be followed up and documented. To capture information about a pregnancy from the partner of a male patient, the male patient's partner consent must be obtained to collect information related to the pregnancy and outcome;

the male patient should not be asked to provide this information. A consent form specific to this situation must be used.

6.7 Management of IMP related toxicities/Dose Reductions

For information on the Dose adaptation scheme, please see Section 4.2.2.

6.8 Study governance and oversight

The safety of the patients in this clinical trial is closely monitored on an on-going basis by AstraZeneca representatives including the study physician. Issues identified will be addressed; for instance this could involve amendments to the study protocol and letters to Investigators.

In addition there is also a Data Safety Monitoring Board (DSMB), see below.

6.8.1 Data Safety Monitoring Board

An internal AstraZeneca Data Safety Monitoring Board (DSMB) that is independent of the study team will be appointed for the study. The DSMB will consist of at minimum a physician as clinical representative and a representative from Patient Safety. The DSMB will be responsible for review of safety of the sentinel patients and approval of enrollment of additional patients into the study. The DSMB will also have general responsibility for oversight of patient safety in this trial. At its discretion, the DSMB may review any available blinded safety data at any time. The DSMB may also request and review unblinded safety data on any patient(s) or group. The DSMB will also have the authority to pause enrollment and/or request safety-related changes to the study protocol. Details of the DSMB membership and planned reviews of safety will be defined in a separate document (DSMB Charter) which will be finalized before the first subject is randomized in the study.

Further details on the DSMB composition and function will be provided in the DSMB Charter. The charter will include information about procedures for unblinding of safety information.

In addition a separate data monitoring committee will evaluate data for a potential Interim Analysis, see Section 8.5.6

7. INVESTIGATIONAL PRODUCT AND OTHER TREATMENTS

7.1 Identity of investigational product(s)

AZD1419 drug substance is an oligodeoxynucleotide (ODN) comprising 22 deoxyribo-nucleotides linked through a phosphorothioate backbone. AZD1419 is a TLR9 agonist with 3 CpG motifs. AZD1419 drug substance is produced as a freeze-dried solid. The molecule is produced as the sodium salt. AZD1419 drug substance is produced by solid phase synthesis and is not a biological medicinal product.

AZD1419 drug product is intended for inhalation via nebulization and is supplied as 2 mg/mL, 8 mg/mL and 16 mg/mL solution of AZD1419 in phosphate-buffered saline and will be

administered once weekly using the commercially available and CE marked I-neb® Adaptive Aerosol Delivery [ADD] System from Philips Respironics.

Investigational product	Dosage form and strength	Manufacturer
AZD1419	Nebuliser solution 2 mg/mL, 8 mg/ml and 16 mg/mL	AstraZeneca
Placebo	Placebo for AZD1419 nebuliser solution	AstraZeneca

The investigational products will be manufacturing in accordance with Good Manufacturing Practice (GMP) supplied by AstraZeneca.

7.2 Dose and treatment regimens

7.2.1 Study Treatments

A total of 70 eligible patients will be randomly assigned 1:1 to receive 13 inhaled once weekly doses of either placebo or AZD1419 during the conduct of the study. Study drug will be administered at the clinic. All eligible patients will be taking ICS and LABA during the screening period, with SABA as rescue therapy during the study.

All patients randomized to AZD1419 will have 4 mg/week of AZD1419 or placebo for 4 doses. After the 4th dose, the 5th dose will be adapted based on tolerability for the final 9 doses. Refer to Section 4.2.2 for details of the dose adaptation procedure.

Instructions for the I-neb will be provided by AstraZeneca.

7.3 Labelling

Label will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. The label will fulfil GMP Annex 13 and Medical Device Directive requirements for labelling. The label text will be translated into local language.

7.4 Storage

All study drugs and placebo should be kept in a secure place under appropriate storage conditions. The investigational product labels specify the appropriate storage. The IP storage area must be temperature monitored and the site will maintain documentation of the temperature monitoring. Handling instruction will be provided separately by AstraZeneca.

7.5 Compliance

The administration of all study drugs (including investigational products) should be recorded in the appropriate sections of the Case Report Form.

7.6 Accountability

The study drug provided for this study will be used only as directed in the Study Protocol. The study personal will account for all study drugs dispensed to and returned from the patient. The study personal will account for all study products (I-nebs) received at the site, unused study

drug at site and study drug returned by the patients and for appropriate destruction. Destruction should not take place until approved by responsible person at AstraZeneca. Certificates of delivery, destruction should be signed.

The I-nebs used in the study should be returned to AstraZeneca after study closure.

7.7 Concomitant and other treatments

The ICS, LABA and SABA treatment should be prescribed by the Investigator and provided locally.

7.7.1 Other concomitant treatment

Medication other than that described above, which is considered necessary for the patient's safety and wellbeing, may be given at the discretion of the Investigator and recorded in the appropriate sections of the Case Report Form.

7.8 Post Study Access to Study Treatment (Not applicable)

8. STATISTICAL ANALYSES BY ASTRAZENECA OR DELEGATE

Analyses will be performed by AstraZeneca or its representatives.

A comprehensive Statistical Analysis Plan (SAP) will be prepared prior to first patient randomized and any subsequent amendments will be documented, with final amendments completed prior to unblinding of the data.

All personnel involved with the analysis of the study will remain blinded until the database is locked and all protocol violations are identified.

8.1 Statistical considerations

The primary outcome measure is loss of asthma control, as defined in Section 2.1.1. A number of secondary outcomes will also be considered (detailed below).

For the primary analysis of time to loss of asthma control, loss of control is considered to be permanent, given that patients are withdrawn from the study in such an event. Patients who withdraw from treatment and/or the study will have time to event censored at the first missed visit.

The primary hypothesis will be tested one-sided, with alpha=0.05. All other hypothesis tests will be two-sided, with alpha=0.05. Confidence intervals will be two-sided, at the 95% level

There will be no adjustments for multiplicity.

All efficacy analyses will be based on the Full Analysis Set, but with no imputation of missing values. For the summary statistics and analyses of secondary parameters, all data available at each time point will be used.

Safety analyses will include all patients who receive at least one dose of IMP (safety population) and all safety parameters will be described using the Safety population, using summary statistics presented by treatment group

8.2 Sample size estimate

This trial has about 90% power to yield a statistically significant (alpha = 0.05, 2-sided) difference between the pooled active and placebo groups in time to loss of asthma control given that the cumulative number of controlled subjects at week 52 is 20% and 60% for control versus active respectively. Assuming a drop-out of about 10-15%, this will require about 70 patients in total (32 events).

8.3 Definitions of analysis sets

All efficacy analyses will be performed using an ITT approach based on the full analysis set. For consistency, demographic and baseline characteristics will be presented using the full analysis set. Safety objectives will be analysed based on the Safety population.

All patients analysis set (All patients): This analysis set comprises all patients screened for the study and will be used for the reporting of disposition and screening failures.

8.3.1 Efficacy analysis set

Full analysis set: All patients randomized and receiving any IP will be included in the full analysis set, irrespective of their protocol adherence and continued participation in the study. Patients will be analyzed according to their randomized treatment, irrespective of whether or not they did not take IP or inadvertently received the wrong IMP, and irrespective of whether they prematurely discontinued the study. For patients who withdraw consent to participate in the study all data will be included up to the date of their study termination.

8.3.2 Safety analysis set

Safety analysis set (Safety): All patients who received any IMP will be included in the safety analysis set. Patients will be classified according to the treatment they actually received. A patient who has on one, or several occasions, received active treatment will be classified as active. All safety summaries will be based on this analysis set.

8.4 Outcome measures for analyses

8.4.1 General Definitions

8.4.1.1 Definition of baseline

In general, the last measurement on or prior to the date of randomization will serve as the baseline measurement for efficacy endpoints, while the last measurement prior to first dose of study treatment will serve as the baseline measurement for safety endpoints.

Change from baseline is computed as (post-randomization value - baseline value), with negative values showing a decrease from baseline.

Percentage change from baseline is computed as ((change from baseline) / baseline value) × 100%.

If either the post-randomization value or the baseline value is missing, then the change or percentage change from baseline value will also be set to missing.

Percentage change from baseline will not be calculated or presented for variables that may take 0 as a value.

8.4.1.2 Visit and period windows

A more detailed definition of visit and period windows will be provided in the statistical analysis plan (before unblinding the study). For analyses of time to event, actual date (if known) will be used in preference to the date of the visit on which the event was recorded.

8.4.2 Calculation or derivation of efficacy variables

8.4.2.1 Time to loss of asthma control

The primary outcome variable, loss of asthma control, is defined in Section 2.1.1.

Time to loss of asthma control will be censored at 52 weeks for patients who do not experience loss of asthma control during the 52-week study period.

For patients who withdraw from the study without reporting loss of asthma control, time will be censored at the date of withdrawal, if known, else at the patient's last clinical visit plus one day.

8.4.3 Calculation or derivation of PRO variables

8.4.3.1 Asthma Control Questionnaire (ACQ-5)

In the ACQ-5 questionnaire the patients are asked to recall the status of their asthma during the previous week with regards to symptoms, Appendix E. The questionnaire include questions on

a) Awoken at night by asthma symptoms
b) Severity of asthma symptoms in the morning
c) Limitation of daily activities due to asthma
d) Shortness of breath
e) Wheeze

The questions of the ACQ-5 are measured on a 7-point scale scored from 0 (totally controlled) to 6 (severely uncontrolled). The ACQ-5 score is computed as the un-weighted mean of the responses.

If ACQ-5 reaches a value of 1.5 or more, the patient is reported as having loss of asthma control (this being one of the 4 criteria that define that outcome).

8.5 Methods for statistical analyses

Summary data will be presented in tabular format by treatment. Categorical data will be summarized by the number and percentage of patients in each category. Continuous variables for parametric data will be summarized by descriptive statistics including N, mean, SD, median, and range.

All data will be listed. Data listings will be sorted by treatment and patient number.

8.5.1 Patient disposition, demography data and patients characteristics

Patient disposition will be summarized using the All patients analysis set.

The number of enrolled patients will be summarized. The number and percentage of patients within each treatment group will be presented by the following categories; randomized, not randomized (and reason), received study treatment, did not receive study treatment (and reason), completed treatment, discontinued treatment (and reason), completed study, and discontinued study (including reason).

Demographic data such as age, gender, and race will be summarized by treatment group for the full analysis set.

Baseline characteristics will also be summarized by treatment for the full analysis set. These include medical, surgical and respiratory disease histories, weight, height and BMI, smoking status, history of allergy, FEV_1 (pre and post-BD) at baseline, asthma duration, age at onset of asthma, asthma medications, the number of asthma exacerbations in the previous 12 months, and the number of asthma exacerbations requiring hospitalizations in the previous 12 months.

Medical and surgical histories will be summarized by MedDRA Preferred Term (PT) within the System Organ Class (SOC) level of MedDRA.

The number and percentage of patients who take concomitant medications, and those who take disallowed concomitant medications during the study, will be presented by treatment group. Concomitant medications will be classified according to the AstraZeneca Drug Dictionary. The summary tables will present data by generic term using Anatomical Therapeutic Chemical (ATC) classification system codes.

8.5.2 Exposure

Exposure to IP will be summarized by treatment group, for the safety analysis set.

8.5.3 Violations and deviations

Only important protocol deviations will be listed and tabulated in the CSR. Protocol deviations that may greatly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a patient's rights, safety, or well-being include:

- Patients who do not meet the inclusion criteria
- Patients who do not meet the randomization criteria

- Patients who meet any of the exclusion criteria
- Patients who use one or more disallowed medication (for any reason, unless otherwise specified) during the randomized treatment period
- Patients who received the incorrect study treatment or study dose at any time during the 52-week double-blind treatment period
- Patients who developed withdrawal criteria during the study but were not withdrawn

8.5.4 Analysis of the primary variable (s)

The primary efficacy variable is the time to loss of asthma control, and the primary analysis is to compare the time to loss of asthma control for AZD1419 with placebo. The Time to loss of control in the AZD1419 group will be compared to that of the placebo group using a log rank test (with accompanying Kaplan-Meier plot)

The hypothesis test will be one-sided, with alpha=0.05.

8.5.4.1 Analysis of loss of asthma control as group proportions

The proportion of patients within each treatment group with loss of asthma control, at each clinical visit, will be modelled longitudinally using a generalized estimating equation (GEE) approach, with loss of control as a binary outcome variable.

Summary statistics will also be presented for each treatment group at each visit.

8.5.5 Analysis of the secondary variable(s)

8.5.5.1 Time to first moderate or severe exacerbation

Moderate and severe asthma exacerbation is defined in Section 5.1.3. Only exacerbations that are classified as moderate or severe will be analysed.

The null hypothesis, that the time to first moderate or severe exacerbation is not different between AZD1419 and placebo groups, will be tested using the log rank test (with accompanying Kaplan-Meier plot).

Time to first moderate or severe exacerbation will be censored at 52 weeks for patients who do not experience loss of asthma control during the 52-week study period.

For patients who withdraw from the study without reporting moderate or severe exacerbation, time will be censored at the date of withdrawal, if known, else at the patient's last clinical visit plus one day.

8.5.5.2 Proportion of patients with ≥1 moderate or severe asthma exacerbation

The proportion of patients with ≥1 asthma exacerbation will be compared between the two treatment groups at each clinical visit, using a generalized estimating equation (GEE) approach, with occurrence of any exacerbation since the start of treatment as a binary outcome variable.

Summary statistics will also be presented for each treatment group at each visit.

8.5.5.3 Forced expiratory volume in 1 second (FEV_1)

FEV_1 is measured at each clinical visit.

FEV_1 will be analysed at each visit longitudinally, using a mixed effects model with treatment, visit, treatment-by-visit interaction and baseline FEV_1 as fixed effects and patient as random effect. At each visit, all available values will be used in this analysis.

Summary statistics will also be presented for each treatment group at each visit.

8.5.5.4 Peak expiratory flow (PEF)

PEF is measured daily using the ePRO device. For the purposes of summary and analysis, a weekly average PEF will be computed.

Weekly average PEF will be analysed longitudinally, using a mixed effects model with treatment, week and baseline PEF as fixed effects and patient as random effect. At each week, all observed values will be used in this analysis.

Summary statistics will also be presented for each treatment group at each week.

8.5.5.5 Analysis of ACQ-5

ACQ-5 is measured weekly using the ePRO recording device.

Weekly average ACQ-5 will be analysed longitudinally, using a mixed effects model with treatment, week and baseline ACQ-5 as fixed effects and patient as random effect. At each week, all observed values will be used in this analysis.

Summary statistics will also be presented for each treatment group at each week.

8.5.5.6 Analysis of fractional exhaled nitric oxide (FeNO)

FeNO is measured using the NIOX Vero® device every other day as well as at clinical visits. For the purposes of summary and analysis, a weekly average FeNO will be computed.

Weekly FeNO will be analysed longitudinally, using a mixed effects model with treatment, period and baseline FeNO as fixed effects and patient as random effect. At each period, all observed values will be used in this analysis.

Summary statistics will also be presented for each treatment group at each week.

8.5.5.7 Other airways measurements

The following collected variables will be compared between treatment groups using summary statistics only: Vital Capacity (VC), Forced Expiratory Flow 25% to 75% (FEF25-75), Inspiratory Capacity (IC) and asthma symptom score and its components, for example night time awakenings and maintenance medication.

8.5.5.8 Reliever medication

Reliever medication is recorded as taken using the ePRO device.

Summary statistics will be presented for each treatment group, grouped by study visit.

8.5.6 Interim analyses

Two types of interim analyses may be performed for this study as defined below. None of them will have an impact on the type I error, hence no adjustment for the type I error is needed. A detailed description will be included in the statistical analysis plan, which will be finalised before first subject in (FSI, first subject receiving first dose).

Blinded monitoring

Blinded interim monitoring of the event rate during the trial will be performed. The monitoring and analysis will be performed by AstraZeneca or its representatives.

Administrative Interim analysis

The study team may decide to do an administrative un-blinded analysis of the study with the intent to trigger internal (AstraZeneca) investment decisions. This interim analysis will not change the conduct of the trial.

To ensure the blinding of each patient's treatment assignment throughout the study, the interim analysis will be performed by a limited number of personnel who are not involved in the conduct of the study. Study site personnel, AstraZeneca or its representatives, directly associated with the conduct of this study and the patients will remain blinded to the treatment assignment for individual patients until the completion of the study. The decision to perform this interim analysis will be done before FSI.

8.4.7 Sensitivity analysis (if applicable)

An analysis will be conducted on the primary outcome variable, loss of asthma control, using the same log rank test as for the primary analysis, but making the assumption that all patients who withdraw from the study without recorded loss of control are classed as loss of control (instead of being censored), in order to test the sensitivity of the results to the use of censoring/lack of information regarding loss of control in patients who withdraw.

8.4.8 Exploratory efficacy analysis

There will be an exploratory analysis of the composite endpoint for exacerbations, CompEx, including an analysis of time to first CompEx event, and the proportion of patients with CompEx events. The CompEx measure is still under development, therefore details of this analysis are deferred to the Statistical Analysis Plan.

The exploratory biomarkers collected during the study (urine, blood and sputum samples) will be analysed if indicated or at the end of the study.

Exploratory biomarker data will be listed by treatment group, as will all data collected in the clinical database, but summaries and analyses will not form part of the clinical study report, being presented instead in a separate bioanalytical report.

8.5.9 Safety analysis

All safety variables will be summarized by treatment group and evaluated descriptively utilizing the safety analysis set. No formal hypothesis testing of safety data is planned.

8.5.9.1 Adverse events

All AEs recorded in the eCRF will be coded according to the terminology of the latest version of MedDRA.

All AEs will be summarized by treatment group for the safety analysis set. Treatment-emergent AEs will be tabulated (number and percentage of patients) by system organ class, preferred term (PT), intensity, and relation to study medication according to the treatment actually received.

In addition, common AEs, AEs with outcome of death, SAEs, DAEs, and OAEs will be summarized separately.

Adverse events will be summarized separately for the periods during which patients are taking ICS+LABA (up until Week 6), during the period of ICS being tapered down (from week 6 to week 9), and during the subsequent remainder of the study.

8.5.9.2 Vital signs

Diastolic and systolic blood pressure, pulse oximetry and pulse at each visit for which they are recorded will be summarized by treatment group with descriptive statistics. Changes from baseline for each of these variables to each visit will also be summarized using descriptive statistics.

8.5.9.3 Diffusing Capacity of the Lung for Carbon Monoxide (DLco)

DLco at each visit for which it is recorded will be summarized by treatment group with descriptive statistics. Changes from baseline to each visit will also be summarized using descriptive statistics.

8.5.9.4 Physical examination and ECG

Physical examination and ECG readings will be summarized by treatment group at each visit for which they are recorded.

8.5.9.5 Haematology, clinical chemistry and urinalysis

Safety laboratory parameters at each visit will be summarized by treatment group with descriptive statistics. Changes from baseline for each of these variables to each visit will also be summarized using descriptive statistics.

9. STUDY AND DATA MANAGEMENT BY ASTRAZENECA

9.1 Training of study site personnel

Before the first patient is entered into the study, an AstraZeneca representative will review and discuss the requirements of the Clinical Study Protocol and related documents with the investigational staff and also train them in any study specific procedures and system(s) utilised.

The Principal Investigator will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information relevant to the performance of this study is forwarded to the staff involved.

The Principal Investigator will maintain a record of all individuals involved in the study (medical, nursing and other staff).

9.2 Monitoring of the study

During the study, an AstraZeneca representative will have regular contacts with the study site, including visits to:

- Provide information and support to the Investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately and timely recorded in the CRFs, that biological samples are handled in accordance with the Laboratory Manual and that study drug accountability checks are being performed
- Perform source data verification (a comparison of the data in the CRFs with the patient's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating patients. This will require direct access to all original records for each patient (e.g., clinic charts)
- Ensure withdrawal of informed consent to the use of the patient's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the patient.

The AstraZeneca representative will be available between visits if the Investigator(s) or other staff at the centre needs information and advice about the study conduct.

9.2.1 Source data

Refer to the Clinical Study Agreement for location of source data.

9.2.2 Study agreements

The Principal Investigator at each/the centre should comply with all the terms, conditions, and obligations of the Clinical Study Agreement, or equivalent, for this study. In the event of any

inconsistency between this Clinical Study Protocol and the Clinical Study Agreement, the terms of Clinical Study Protocol shall prevail with respect to the conduct of the study and the treatment of patients and in all other respects, not relating to study conduct or treatment of patients, the terms of the Clinical Study Agreement shall prevail.

Agreements between AstraZeneca and the Principal Investigator should be in place before any study-related procedures can take place, or patients are enrolled.

9.2.3 Archiving of study documents

The Investigator follows the principles outlined in the Clinical Study Agreement (CSA).

9.3 Study timetable and end of study

The end of the study is defined as 'the last visit of the last patient undergoing the study'.

The study is expected to start in Q4 2016 and to end by Q4 2018

The investigator(s) will be notified by the Sponsor when study recruitment is complete. The study may be terminated at individual centres if the study procedures are not being performed according to GCP, or if recruitment is slow. AstraZeneca may also terminate the entire study prematurely if concerns for safety arise within this study or in any other study with TLR9 agonists.

If AstraZeneca decides to prematurely terminate or suspend the study, the Principal Investigator/Investigator, the head of the study site, and regulatory authorities should receive written notification of the reasons for the premature termination or suspension.

Completion of the study

Upon terminating the study, the Principal Investigator/Investigator will report in writing the completion of the study as well as the summary of the results to the head of the study site in accordance with the study site's rules. The head of the study site, who is informed of the termination by the Investigator, will provide a written notification of the results to the IRB and AstraZeneca.

9.4 Data management by AstraZeneca or delegate

Data management will be performed by AstraZeneca/Cognizant Data Management Centre staff according to the Data Management Plan. Adverse events and medical/surgical history will be classified according to the terminology of the latest version the Medical Dictionary for Regulatory Activities (MedDRA). Medications will be classified according to the AstraZeneca Drug Dictionary. Classification coding will be performed by the Medical Coding Team at the AstraZeneca/Cognizant Data Management Centre.

The data collected through third party sources will be obtained and reconciled against study data.

Data queries will be raised for inconsistent, impossible or missing data. All entries to the study database will be available in an audit trail.

The data will be validated as defined in the Data Management Plan. Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly. The Data Management Plan will also clarify the roles and responsibilities of the various functions and personnel involved in the data management process

When all data have been coded, validated, signed and locked, clean file will be declared. Any treatment revealing data may thereafter be added and the final database will be locked.

Serious Adverse Event (SAE) Reconciliation

SAE reconciliation reports are produced and reconciled with the Patient Safety database and/or the investigational site.

Data associated with human biological samples

Data associated with biological samples will be transferred from laboratory(ies) internal or external to AstraZeneca.

10. ETHICAL AND REGULATORY REQUIREMENTS

10.1 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice, applicable regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples.

10.2 Patient data protection

The Informed Consent Form will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation.

AstraZeneca will not provide individual genotype results to patients, any insurance company, any employer, their family members, general physician or any other third party, unless required to do so by law**.**

Precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the patient. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a patient. For example, in the case of a medical emergency, an AstraZeneca Physician or an Investigator might know a patient's identity and also have access to his or her genetic data. Also Regulatory authorities may require access to the relevant files, though the patient's medical information and the genetic files would remain physically separate.

10.3 Ethics and regulatory review

An Ethics Committee should approve the final study protocol, including the final version of the Informed Consent Form and any other written information and/or materials to be provided to

the patients. The Investigator will ensure the distribution of these documents to the applicable Ethics Committee, and to the study site staff.

The opinion of the Ethics Committee should be given in writing. The Investigator should submit the written approval to AstraZeneca before enrolment of any patient into the study.

The Ethics Committee should approve all advertising used to recruit patients for the study.

AstraZeneca should approve any modifications to the Informed Consent Form that are needed to meet local requirements.

If required by local regulations, the protocol should be re-approved by the Ethics Committee annually.

Before enrolment of any patient into the study, the final study protocol, including the final version of the Informed Consent Form, is approved by the national regulatory authority or a notification to the national regulatory authority is done, according to local regulations.

AstraZeneca will handle the distribution of any of these documents to the national regulatory authorities.

AstraZeneca will provide Regulatory Authorities, Ethics Committees and Principal Investigators with safety updates/reports according to local requirements.

10.4 Informed consent

The Principal Investigator(s) at each centre will:

- Ensure each patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study
- Ensure each patient is notified that they are free to discontinue from the study at any time
- Ensure that each patient is given the opportunity to ask questions and allowed time to consider the information provided
- Ensure each patient provides signed and dated informed consent before conducting any procedure specifically for the study
- Ensure the original, signed Informed Consent Form(s) is/are stored in the Investigator's Study File
- Ensure a copy of the signed Informed Consent Form is given to the patient
- Ensure that any incentives for patients who participate in the study as well as any provisions for patients harmed as a consequence of study participation are described in the informed consent form that is approved by an Ethics Committee.

10.5 Changes to the protocol and informed consent form

If there are any substantial changes to the study protocol, then these changes will be documented in a study protocol amendment and where required in a new version of the study protocol (Revised Clinical Study Protocol).

The amendment is to be approved by the relevant Ethics Committee and if applicable, also the national regulatory authority approval, before implementation. Local requirements are to be followed for revised protocols.

AstraZeneca will distribute any subsequent amendments and new versions of the protocol to each Principal Investigator(s). For distribution to Ethics Committee see Section 10.3.

If a protocol amendment requires a change to a centre's Informed Consent Form, AstraZeneca and the centre's Ethics Committee are to approve the revised Informed Consent Form before the revised form is used.

If local regulations require, any administrative change will be communicated to or approved by each Ethics Committee.

10.6 Audits and inspections

Authorised representatives of AstraZeneca, a regulatory authority, or an Ethics Committee may perform audits or inspections at the centre, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the protocol, Good Clinical Practice (GCP), guidelines of the International Conference on Harmonisation (ICH), and any applicable regulatory requirements. The Investigator will contact AstraZeneca immediately if contacted by a regulatory agency about an inspection at the centre.

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Appendix A Additional Safety Information

Further Guidance on the Definition of a Serious Adverse Event (SAE)

Life threatening

'Life-threatening' means that the patient was at immediate risk of death from the AE as it occurred or it is suspected that use or continued use of the product would result in the patient's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

Hospitalisation

Outpatient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (eg, bronchospasm, laryngeal oedema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the patient was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important medical event or medical intervention

Medical and scientific judgement should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life threatening or result in death, hospitalisation, disability or incapacity but may jeopardize the patient or may require medical intervention to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgement must be used.

- Angioedema not severe enough to require intubation but requiring iv hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (eg, neutropenia or anaemia requiring blood transfusion, etc) or convulsions that do not result in hospitalisation

Development of drug dependency or drug abuse

A Guide to Interpreting the Causality Question

When making an assessment of causality consider the following factors when deciding if there is a 'reasonable possibility' that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the patient actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?
- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?
- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?
- No alternative cause. The AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, other host or environmental factors.
- Re-challenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a re-challenge.
- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

In difficult cases, other factors could be considered such as:

- Is this a recognized feature of overdose of the drug?
- Is there a known mechanism?

Causality of 'related' is made if following a review of the relevant data, there is evidence for a 'reasonable possibility' of a causal relationship for the individual case. The expression 'reasonable possibility' of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data including enough information to make an informed judgment. With limited or insufficient information in the case, it is likely that the event(s) will be assessed as 'not related'.

Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

Appendix B International Airline Transportation Association (IATA) 6.2 Guidance Document

Labelling and shipment of biohazard samples

International Airline Transportation Association (IATA) classifies biohazardous agents into 3 categories. For transport purposes the classification of infectious substances according to risk groups was removed from the Dangerous Goods Regulations (DGR) in the 46th edition (2005). Infectious substances are now classified either as Category A, Category B or Exempt. There is no direct relationship between Risk Groups and categories A and B.

Category A Infectious Substances are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals. Category A pathogens are eg, Ebola, Lassa fever virus:

- are to be packed and shipped in accordance with IATA Instruction 602.

Category B Infectious Substances are infectious Substances that do not meet the criteria for inclusion in Category A. Category B pathogens are eg, Hepatitis A, B, C, D, and E viruses, Human immunodeficiency virus (HIV) types 1 and 2. They are assigned the following UN number and proper shipping name:

- UN 3373 - Biological Substance, Category B
- are to be packed in accordance with UN3373 and IATA 650

Exempt - all other materials with minimal risk of containing pathogens

- Clinical trial samples will fall into Category B or exempt under IATA regulations
- Clinical trial samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging
- Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content
- IATA compliant courier and packaging materials should be used for packing and transportation and packing should be done by an IATA certified person, as applicable
- Samples routinely transported by road or rail are patient to local regulations which require that they are also packed and transported in a safe and appropriate way to contain any risk of infection or contamination by using approved couriers and packaging / containment materials at all times. The IATA 650 biological sample containment standards are encouraged wherever possible when road or rail transport is used.

Appendix C Pharmacogenetics Research

Background and Rationale

AstraZeneca intends to perform genetic research in the AZD1419 clinical development programme to explore how genetic variations may affect the clinical parameters associated with AZD1419 and/or agents used in combination or as comparators. Collection of DNA samples from populations with well described clinical characteristics may lead to improvements in the design and interpretation of clinical trials and, possibly, to genetically guided treatment strategies.

It is emphasised that AstraZeneca will only look for markers within genes relevant to the mode of action of and response to AZD1419 and asthma. No other research will be performed on the samples.

Genetic Research Objectives

The objective of this research is to collect and store DNA for future exploratory research into genes/genetic variation that may influence response (ie, distribution, safety, tolerability and efficacy) to AZD1419 and/or susceptibility to asthma.

Genetic Research Plan and Procedures

Selection of genetic research population

Study selection record

All randomized patients will be asked to participate in this genetic research. Participation is voluntary and if a patient declines to participate there will be no penalty or loss of benefit. The patient will not be excluded from any aspect of the main study.

Inclusion criteria

For inclusion in this genetic research, patients must fulfil all of the inclusion criteria described in the main body of the Clinical Study Protocol **and**:

- Provide informed consent for the genetic sampling and analyses.

Exclusion criteria

Exclusion from this genetic research may be for any of the exclusion criteria specified in the main study or any of the following:

- Previous allogeneic bone marrow transplant
- Non-leukocyte depleted whole blood transfusion in 120 days of genetic sample collection

Discontinuation of patients from this genetic research

Specific reasons for discontinuing a patient from this genetic research are:

Withdrawal of consent for genetic research: Patients may withdraw from this genetic research at any time, independent of any decision concerning participation in other aspects of the main study. Voluntary discontinuation will not prejudice further treatment. Procedures for discontinuation are outlined in Section 3.10 of the main Clinical Study Protocol.

Collection of samples for genetic research

The blood sample for genetic research will be obtained from the patients at Visit 2 or at any other Visit after randomisation. Although genotype is a stable parameter, early sample collection is preferred to avoid introducing bias through excluding patients who may withdraw due to an adverse event (AE), such patients would be important to include in any genetic analysis. If for any reason the sample is not drawn at Visit 2, it may be taken at any visit until the last study visit. Only one sample should be collected per patient for genetics during the study. Samples will be collected, labelled, stored and shipped as detailed in the Laboratory Manual.

For blood volume, see Table 4 of the Clinical Study Protocol.

Coding and storage of DNA samples

The processes adopted for the coding and storage of samples for genetic analysis are important to maintain patient confidentiality. Samples will be stored for a maximum of 25 years, from the date of last patient last visit, after which they will be destroyed. DNA is a finite resource that is used up during analyses. Samples will be stored and used until no further analyses are possible or the maximum storage time has been reached.

For all samples irrespective of the type of coding used the DNA will be extracted from the blood sample. The DNA sample will be assigned a unique number replacing the information on the sample tube. Thereafter, the DNA sample will be identifiable by the unique DNA number only. The DNA number is used to identify the sample and corresponding data at the AstraZeneca genetics laboratories, or at the designated contract laboratory. No personal details identifying the individual will be available to any person (AstraZeneca employee or contract laboratory staff working with the DNA.)

The samples and data for genetic analysis in this study will be single coded. The link between the patient enrolment/randomisation code and the DNA number will be maintained and stored in a secure environment, with restricted access WITHIN the Clinical Genotyping Group Laboratory Information Management System (LIMS) at AstraZeneca. The link will be used to identify the relevant DNA samples for analysis, facilitate correlation of genotypic results with clinical data, allow regulatory audit and to trace samples for destruction in the case of withdrawal of consent.

Ethical and Regulatory Requirements

The principles for ethical and regulatory requirements for the study, including this genetics research component, are outlined in Section 8 of the main Clinical Study Protocol.

Informed consent

The genetic component of this study is optional and the patient may participate in other components of the main study without participating in the genetic component. To participate in the genetic component of the study the patient must sign and date both the consent form for the main study and the genetic component of the study. Copies of both signed and dated consent forms must be given to the patient and the original filed at the study centre. The principal investigator(s) is responsible for ensuring that consent is given freely and that the patient understands that they may freely discontinue from the genetic aspect of the study at any time.

Patient data protection

AstraZeneca will not provide individual genotype results to patients, any insurance company, any employer, their family members, general physician or any other third party, unless required to do so by law.

Extra precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the patient. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a patient. For example, in the case of a medical emergency, an AstraZeneca Physician or an investigator might know a patient's identity and also have access to his or her genetic data. Also Regulatory authorities may require access to the relevant files, though the patient's medical information and the genetic files would remain physically separate.

Data management

Any genotype data generated in this study will be stored in the AstraZeneca genotyping LIMS database, or other appropriate secure system within AstraZeneca and/or third party contracted to work with AstraZeneca to analyze the samples.

The results from this genetic research may be reported in the CSR for the main study, or in a separate report as appropriate.

Some or all of the clinical datasets from the main study may be merged with the genetic data in a suitable secure environment separate from the clinical database.

Statistical Methods and Determination of Sample Size

The number of patients that will agree to participate in the genetic research is unknown. It is therefore not possible to establish whether sufficient data will be collected to allow a formal statistical evaluation or whether only descriptive statistics will be generated. A statistical analysis plan will be prepared where appropriate.

Appendix D Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law

Introduction

This Appendix describes the process to be followed in order to identify and appropriately report cases of Hy's Law. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries.

During the course of the study the Investigator will remain vigilant for increases in liver biochemistry. The investigator is responsible for determining whether a patient meets potential Hy's Law (PHL) criteria at any point during the study.

The Investigator participates, together with AstraZeneca clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether Hy's Law (HL) criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than Drug Induced Liver Injury (DILI) caused by the Investigational Medicinal Product (IP).

The Investigator is responsible for recording data pertaining to PHL/HL cases and for reporting Adverse Events (AE) and Serious Adverse Events (SAE) according to the outcome of the review and assessment in line with standard safety reporting processes.

Definitions

Potential Hy's Law (PHL)

Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) ≥ 3x Upper Limit of Normal (ULN) **together with** Total Bilirubin (TBL) ≥ 2xULN at any point during the study following the start of study medication irrespective of an increase in Alkaline Phosphatase (ALP).

Hy's Law (HL)

AST or ALT ≥3x ULN **together with** TBL ≥2xULN, where no other reason, other than the IP, can be found to explain the combination of increases, eg, elevated ALP indicating cholestasis, viral hepatitis, another drug.

For PHL and HL the elevation in transaminases must precede or be coincident with (i.e. on the same day) the elevation in TBL, but there is no specified timeframe within which the elevations in transaminases and TBL must occur.

Identification of Potential Hy's Law Cases

In order to identify cases of PHL it is important to perform a comprehensive review of laboratory data for any patient who meets any of the following identification criteria in isolation or in combination:

- ALT ≥3xULN

- AST ≥3xULN
- TBL ≥2xULN

When a patient meets any of the identification criteria, in isolation or in combination, the central laboratory will immediately send an alert to the Investigator (also sent to AstraZeneca representative).

The Investigator will also remain vigilant for any local laboratory reports where the identification criteria are met, where this is the case the Investigator will:

- Notify the AstraZeneca representative
- Request a repeat of the test (new blood draw) by the central laboratory
- Complete the appropriate unscheduled laboratory CRF module(s) with the original local laboratory test result

When the identification criteria are met from central or local laboratory results the Investigator will without delay:

- Determine whether the patient meets PHL criteria (see Definitions within this Appendix for definition) by reviewing laboratory reports from all previous visits (including both central and local laboratory results)

The Investigator will without delay review each new laboratory report and if the identification criteria are met will:

- Notify the AstraZeneca representative
- Determine whether the patient meets PHL criteria (see Definitions within this Appendix for definition) by reviewing laboratory reports from all previous visits

Follow-up

Potential Hy's Law Criteria not met

If the patient does not meet PHL criteria the Investigator will:

- Perform follow-up on subsequent laboratory results according to the guidance provided in the Clinical Study Protocol.

Potential Hy's Law Criteria met

If the patient does meet PHL criteria the Investigator will:

- Notify the AstraZeneca representative who will then inform the central Study Team

The Study Physician contacts the Investigator, to provide guidance, discuss and agree an approach for the study patients' follow-up and the continuous review of data. Subsequent to this contact the Investigator will:

- Monitor the patient until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated
- Investigate the etiology of the event and perform diagnostic investigations as discussed with the Study Physician. << For studies using a central laboratory add: This includes deciding which the tests available in the Hy's law lab kit should be used>>
- Complete the three Liver CRF Modules as information becomes available
- If at any time (in consultation with the Study Physician) the PHL case meets serious criteria, report it as an SAE using standard reporting procedures

Review and Assessment of Potential Hy's Law Cases

The instructions in this Section should be followed for all cases where PHL criteria are met.

No later than 3 weeks after the biochemistry abnormality was initially detected, the Study Physician contacts the Investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the IP. The AstraZeneca Medical Science Director and Global Safety Physician will also be involved in this review together with other patient matter experts as appropriate.

According to the outcome of the review and assessment, the Investigator will follow the instructions below.

If there is an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE:

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate CRF
- If the alternative explanation is an AE/SAE, record the AE /SAE in the CRF accordingly and follow the AZ standard processes

If it is agreed that there is **no** explanation that would explain the ALT or AST and TBL elevations other than the IP:

- Report an SAE (report term 'Hy's Law') according to AstraZeneca standard processes.

– The 'Medically Important' serious criterion should be used if no other serious criteria apply

- As there is no alternative explanation for the HL case, a causality assessment of 'related' should be assigned.

If, there is an unavoidable delay, of over 3 weeks, in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Report an SAE (report term 'Potential Hy's Law') applying serious criteria and causality assessment as per above
- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are met. Update the SAE report according to the outcome of the review.

References

FDA Guidance for Industry (issued July 2009) 'Drug-induced liver injury: Premarketing clinical evaluation':
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

Appendix E ACQ-5

ASTHMA CONTROL QUESTIONNAIRE (ACQ-5)

(SYMPTOMS ONLY)

QOL TECHNOLOGIES LTD.

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DECEMBER 2002

SYMPTOMS ONLY MODIFIED JUNE 2014 NORTH AMERICAN ENGLISH

Please answer questions 1 - 5.

Circle the number of the response that best describes how you have been during the past week.

1.	On average, during the past week, how often were you **woken by your asthma** during the night?	0 Never 1 Hardly ever 2 A few times 3 Several times 4 Many times 5 A great many times 6 Unable to sleep because of asthma
2.	On average, during the past week, how **bad were your asthma symptoms when you woke up** in the morning?	0 No symptoms 1 Very mild symptoms 2 Mild symptoms 3 Moderate symptoms 4 Quite severe symptoms 5 Severe symptoms 6 Very severe symptoms
3.	In general, during the past week, how **limited were you in your activities** because of your asthma?	0 Not limited at all 1 Very slightly limited 2 Slightly limited 3 Moderately limited 4 Very limited 5 Extremely limited 6 Totally limited

4. In general, during the past week, how much **shortness of breath** did you experience because of your asthma?	0 None 1 A very little 2 A little 3 A moderate amount 4 Quite a lot 5 A great deal 6 A very great deal
5. In general, during the past week, how much of the time did you **wheeze?**	0 Not at all 1 Hardly any of the time 2 A little of the time 3 A moderate amount of the time 4 A lot of the time 5 Most of the time 6 All the time

Appendix F Asthma Daily Diary

Asthma Diary as used in AZ studies (from NIMBUS, slight variations exists, eg asking about reliever instead of rescue medication)

Endpoint/Variable	Item/question	Response
Morning diary		
Asthma symptoms	Please describe your asthma symptoms during the night	0 = no asthma symptoms 1 = you are aware of your asthma symptoms but you can easily tolerate the symptoms 2 = your asthma is causing you enough discomfort to cause problems with normal activities (or with sleep) 3 = you are unable to do your normal activities (or to sleep) because of your asthma
Night-time awakenings	Did your asthma cause you to wake up last night?	Yes No
Rescue medication	Since bedtime, did you use rescue medication during the night to relieve your asthma symptoms?	Yes No
(if "yes")	Since bedtime, how many puffs of rescue medication did you take to relieve your asthma symptoms?	
Lung function	PEF/FEV_1	
Evening diary		

Asthma symptoms	Please describe your asthma symptoms since this morning	0 = no asthma symptoms 1 = you are aware of your asthma symptoms but you can easily tolerate the symptoms 2 = your asthma is causing you enough discomfort to cause problems with normal activities (or with sleep) 3 = you are unable to do your normal activities (or to sleep) because of your asthma
Rescue medication	Since this morning, did you use rescue medication during the day to relieve your asthma symptoms?	Yes No
(if "yes")	Since morning, how many puffs of rescue medication did you take to relieve your asthma symptoms?	
Lung function	PEF/FEV_1	

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