Clinical Study Protocol

Drug Substance	AZD8848
Study Code	D0540C00014
Edition Number	1
Date	

A double-blind, placebo controlled, randomised, parallel group phase IIa study to investigate the efficacy, tolerability, and safety of different dosing regimens of AZD8848 administered intranasally to seasonal allergic rhinitis patients out of pollen season in a nasal allergen challenge model

Sponsor: AstraZeneca AB, .

The following Amendment(s) and Administrative Changes have been made to this protocol since the date of preparation:

Amendment No.	Date of Amendment	Local Amendment No:	Date of Local Amendment

Administrative Change No.	Date of Administrative Change	Local Administrative Change No.	Date of Local Administrative Change

PROTOCOL SYNOPSIS

A double-blind, placebo controlled, randomised, parallel group phase IIa study to investigate the efficacy, tolerability, and safety of different dosing regimens of AZD8848 administered intranasally to seasonal allergic rhinitis patients out of pollen season in a nasal allergen challenge model

National Co-ordinating Investigator

Associate Professor

Study centre(s) and number of patients planned

Approximately 80 allergic rhinitis female and male patients out of pollen season will be randomised in order to reach 70 completed patients.

The study is planned to be carried out at the Hospital Departments of Otorhinolaryngology in Lund and Helsingborg, Sweden.

Study period	Phase of development
Estimated date of first patient enrolled	IIa
Estimated date of last patient completed	

Objectives

The primary objective of the study is to compare the efficacy of 60 µg AZD8848 once weekly with 20 µg AZD8848 three times weekly and with placebo when administered intranasally to seasonal allergic rhinitis patients out of season in a nasal allergen challenge model.

Secondary objectives of the study are:

- To investigate the tolerability and safety of AZD8848 administered intranasally up to three (3) times weekly for one (1) month to seasonal allergic rhinitis patients out of season
- To investigate the pharmacodynamic effects of AZD8848 on systemic and local biomarkers

- To investigate the influence of butyrylcholinesterase genotype on pharmacodynamic responses where appropriate.

Study design

This is a double-blind, placebo-controlled, randomised, parallel group phase IIa study performed out of pollen season in female and male patients with allergic rhinitis. The patients are randomised to one out of three treatment arms, ie,:

(a) 60 µg AZD8848 once weekly + placebo twice weekly

(b) 20 µg AZD8848 three (3) times weekly

(c) placebo three times (3) weekly.

The treatment period will be one month followed by a 7-day allergen challenge period.

Participation in the genetic research activities of the study is optional.

Target patient population

Randomised patients, aged 18 to 55 years, who have had birch and/or timothy grass pollen induced seasonal allergic rhinitis for at least the previous 2 years and need for treatment for nasal symptoms during the pollen season. They will show a reaction to a nasal allergen challenge out of pollen season.

Investigational product, dosage and mode of administration

AZD8848 will be provided as nasal spray solutions in 10 mL clear glass vials provided with a 50 µL spray pump and a nasal applicator.

AZD8848 and/or placebo will be administered three times weekly during 1 month (13 doses). One spray in each nostril will be counted as 1 dose.

Comparator, dosage and mode of administration

A matching placebo for AZD8848 nasal spray solution will be provided.

Duration of treatment

Three doses per week of AZD8848 and/or placebo will be given and the total treatment period will not exceed 1 month (27 to 31 days). The duration of patient participation in the study (including a long-term safety follow-up period) will be maximum 15 months.

Outcome variable(s):

- Efficacy:

  Reflective Total Nasal Symptom Score (TNSS) during allergen challenge

  Peak Nasal Inspiratory Flow (PNIF) during allergen challenge

- Pharmacodynamics:

  Blood: CXCL-10 (IP-10) and additional exploratory biomarkers (eg, IFN-γ, Tumour Necrosis Factor, IL-10 and mRNA expression of genes related to eg, IFN-α, T-helper cell phenotypes and inflammatory functions)

  Nasal lavage: CXCL-10 (IP-10), myeloperoxidase, α2-macroglobulin, tryptase, eosinophilic cationic protein (ECP) and additional exploratory biomarkers (eg,. IFN-γ, Tumour Necrosis Factor, IL-10 and mRNA expression of genes related to eg, IFN-α, T-helper cell phenotypes and inflammatory functions)

- Safety:

  Incidence and nature of Adverse Events

  Instantaneous Total Nasal Symptom Score (TNSS) during treatment period

  Peak Nasal Inspiratory Flow (PNIF) during treatment period

  Electrocardiogram parameters, blood pressure, pulse, physical examination, clinical chemistry, haematology, urinalysis, clinical inspection of the nose, auto-antibodies

Statistical methods

For efficacy and pharmacodynamic parameters, analysis of variance models will be used for comparison between treatments. Safety data will be summarized using descriptive statistics.

TABLE OF CONTENTS PAGE

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

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
AE	Adverse event (see definition in Section 6.4.1)
anti-dsDNA	anti-double stranded DNA
ANA	anti-Nuclear Antibodies
anti-PR3	anti-Proteinase 3
ALAT	Alanine aminotransferase
ASAT	Aspartate aminotransferase
BChE	Butyrylcholinesterase
CpG-ODN	CpG oligodeoxynucleotide
eCRF	Case Report Form (electronic)
CRP	C-Reactive Protein
CSA	Clinical Study Agreement
CSR	Clinical Study Report
CXCL-10 (IP-10)	Biomarker to indicate interferon production by TLR-7 agonist locally and systemically
DAE	Discontinuation of Investigational Product due to Adverse Event
DNA	Deoxyribonucleic acid
DUS	Disease under Study
ECG	Electrocardiogram
ECP	Eosinophilic Cationic Protein
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
GCP	Good Clinical Practice
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IFN-α	Interferon α
IL	Interleukin
IUD	Intra Uterine Device
IUS	Intra Uterine System

Abbreviation or special term	Explanation
IP	Investigational Product
ISF	Investigator's Study File
LIMS	Laboratory Information Management System
LLOQ	Lower Limit of Quantification
LPLV	Last Patient Last Visit
OAE	Other Significant Adverse Event (see definition in Section 11.2.1)
PGx	Pharmacogenetic research
PI	Principal Investigator
PNIF	Peak Nasal Inspiratory Flow
PoM	Proof of Mechanism
RF	Rheumatoid Factor
RNA	Ribonucleic Acid
SAE	Serious adverse event (see definition in Section 6.4.2).
SAD	Single Ascending Dose
TLR	Toll Like Receptor
TNF	Tumour Necrosis Factor
TNSS	Total Nasal Symptom Score
Tol/PoP	Tolerability and Proof of Principle
ULN	Upper Limit of Normal
WBDC	Web Based Data Capture
WOCBP	Women Of Child Bearing Potential

1. INTRODUCTION

1.1 Background

The incidence of asthma and rhinitis is increasing, especially in developed countries. A theoretical explanation for this increase is the "hygiene hypothesis", which proposes that childhood infections might be important for the maturation of the immune system. Vaccination, antibiotics, and improved sanitation have reduced the frequency of childhood infections, possibly leading to a less developed Type 1 immunity. This gives Type 2 immune responses the opportunity to become dominant and may result in allergic reactions to common environmental antigens, ie, allergens (Schaub B et al 2006).

Toll Like Receptors (TLR) plays a key role in the first line innate immune responses to microbes. The TLR7 is expressed in particular on B lymphocytes, monocytes/macrophages, and plasmacytoid dendritic cells. The role of the TLR7 is to detect infection by single stranded Ribonucleic Acid (RNA) viruses and mobilize Type 1 immune responses against the virus (Kawai T and Akira S 2006). Asthma and allergic rhinitis are associated with a Type 2 immune response to allergens, a response that can be inhibited by TLR7 agonists such as AZD8848. AZD8848 is intended for topical inhaled or intranasal treatment of asthma and allergic rhinitis. To minimize systemic exposure, and limit the potential for systemic immune activation, AZD8848 is designed as a metabolically labile ester, which is rapidly converted to a weakly active acidic form by butyrylcholinesterase (BChE) in plasma.

TLR7-induced inhibition of the Type 2 adaptive response to allergens has been demonstrated in both rat and human cells *in vitro*. In a rat allergic asthma model, as well as in a guinea-pig model of allergic rhinitis, AZD8848 showed comparable efficacy to steroids at inhibiting Type 2 cytokines and allergic airway inflammation. In addition, a clinical study in allergic rhinitis patients showed that AZD8848 improved nasal symptoms induced by allergen challenge. Thus, TLR7 agonists have a potential to become first-line treatment for prolonged control of asthma and allergic rhinitis. A study aiming to evaluate the clinical effect of AZD8848 in asthmatics is ongoing.

1.2 Research hypothesis

Administration of 20 µg AZD8848 three times weekly, as compared to 60 µg once weekly, will result in prolonged reduction of nasal symptoms after allergen challenge and/or increased tolerability to the substance.

1.3 Rationale for conducting this study

AZD8848 is currently in Phase I/IIa clinical development. The single ascending dose studies (carried out in Caucasian and Japanese subjects) indicated that single intranasal administration of up to 60 µg AZD8848, in healthy subjects and allergic rhinitis patients, was well tolerated and doses up to 600 µg were considered safe. The tolerability and proof of principle (Tol/PoP) study (D0540C00003) in allergic rhinitis patients indicated that 5 weekly intranasal

administrations of up to 60 µg AZD8848 was safe and tolerated and improved nasal symptoms 10 minutes after allergen challenge. Another study with AZD8848 is ongoing, aiming to evaluate the effect of eight weekly intranasal doses of AZD8848 on the late asthmatic response in mild to moderate allergic asthma patients challenged with inhaled allergen.

Results from preclinical and toxicology studies together with results from previous clinical studies are described in more detail in the Investigator's Brochure (IB).

The rationale for this study is to investigate whether increased frequency of dosing of AZD8848, at a lower dose level, results in prolonged reduction of nasal symptoms after allergen challenge and/or increased tolerability to the substance.

1.4 Benefit/risk and ethical assessment

The allergic rhinitis patients receiving active drug are not likely to benefit from participation in the study even if AZD8848 may ameliorate nasal symptoms induced by allergen challenge. Furthermore, since no drug will be available to patients after completion of the dosing period, follow-up treatment cannot be initiated.

Data from previous studies suggest that intranasal administration of single and multiple doses of AZD8848 is coupled, with some dose-dependency, to the appearance of mild to severe influenza-like symptoms (eg, headache, pyrexia, myalgia, malaise and chills) of a transient (12 to 48 hours post dose) and non-serious nature. The patients experiencing influenza-like symptoms responded well to paracetamol. Previous clinical experiences from studies with other TLR7 agonists, eg, Imiquimod, also indicate that influenza-like symptoms may arise. Should symptoms occur, they will be treated per standard medical practice, based on the judgment of the Investigator.

Analysis of safety data from the Tol/PoP (D0540C00003) study indicates that 5 weekly intranasal administrations of up to 60 µg AZD8848, in an allergic rhinitis population, is safe and tolerable. No signs of increasing response to repeated doses were observed. AZD8848 has previously been dosed up to 60 µg once weekly for up to 8 weeks in asthmatics (ongoing), and single doses up to 600 µg have been safely administered to healthy volunteers. In the present study, patients will receive repeated intranasal doses of 60 µg AZD8848 per week for one (1) month, administered as 60 µg once weekly, or as 20 µg three times weekly. Toxicology studies with alternate day dosing of AZD8848 for one month (14 doses) support 3 times weekly dosing. Further, twice weekly dosing for one month with the oral TLR7 agonist resiquimod, was found to be safe and tolerated in patients with hepatitis C (Pockros et al 2007), and a clinical trial in healthy volunteers found the TLR7 agonist 852a to be safe and tolerated when administered intravenously 3 times weekly for 2 weeks (Dudek et al 2007). In addition, the TLR7 agonist imiquimod is approved for local application 3 and 5 times weekly for the treatment of genital warts and basalioma, respectively. The adverse effects experienced after dosing up to five times weekly with imiquimod are of the same type as what

is seen after once weekly dosing of AZD8848, ie, influenza-like symptoms and local inflammatory reactions. This will be continuously monitored throughout the study.

TLR7 agonists could potentially contribute to the development of autoimmunity. In order to mitigate the potential risk for autoimmune reactions a cautious approach will be taken. Patients with a personal or family history of autoimmune disease will be excluded from taking part in the study and patients will be screened for anti-PR3 and excluded if detectable titres are found. Furthermore, all patients will be included in a long-term safety follow-up for 11 to 13 months after last dose (for further details see Section 3.2).

This is one of the first studies with AZD8848 to include females. Toxicology studies (including reproductive toxicity studies) and safety pharmacology studies conducted to date indicate that there are no findings that preclude intranasal administration to female or male patients with allergic rhinitis, provided sufficient contraceptive protection is used and pregnancy testing conducted as described in this document. There is no indication that AZD8848 may be associated with any clinically relevant drug – drug interactions with contraceptives. This supports that women of child-bearing potential can be included in the early (Phase I/IIa) clinical trials.

An aqueous nasal spray will be used for the study. The major mass fraction of such a spray is contained in large droplets with near-zero probability of entering the lung. However, a small fraction with small droplets is also produced. Normal instructions for aqueous nasal sprays are to inhale through the nose (sniffing) while spraying. Although scintigraphic measurements following intranasal aqueous sprays found no deposition in the lungs (Newman et al 1987, Suman et al 1999), there is a theoretical risk that a small percentage of the nasal dose could reach the lungs using the standard manoeuvre. Therefore, the procedure will be to instruct patients to orally exhale against a resistance in order to close connection between the lungs and the nasal airways. During this manoeuvre, the study personnel will administer the spray. Patients will practice before being given study drug to ensure proficiency with the manoeuvre. With this dosing procedure, the risk for pulmonary exposure of the drug is considered negligible.

By close monitoring in a controlled setting, the risks to the patients have been minimised. Thus the study is considered to be ethically justified and will give scientifically valuable information which will enable prudent and safe exposure of patients in this study and in subsequent clinical trials with this compound.

An overall risk benefit assessment of AZD8848 can be found in the IB.

2. STUDY OBJECTIVES

2.1 Primary objective

Table 1 Primary Objective

To compare the efficacy of 60 µg AZD8848 once weekly with 20 µg AZD8848 three (3) times weekly and with placebo when administered intranasally to seasonal allergic rhinitis patients out of season in a nasal allergen challenge model.

Variables	Description
Reflective Total Nasal Symptom Score (TNSS) (recall period 12 h, twice daily during Visit 15)	Nasal symptoms
Reflective TNSS (recall period 10 min) after allergen challenge	Nasal symptoms
Peak Nasal Inspiratory Flow (PNIF) (twice daily during Visit 15)	
PNIF 10 min after allergen challenge	

2.2 Secondary objectives

Table 2 Secondary Objective 1

To investigate the tolerability and safety of AZD8848 administered intranasally up to three (3) times weekly for one month to seasonal allergic rhinitis patients out of season.

Variables	Description
Incidence and nature of adverse events	
Instantaneous TNSS and PNIF during treatment	Nasal symptoms
Electrocardiogram parameters, blood pressure, pulse, physical examination, clinical chemistry, haematology, urinalysis, clinical inspection of the nose, auto-antibodies	

Table 3 Secondary Objective 2

To investigate the pharmacodynamic effects of AZD8848 on systemic and local biomarkers.

Variables	Description
CXCL-10 (IP-10) in nasal lavage and blood	Local and Systemic Proof of Mechanism (PoM) marker
Myeloperoxidase, α2-macroglobulin, tryptase and eosinophilic cationic protein (ECP) in nasal lavage	Indication of activation of local inflammatory processes
Soluble immune/inflammatory proteins in nasal lavage and blood, e.g. IFN-γ, Tumour Necrosis Factor (TNF), IL-10	Indication of changed immune responses locally and systemically.
mRNA expression in nasal lavage and blood, e.g. genes related to IFN-α, T-helper cell phenotypes and inflammatory functions	Indication of changed immune responses locally and systemically.

Table 4 Secondary Objective 3

To investigate the influence of butyrylcholinesterase genotype on pharmacodynamic responses where appropriate.

Variables	Description
Butyrylcholinesterase genotypes	

2.3 Safety objective (Not applicable)

2.4 Exploratory objectives (Not applicable)

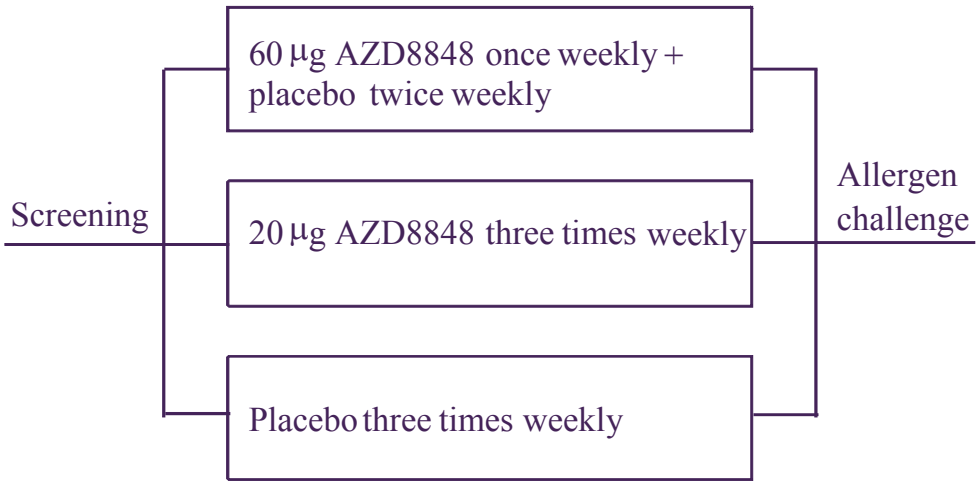
3. STUDY PLAN AND PROCEDURES

This Clinical Study Protocol has been subject to a peer review according to AstraZeneca standard procedures.

3.1 Overall study design and flow chart

This is a double-blind, placebo-controlled, randomised, parallel group phase IIa study performed out of pollen season in female and male patients with allergic rhinitis. The patients are randomised to one out of three treatment arms in a 1:3:1 ratio (60µg once weekly: 20µg three times weekly: placebo), see Figure 1. Approximately 80 patients with allergic rhinitis will be randomised in order to reach 70 completed patients.

Figure 1 Overview of treatment arms



Data will be pooled with data from the Tol/PoP study (D0540C00003) for efficacy analysis (See Section 12.2).

The study will be performed at the Hospital Departments of Otorhinolaryngology in Lund and Helsingborg.

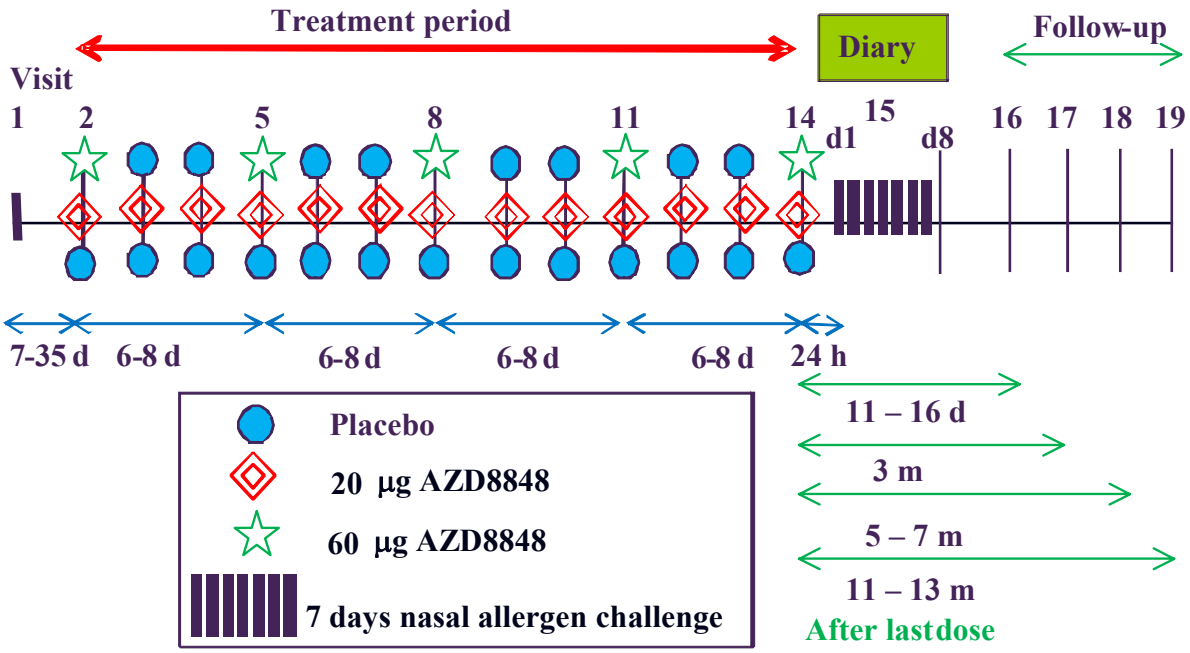
The treatment period lasts for one month and is followed by a 7-day allergen challenge period and a long-term safety follow-up period. The total duration of patient participation in the study (including the long-term safety follow-up) will be maximum 15 months.

Participation in the genetic research activities of the study is optional

3.1.1 Study visits

Figure 2 and Table 5 for an overview of the study visits and study assessments.

Figure 2 Study visits



Visits 1 to 16 and 18 are policlinic visits. Visits 17 and 19 are telephone contacts.

Visit 1-Enrolment
Visit 1 is an enrolment visit where Patient Informed Consent will be obtained and patient eligibility criteria will be established. Visit 1 assessments may take place during more than 1 day. Allergen titration will be performed according to Section 6.2.7.

Visits 2 to 14 – Treatment
AZD8848 or placebo is administered intranasally. Dosing constraints are three weekly (within 6-8 days) doses with at least 44 hours in between and total treatment period is one month (27-31 days). The treatment will be given in the morning and preferably at the same time-points at each dosing occasion.

Visits 2 to 14 are treatment visits where the patients will be resident in the clinic at least until safety assessments are performed, ie, 15 minutes after dosing. The residential time will be longer at visits including other than safety assessments, for details see Table 6.

A dose must not be given if the patient has a medical condition (eg, cold, ongoing nasal bleeding, clinically important nasal ulcer) that may jeopardise the well-being of the patient as judged by the Investigator. If a dose is not given, the reason should be recorded in the medical record.

If, for any reason, a patient misses one or more doses, he/she may still continue in the study and receive the remaining doses, if found appropriate by the Investigator and AstraZeneca. Should this occur, timings for safety assessments for such a patient may be rescheduled by the Investigator to ascertain that individual safety not is compromised.

Visit 15 - Allergen challenge
The allergen challenge will start approximately 24 h after last dose (see Table 7). The patients will be challenged with the individually titrated dose of birch or timothy grass pollen once daily in the morning for 7 days. For details regarding allergen titration see Section 6.2.7. For nasal symptom evaluation, TNSS will be recorded 10 minutes after allergen challenge (recall period 10 minutes), and in a diary twice daily at 12 and 24 h after each challenge (recall periods of 12 h). PNIF will be recorded at the same time points as TNSS.

Nasal lavage and blood samples will be collected according to Table 7.

For details regarding TNSS and PNIF see Section 6.3.2 and Section 6.3.3. For details regarding nasal lavage, see Section 6.7.2.

Visit 16 – Treatment follow-up
The primary follow-up will be performed at 11-16 days after last study drug administration.

Visit 17 – Safety follow-up (Women Of Child Bearing Potential (WOCBP) only); telephone contact
A telephone contact to be scheduled 3 months after last dose of study drug to collect contraceptive history and the result of a pregnancy test taken at home (urine dipstick to be provided in advance).

Visit 18 – Long-term safety follow-up
Safety evaluation, including blood sampling for auto-antibody analyses, will be performed 5 to 7 months after last dose of study drug.

Visit 19 – Long-term safety follow-up (telephone contact)
Safety evaluation will be performed 11 to 13 months after last dose of study drug.

Table 5 gives an overview of the study assessments

Table 6 shows a detailed scheme of the study assessments during treatment (V2 to V14)

Table 7 shows a detailed scheme of the study assessments during allergen challenge (V15)

Table 5 Overview of Study Assessments

Assessment	Enrolment	Treatment	Allergen challenge	Treatment follow-up	Safety follow-up (3 m, WOCBP only)	Long-term safety follow-up (5-7 m)	Long-term safety follow-up (11-13 m)
	Visit 1	Visits 2-14	Visit 15	Visit 16	Visit 17	Visit 18	Visit 19
Run-in assessments[a]	X						
Contraceptive history (WOCBP only)	X	X	X	X	X		
Pregnancy test[b]	X	X (V2, V8)[b]	X[b]	X[b]	X[b]		
Skin Prick Test[c]	X						
Allergen titration	X						
BChE activity	X						
Pulse, blood pressure	X			X			
Clinical inspection of nose[d]	X			X			
Physical examination	X			X			
ECG	X			X			
Concomitant medication	X	X	X	X		X[e]	X[e]
Eligibility criteria	X	X (V2)					
Drug of abuse test and alcohol breath test	X	X (random once)					
Clinical chemistry, haematology	X[f]	X (V2, V5, V8)	X (Day 2)	X			
Differential blood cell count			X (Day 1, 4, 8)				

Table 5 Overview of Study Assessments

Assessment	Enrolment	Treatment	Allergen challenge	Treatment follow-up	Safety follow-up (3 m, WOCBP only)	Long-term safety follow-up (5-7 m)	Long-term safety follow-up (11-13 m)
Urinalysis	X			X			
Blood for auto-antibodies (ANA, RF, dsDNA)[g]	X	X (V8)		X		X	
Blood for non-predefined auto-antibodies	X					X	
Allocation of randomisation code		X (V2)					
Administration of study drug		X[h]					
Blood for pharmacogenetics		X[i]	(X)	(X)			
Adverse Events		X	X	X		X[j]	X[j]
Nasal lavage[k]; mRNA + soluble biomarkers		X (V2)	X (Day 1, 8)				
Blood; mRNA		X (V2, V3, V5, V8, V12, V14)	X (Day 1, 2, 4, 8)				
Blood; soluble biomarkers		x (V2)	x (Day 1, 8)				
Instantaneous TNSS and PNIF		X(V2, V5, V8, V11)					
Allergen challenge			X				
Reflective TNSS (recall period 10 min, recall period 12 h twice daily), PNIF in diary			X				

a Enrolment assessment: informed consent, allocation enrolment code, demography, medical and surgical history including respiratory disease, height, weight, Human Immunodeficiency Virus (HIV), hepatitis B and C test, screening for anti-PR3 auto antibodies

b The results of the tests prior to dosing (V2 and V8) must be available before drug administration. Women of non-child bearing potential will make pregnancy test only at Visits 1, 2, and 16

c Skin prick test will only be performed in the absence of a documented skin prick test within the previous 24 months

d Clinical inspection of the nose should also be performed upon symptoms

e Only vaccinations and, in case of serious adverse event (SAE), any concomitant medication from start date of SAE until stop date of SAE should be collected

f Including Follicle-stimulating hormone (FSH) and Luteinizing hormone (LH) at Visit 1 for females of non-childbearing potential under 50 years old to be able to confirm that they are of non-childbearing potential and thereby not need any contraceptives

g The results of these samples will not be available to the Investigator or AstraZeneca during the study. The samples will be evaluated after the last sample (in the study) has been drawn. Samples should be collected prior to dose

h Training of study drug administration to be performed at Visit 2

i Optional, to be taken at any visit between randomisation and Visit 16

j Only data on SAEs will be recorded at Visit 18 and at the telephone contact (Visit 19). Auto Immune Disease diagnosis or suspected symptoms or medication suggesting treatment of such disease, irrespective of severity, should be reported as an SAE

k At Visit 2 only saline nasal lavage is collected. During Visit 15 lavages are performed first with saline and thereafter with addition of histamine

Table 6 Detailed scheme of Study Assessments during Visits 2 to 14

Assessment	Pre-dose	0	15 min
Eligibility criteria + Randomisation	X (V2)		
Contraceptive history (only WOCBP)	x		
Pregnancy test [a]	X (V2, V8)		
Adverse Events	X		X
Administration of study drug		X	
Clinical chemistry, haematology	X (V2, V5, V8)		
Blood for auto-antibodies (ANA, RF, dsDNA)	X (V8)		
Instantaneous TNSS, PNIF	X (V2, V5, V8, V11)		X (V2, V5, V8, V11)
Nasal lavage[b]; mRNA + soluble biomarkers	X (V2)		
Blood; mRNA	X (V2, V3, V5, V8, V12, V14)		
Blood; soluble biomarkers	X (V2)		

a The result of the test must be available before drug administration. Women of non-child bearing potential will make pregnancy test only at Visit 2

b At Visit 2 only saline nasal lavage is collected

Table 7 Detailed scheme of Study Assessments during allergen challenge, Visit 15

Assessment	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8
Allergen challenge[a]	X	X	X	X	X	X	X	
Contraceptive history[b]	X	X	X	X	X	X	X	X
Pregnancy test[b]	X							
Reflective TNSS[c] (recall period 10 min), PNIF	X	X	X	X	X	X	X	
Clinical chemistry, haematology		X						
Differential blood cell count	X[d]			X				X
Blood; mRNA	X[d]	X		X				X
Blood; soluble biomarkers	X[d]							X
Nasal lavage[e]; mRNA + soluble biomarkers	X[d]							X
Reflective TNSS (recall period 12h twice daily) + PNIF in patient diary	X	X	X	X	X	X	X	X

a After sampling of blood and nasal lavage

b Only women of child bearing potential

c To be measured once daily 10 min after allergen challange

d 24 h after last dose of AZD8848, but prior to allergen challenge

e During Visit 15 lavages are performed first with saline and thereafter with addition of histamine

3.2 Rationale for study design, doses and control groups

Allergic rhinitis patients are included to generate data in one of the potential target populations. A double-blind design is selected to avoid bias resulting from knowledge of the treatment by either patients or centre staff. A randomised placebo control arm is included to obtain reference data to aid interpretation of efficacy, safety, and tolerability. A parallel group design has been chosen to avoid the influence of a potential drug-induced prolonged response (carry-over effect).

The allergen challenge model and the primary endpoints have been chosen to determine if AZD8848 controls nasal inflammation and decreases nasal symptoms. Analysis of local and systemic biomarkers may generate data on mechanisms of action of AZD8848.

AZD8848 is a metabolically labile ester, which is rapidly converted to a weakly active acidic form of the molecule by butyrylcholinesterase cleavage. To ensure that only patients with the ability to rapidly convert AZD8848 are included in the early clinical studies, *in vitro* screening of BchE activity will be performed before inclusion. This ensures low systemic exposure and limits the potential for systemic immune activation. However, type 1 interferons produced as a consequence of TLR7 activation will have a systemic distribution. In order to mitigate the potential risk for subsequent autoimmune reactions a cautious approach will be taken: Patients with a personal or family history of autoimmune disease will be excluded from taking part in the study and patients will be screened for anti-PR3 and excluded if detectable titres are found. All patients who receive AZD8848 will donate blood samples for determination of autoantibody titers of ANA, RF and dsDNA to be able to detect and define the potential risk of autoimmune reactions. The results of these samples will not be available to the Investigator during the study, but will be evaluated after the last sample in the study has been drawn. Furthermore, all patients will donate blood samples at baseline and 5 to 7 months after last dose for possible retrospective determination of autoantibody titres. At the long-term safety follow-up visit 5 to 7 months after last dose, and at the scheduled investigator telephone contact 11 to 13 months after last dose, diagnoses, symptoms or medication suggestive of autoimmune activation will be collected and patients presenting with such safety signals will be further investigated for diagnosis of autoimmune disease.

Fewer patients will be randomised to the 60 µg once weekly and placebo arms, than to the 20 µg three times weekly arm, since these arms will be pooled with data from the Tol/PoP study. See Section 1.4 for rational for dose selection.

AZD8848 is intended for asthma and allergic rhinitis, and a significant proportion of this population is female. Reproductive toxicology studies do not preclude the inclusion of women of child-bearing potential, provided that adequate contraceptive protection is used and pregnancy testing is conducted. As a consequence, both male and female patients will be included in this study.

AstraZeneca intends to perform genetic research in the AZD8848 clinical development programme to explore how genetic variations may affect the clinical parameters associated

with AZD8848. Collection of Deoxyribonucleic Acid (DNA) samples from populations with well described clinical characteristics may aid in the identification of future drug targets and projects to validate identified targets. Future research may suggest other genes or gene categories as candidates for influencing not only response to AZD8848 but also susceptibility to allergic rhinitis for which AZD8848 may be evaluated. Thus, this genetic research may involve study of additional unnamed genes or gene categories, but only as related to disease susceptibility and drug action.

4. PATIENT SELECTION CRITERIA

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

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.

4.1 Inclusion criteria

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

1. Provision of signed and dated informed consent prior to any study specific procedures

2. Female and/or male patients, aged 18 to 55 years inclusive. Females must be of non-childbearing potential (for definition see Section 5.1.1) or must have been stable on highly effective contraceptive method (see Section 5.1.2) for at least 3 months prior to Visit 1 and be willing to continue on the chosen method, with additional use of a condom by male partner, until 3 months after the last dose

3. Females must have a negative pregnancy test and a date of last menstruation consistent with non-pregnancy at Visit 1

4. Have a body mass index (BMI) between 19 and 30 kg/m^2 and a weight between 50 and 100 kg

5. Seasonal allergic rhinitis patients out of pollen season

6. Have a history of birch and/or timothy grass pollen induced seasonal allergic rhinitis for at least the previous 2 years

7. Have presence of allergic sensitivity to birch and/or timothy grass pollen verified by a positive skin prick test documented within the previous 24 months or at Visit 1

8. Have a need of treatment for their nasal symptoms during the pollen season

9. Have reaction to an individually titrated dose of nasal allergen resulting in at least 5 sneezes and/or recorded score of 2 or more on a scale from 0 to 3 in either of the symptoms nasal blockage or runny nose

10. Be able to metabolise AZD8848 (an *in vitro* screening assay will determine BChE activity in a blood sample taken at Visit 1 using a pre-defined limit)

For inclusion in the genetic component of the study, patient must fulfill the following criterion:

11. Provision of informed consent for genetic research.

If a patient declines to participate in the genetic component of the study, there will be no penalty or loss of benefit to the patient. The patient will not be excluded from other aspects of the study as long as they are consenting to the main study.

4.2 Exclusion criteria

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

1. Any clinically relevant disease and/or abnormality (past or present), which, in the opinion of the Investigator, may either put the patient at risk because of participation in the study, or influence the results of the study, or the patient's ability to participate in the study

2. Any clinically relevant abnormal findings in physical examination, clinical chemistry, hematology, urinalysis, vital signs, or ECG at baseline which, in the opinion of the Investigator, may put the patient at risk because of participation in the study

3. QTcF > 450 ms (confirmed with repeated measurements) at Visit 1

4. Rhythm, conduction (e.g. intermittent or constant Bundle branch block; Intraventricular conduction disturbance with repolarization changes; intermittent or constant AV block [including 1st degree AV block with PR interval > 220 msec, 2nd or 3rd degree AV block]); or morphologic changes affecting repolarization (eg, flat, biphasic or inverted T waves in primary lead V2), that may limit ability to measure QTc and assess changes in QTc intervals or QTc morphology

5. History of additional risk factors for Torsade de pointes (eg, heart failure, hypokalemia, family history of Long QT syndrome, or sudden death)

6. Medical history suggesting or confirming abnormal immune function, apart from allergic rhinitis

7. Family history (parent or sibling) of autoimmune disease including, but not limited to, Wegeners granulomatosis, systemic lupus erythematosus, rheumatoid arthritis, Sjögren´s syndrome, multiple sclerosis, autoimmune thrombocytopenia, primary biliary cirrhosis, Mb Crohn, ulcerative colitis, type 1 diabetes or other autoimmune disease considered relevant by the Investigator

8. History of asthma

9. Symptomatic perennial allergic or non-allergic rhinitis, except for cat and dog sensitivity under the condition that these patients will not be exposed to cats and dogs during the study up until Visit 16, as judged by the Investigator

10. History of or ongoing immunotherapy, including but not limited to specific immunotherapy (SIT)

11. Topical or inhaled glucocorticosteroid treatment within 1 month prior to Visit 1

12. Systemic glucocorticosteroid therapy for any reason during 6 weeks prior to Visit 1

13. Antihistamine treatment within 1 week prior to Visit 1

14. Use of any medication (including vaccinations, over-the-counter drugs, herbal medicines and nutritional supplements,) or therapy within 2 weeks prior to Visit 2 (or longer if the medication has a half-life long enough to potentially expose the patient to any significant systemic exposure that may interfere with the objectives of the study or the safety of the patients) as judged by the Investigator, except for occasional intake of paracetamol

15. Suspicion of Gilbert's syndrome

16. A suspected/manifested infection according to World Health Organisation (WHO) risk groups 2, 3, or 4, see Appendix E

17. Positive results on screening tests for serum Hepatitis B surface antigen, Hepatitis C antibodies, and/or HIV

18. Any upper respiratory tract infection (bacterial, viral or fungal infections of the airways) or any other clinically significant illness within 2 weeks prior to Visit 2 being symptomatic enough to affect study conduct or the wellbeing of the patient as judged by the Investigator

19. Structural abnormalities of the nose or nasal disorder symptomatic enough to cause significant nasal obstruction as judged by the Investigator

20. Known or suspected hypersensitivity to investigational drug or any excipients

21. Definite or suspected personal history of significant adverse drug reactions/any anaphylactic reaction

22. Use of drugs with CYP3A4 enzyme inducing properties, including herbal medicines such as St John's Worth, within 3 weeks prior to Visit 2

23. History of or current alcohol and/or drug abuse, as judged by the Investigator, or positive drugs of abuse test

24. Planned surgery, dental procedure, or hospitalization during the study, and/or major surgery or significant trauma within 3 months of Visit 1

25. Participation in another study within 3 months before the start of the present study (or within 1 month for methodology studies in which no drugs were administered)

26. Donation of blood within 2 months prior to Visit 1 or donation of more than 1350 mL within 12 months prior to Visit 1

27. Patients who, in the opinion of the Investigator, should not participate in the study

28. Pregnancy or lactation

29. Detection of anti-PR3 autoantibodies in the blood

30. Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study centre)

31. Previous randomisation of treatment in the present study

32. History of habitual nicotine use equivalent to 10 or more pack years (1 pack year = 20 cigarettes smoked per day), as judged by the Investigator

The following is regarded as a criterion for exclusion from the genetic component of the study:

33. Previous allogeneic bone marrow transplant

34. Non-leukocyte depleted whole blood transfusion in 120 days of genetic sample collection.

Procedures for withdrawal of incorrectly randomised patients see Section 5.3.

5. STUDY CONDUCT

5.1 Restrictions during the study

Patients will be required to:

1. Abstain from scheduled in-patient surgery or hospitalisation from Visits 1 to 16
2. Abstain from taking any medication other than specified in Section 5.6
3. Abstain from drugs of abuse
4. Abstain from alcohol during Visit 1 and for 48 hours prior to and during Visits 2, 5, 8, 15, and 16 (safety blood sampling visits)
5. Abstain from strenuous physical activity that is not within the patient's normal weekly routine (eg, weight lifting, fitness room exercise, and contact sports) during Visit 1 and for 48 hours prior to and during Visits 2, 5, 8, 15, and 16
6. Abstain from visiting geographical areas with high endemic risk for serious infectious, bacterial or viral, or parasitic disease during the study (from Visit 1) and until 1 month after Visit 16
7. Abstain from taking vaccination during the study and for one month after last study drug administration
8. Abstain from donation of blood or plasma during the study (from Visit 1) until 3 months after Visit 16
9. Women of childbearing potential should use a highly effective contraceptive method (See Section 5.1.2), with additional use of condom by male partner, to prevent pregnancy from Visit 1 until 3 months after last dose
10. Male patients should avoid unprotected intercourse from first dose until Visit 16 plus 1 week with pregnant women and from first dose until Visit 16 plus 3 weeks with WOCBP not using birth control, and avoid sperm donation
11. Abstain from participation in another clinical study during the study (from Visit 1) and until Visit 18.

5.1.1 Women of non-childbearing potential

Females are considered to be of non-childbearing potential if they meet one of the following criteria:

- Aged < 50 years and have been amenorrheic for 12 months or more, without an alternative medical cause, following cessation of sex hormone treatment and with

Luteinizing hormone (LH) and Follicle-stimulating hormone (FSH) levels in the post-menopausal range as defined by the laboratory

- Aged ≥ 50 years and have been amenorrheic for 12 months or more, without an alternative medical cause, following cessation of sex hormone treatment
- Permanent sterilisation by hysterectomy and/or bilateral oopherectomy and/or bilateral salpingectomy (bilateral tubal occlusion excluded).

5.1.2 Highly effective contraceptive methods

Women of childbearing potential must use a highly effective contraceptive method with additional use of a condom by male partner. The following contraceptive methods are considered to be highly effective:

- Total sexual abstinence
- Vasectomised sexual partner (with participant assurance that partner received post-vasectomy confirmation of azoospermia)
- Tubal occlusion
- Intra Uterine Device (IUD) (provided coils are copper banded)
- Intra Uterine System (IUS) containing Levonorgestrel (eg, Mirena®)
- Medroxyprogesterone injections (eg, Depo-Provera®)
- Etonogestrel slow-release subcutaneous implants (eg, Implanon® , Norplan®)
- Normal or low dose combined oral contraceptives (COCs) with fixed doses of estrogen and progestin. Note: Triphasic pills, which have different strength pills in the same pack, are not considered highly effective and are therefore excluded from this instruction
- Norelgestromin/ethinyl estradiol transdermal system (eg, Evra®)
- Intravaginal device containing ethinyloestradiol and etonogestrel (eg, NuvaRing®)
- Cerazette®

Women of childbearing potential must have been stable on a highly effective contraceptive method for at least 3 months prior to Visit 1 and continue on this chosen method, with additional use of a condom by male partner, until 3 months after last dose.

Vomiting within 3 hours of taking oral contraception does pose a risk equivalent to a missed pill. Patients will be instructed to contact the Investigator on how to follow the WHO guidelines (WHO 2004) for a missed pill whenever they suspect unprotected intercourse.

Patients should be made aware of the availability of emergency "post-coital" contraception if there is an indication for it (e.g. missing IUD threads or a late injection).

Birth control method will be verified in medical records prior to study start (contraceptive history) and WOCBP will be asked to verify compliance at each visit up to 3 months after last dose (Visit 17).

5.1.3 Unacceptable contraceptive methods

The following methods are considered not to be highly effective and are therefore not acceptable contraceptive methods in AstraZeneca clinical trials:

- Triphasic COCs
- All progesterone only pills except Cerazette™
- All barrier methods, if intended to be used alone
- Non copper containing IUDs
- Fertility awareness methods
- Coitus interruptus.

5.2 Patient enrolment and randomisation and initiation of investigational product

The Principal Investigator or delegate 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', followed by 7 digits
3. Determine patient eligibility. See Sections 4.1 and 4.2
4. Assign eligible patient unique randomisation code (patient number).

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

If a patient discontinues his/her participation in the study after randomisation, he/she cannot re-enter into the study.

5.2.1 Procedures for randomisation

The randomisation code will be assigned from a randomisation list generated by the computer software Global Randomisation System at AstraZeneca. The randomisation will be in blocks.

The patients will be randomised to receive AZD8848 60 µg once weekly, AZD8848 20 µg three times weekly or placebo in the proportions 1:3:1.

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

5.3 Procedures for handling patients incorrectly enrolled, randomised or initiated on investigational product

Patients who fail to meet the inclusion/exclusion criteria should not, under any circumstances, be randomised. There can be no exceptions to this rule.

Where patients have been incorrectly randomised but not yet initiated on treatment, the patient must be discontinued from the study.

Where patients that do not meet the selection criteria are randomised in error or incorrectly started on treatment or where patients subsequently fail to meet the study criteria post initiation, a discussion should occur between the AstraZeneca Study Delivery Team Physician and the Investigator regarding whether to continue or discontinue the patient from treatment or whether replacement should be considered. If treatment is discontinued, the patient should continue assessments to ensure the safety of the patient (see further Section 5.8.1). The AstraZeneca Study Delivery Team Physician is to ensure all such decisions are appropriately documented. In situations where an agreement cannot be reached, the patient should have their study therapy stopped.

5.4 Blinding and procedures for unblinding the study

5.4.1 Methods for ensuring blinding

The study will be randomised and double-blind. The randomisation will be carried out in such a way that the patients will receive either AZD8848 or placebo treatment. All packaging and labelling will be performed in such a way to ensure blinding and the 2 treatments, AZD8848 and placebo, will be of identical appearance.

The following personnel will have access to the randomisation list:

- The personnel generating the randomisation list
- The personnel carrying out packaging and labelling of Investigational Product

- The personnel creating the reporting database

The information in the randomisation list must be kept from other AstraZeneca personnel involved in the conduct of the study in a secure location until clean file.

5.4.2 Methods for unblinding the study

Individual treatment code envelopes, indicating the treatment randomisation for each randomised patient, will be available to the Investigator at the study centre.

The treatment code envelopes 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. Patients, for whom the treatment code has prematurely been broken by the Investigator, should be asked to complete the follow-up visits (Visits 16, 17 [only WOCBP], 18, and 19).

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 up to and including Visit 16 until all decisions on the evaluability of the data from each individual patient have been made and documented.

The treatment code envelopes must be kept in a secure but accessible place.

5.5 Treatments

5.5.1 Identity of investigational product(s)

AZD8848 and matching placebo will be administered as nasal spray solutions.

The AZD8848 nasal spray solution and placebo will be filled into individual 10 mL clear glass vials provided with a 50 µL spray pump and a nasal applicator for each randomised patient (see Table 8 for further details).

Table 8 Identity of Investigational Product(s)

Investigational product	Dosage form and strength	Manufacturer
AZD8848 Nasal spray	Solution, 0.6 mg/mL	AstraZeneca
AZD8848 Nasal spray	Solution, 0.2 mg/mL	AstraZeneca
Placebo AZD8848 Nasal spray	Solution	AstraZeneca

The investigational product contains AZD8848, sodium chloride, benzalkonium chloride solution, citric acid anhydrous, sodium citrate, hydrochloric acid (concentrated), sodium hydroxide and water purified. The placebo product has the same composition, except for AZD8848.

5.5.2 Doses and treatment regimens

Each patient will receive AZD8848 and/or placebo administered three times weekly during 1 month (13 doses). One spray in each nostril will be counted as 1 dose.

At Visit 2 the patients will be randomised to receive either AZD8848 and/or placebo to 1 out of 3 treatment arms:

(a) 60 µg AZD8848 once weekly + placebo twice weekly

(b) 20 µg AZD8848 three (3) times weekly

(c) placebo three (3) times weekly

Randomised study drugs will be administered at Visits 2 to 14.

One box containing three vials of AZD8848/placebo will be allocated to each patient. Each vial will be marked with visit numbers and the administration of the dose for each visit will be documented in the eCRF. Each of the three bottles are used once a week according to the visit number printed on label in order to get the correct dosing regimen without unblinding the study.

The patients will practice study drug administration technique at Visit 2 before dosing using placebo nasal spray solution.

Study drug administration will be performed at the clinic according to separate instructions in the Manual of Procedures. Briefly, the individual nasal spray vials will be primed according to separate instructions before study drug administration. The Investigator or study nurse will instruct the patient to orally exhale against a resistance to close the connection between the lungs and the nasal airways. During this manoeuvre the Investigator or study nurse will administer the spray. One spray will be administered in each nostril.

The following precautions will be taken to reduce the risk of contamination:

- Patients and personnel involved in study drug administration will wear protective gloves and clothing
- Study drug administration including priming will be performed in a separate room equipped with a fume chamber. Study drug should not be administered in the same room where blood sampling is performed

5.5.3 Labelling

The packaging and labelling will be performed at AstraZeneca R&D Lund, Sweden or AstraZeneca R&D Mölndal, Sweden. All supplies and labels will be in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. The labels will fulfil GMP Annex 13 requirements for labelling. Label text will be translated into local language.

Nasal spray vials containing placebo to be used for practise will have a label with a blank field for the E-code to be filled in by the study personnel, and the vials will be packed in a box.

5.5.4 Storage

All investigational products must be kept in a secure place under appropriate storage conditions. The investigational product label on the bottle specifies the appropriate storage conditions.

5.6 Concomitant and post-study treatment(s)

Medications not allowed before and during the study are:

- Immunotherapy (including but not limited to SIT) is not allowed before the study and until Visit 16
- Topical or inhaled glucocorticosteroid treatment within 1 month prior to Visit 1 and until Visit 16
- Systemic glucocorticosteroid therapy for any reason during 6 weeks prior to Visit 1 and until Visit 16
- Antihistamine treatment within 1 week prior to Visit 1 and until Visit 16, except reliever medication provided by the clinic
- Use of any medication (including over-the-counter drugs, herbal medicines and nutritional supplements) or therapy within 2 weeks prior to Visit 2 (or longer if the medication has a half-life long enough to potentially expose the patient to any significant systemic exposure that may interfere with the objectives of the study or the safety of the patients) as judged by the Investigator, and until Visit 16, except for occasional intake of paracetamol
- Use of drugs with CYP3A4 enzyme inducing properties, including herbal medicines such as St John's Worth, within 3 weeks prior to Visit 2 and until Visit 16. For WOCBP using hormonal contraceptives, these medicines are not allowed until Visit 17.

Medication allowed during the allergen challenge period (Visit 15) is:

- Occasional use of antihistamine tablets (Loratadine) for symptom relief, which will be provided by the Investigator on patient request

Medication allowed during the study:

- Influenza-like symptoms that may be induced by AZD8848, respond well to paracetamol. Occasional intake of paracetamol is allowed in the study but must be reported to the Investigator.

Other medication, which is considered necessary for the patient's safety and well being, may be given at the discretion of the Investigator .All concomitant medication will be recorded in the appropriate sections of the electronic Case Report Form (eCRF).

During the long-term safety follow-up period (i.e. after Visit 16) there are no restrictions regarding medication (except for WOCBP, which have restrictions up until Visit 17). At Visit 18 and Visit 19, data regarding any vaccinations and, in case of SAE, medications from start date of SAE until stop date of SAE will be collected.

5.7 Treatment compliance

The administration of all study drugs (including investigational products) must be recorded in the appropriate sections of the eCRF.

Compliance will be assured by administration of the investigational product by the Investigator or his/her delegate. Study drug administration will be practised at Visit 2, before first study drug administration to ensure proficiency with the manoeuvre.

5.7.1 Accountability

The study drug provided for this study is for use only as directed in the clinical study protocol. At completion of the study, unused investigational products will be destroyed appropriately at the Hospital Pharmacy by authorized personnel according to approved procedures. The study personnel will account for all drugs dispensed. Certificate of delivery, destruction, and return must be signed.

5.8 Discontinuation of investigational product

Patients may be discontinued from investigational product (IP) 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 to study protocol

- Incorrectly randomised patients
- Pregnancy

Study specific reasons to consider discontinuation of a patient are:

- TNSS ≥ 7 (not considered during the allergen challenge period) (confirmed by a new assessment)
- A reduction in PNIF of ≥ 50 % compared with baseline measurement pre-dose at Visit 2 in the absence of other explanations not related to treatment as judged by the Investigator (not considered during the allergen challenge period) (confirmed by a new assessment)
- A fall in haemoglobin below 115 g/L (male) or 105 g/L (female) or a fall of 20 g/L or more from baseline measurement pre-dose at Visit 2; or a fall in haematocrit below 0.32 (male) or 0.29 (female) or a fall of 0.1 or more from baseline measurement pre-dose at Visit 2 (confirmed by a new assessment 24-48 hours later)
- Alanine aminotransferase (ALAT) level and/or Aspartate aminotransferase (ASAT) ≥ 3 x ULN (confirmed by a new assessment)
- ALAT level and/or ASAT ≥ 2 x ULN and a bilirubin level ≥ 1.5 x ULN (confirmed by a new assessment)
- An isolated increase in bilirubin level ≥ 2 x ULN (confirmed by a new assessment)
- A sustained reduction in total blood lymphocytes below $0.5x10^9$/L (confirmed by a new assessment 24-48 hours later)
- Any other clinically relevant changes and significant changes in the safety variables (e.g. ECG variables, blood pressure, pulse rate, laboratory values or AEs) making the continuation of dosing unjustified, as judged by the Investigator
- A suspected/manifested infection according to WHO risk groups 2, 3, and 4 (see Appendix E)
- Positive test for alcohol and drugs of abuse during the study.

5.8.1 Procedures for discontinuation of a patient from investigational product

A patient that decides to discontinue Investigational Product will always be asked about the reason(s) and presence of any adverse events. If possible, they will be seen and assessed by an Investigator(s). Adverse events will be followed up (Section 6.4.3 and Section 6.4.4).

Patients who discontinue Investigational Product will be withdrawn from study, see Section 5.9.

5.9 Withdrawal from study

Patients are at any time free to withdraw from study (Investigational Product and assessments), without prejudice to further treatment. Such patients will always be asked about the reason(s) and the presence of any adverse events. However, patients are not obliged to provide a reason for withdrawal. If possible, they will be seen and assessed by an Investigator. Adverse events will be followed up (See Section 6.4.3 and Section 6.4.4).

If a patient prematurely discontinues participation in the study after receiving at least one dose of Investigational Product, the patient should be asked to complete the follow-up visits (Visits 16, 17 (only WOCBPs), 18 and 19). This is also applicable to patients withdrawn due to incorrect inclusion.

Patients who discontinue the study should always be asked specifically whether they are withdrawing or continuing their consent for the genetic research, see Appendix D.

Patients withdrawn from the study after randomisation may be replaced to reach 70 completed patients. The randomisation numbers will not be reused.

6. COLLECTION OF STUDY VARIABLES

The study assessments are described in the section below and the timing of these assessments are detailed in Table 5 and Figure 2.

6.1 Recording of data

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 eCRF as specified in the study protocol and in accordance with the instructions provided.

During Visit 15, patients will complete a paper diary card daily (morning and evening) according to Section 6.3.2 and 6.3.3.

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 centre.

6.2 Data collection and enrolment

In order to include eligible patients the Investigator will be asked to screen for suitable patients based upon inclusion and exclusion criteria, see Section 4.1 and 4.2. If a patient is found to be a suitable candidate for the study, the Investigator will inform the patient of the

study and full written informed consent will be obtained (see Section 8.4). After the patient has signed the informed consent form, the following study measurements will be collected for each patient and applicable data will recorded in the eCRF:

- Date of birth, sex and race
- Medical and surgical history relevant for the purpose of the study and prescribed medication
- History of allergic seasonal rhinitis, duration, and current prescribed rhinitis medication
- Physical examination including clinical inspection of the nose, see Section 6.4.6 and 6.4.7
- Vital signs (pulse and blood pressure), see Section 6.4.9
- Height and weight; height will be measured in cm (no shoes) and weight in kg (light clothing and no shoes)
- Contraceptive history, see Section 5.1.2 and 5.1.3 (also to be recorded in medical records)
- Pregnancy test, see Section 13.3.1
- Fertility test, see Section 6.2.1
- Skin prick test, see Section 6.2.2
- ECG, see Section 6.4.8
- Haematology and clinical chemistry, see Section 6.4.5
- Urinalysis, see Section 6.4.5
- HIV, Hepatitis B and C test, see Section 6.2.3
- Drugs of abuse test and alcohol breath test, see Section 6.2.4 and 6.2.5
- Blood sample for BChE activity test, see Section 6.2.6
- Blood samples for autoantibodies (anti PR3, ANA, RF, dsDNA, non-predefined), see Section 6.4.5.1 and 6.4.5.2
- Allergen titration, see Section 6.2.7

- Smoking / Nicotine habits
- Concomitant medication, see Section 5.6.

6.2.1 Fertility test

For women under the age of 50 considered to be post-menopausal, the blood sample for clinical chemistry at Visit 1 will also be analysed with regards to FSH and LH to determine that the hormones are in the post-menopausal range and that the women thereby not need any contraceptives.

6.2.2 Skin prick test

In the absence of a documented skin prick test within the previous 24 months of Visit 1, the patients will undergo skin prick testing for birch and timothy grass pollen allergens according to local routines at the clinic. The test will be read after 15 minutes. A positive reaction is defined as the largest wheal diameter at least 3 mm greater than the negative control or equal to the positive control. The results will only be recorded as source data sheet in the Investigator study file.

6.2.3 HIV, hepatitis B and C tests

For safety reason, all patients will be tested for antibodies to HIV, hepatitis B surface antigen, and for antibodies to hepatitis C virus at Visit 1. If a patient is found positive to any of these tests, he/she will be referred for further examination and treatment and will not be included in the study. The samples will be handled and analysed at a local hospital laboratory and the results will only be filed in the medical records.

6.2.4 Drugs of abuse screen

A drug screen (cannabis, methamphetamines, opiates, cocaine, methadone, benzodiazepines, barbiturates, tricyclic anti depressants, phencyclidine, and amphetamines) in the urine will be done to exclude or withdraw patients with drug abuse. The samples will be analysed at the clinic according to local routines. If a patient tests positive in the drugs of abuse test, a confirming test will be sent to a local hospital laboratory. If the drug is illegal, counselling and advice will be offered. The samples will be disposed of after analysis and the results will only be recorded in the medical records.

Drug screen will be performed at Visit 1 and once during treatment (randomly chosen visit).

6.2.5 Alcohol breath test

The alcohol breath test will be performed at the clinic according to local routines. If the alcohol breath test is positive, and a repeated test is confirmatory, the patient will be withdrawn from further participation in the study. The results will only be recorded in the medical records.

Alcohol breath test will be performed at Visit 1 and once during treatment (randomly chosen visit).

6.2.6 Determination of BChE activity

A blood sample for determination of BChE activity, will be collected at Visit 1. *In vitro* BChE activity will be determined. Patients with an *in vitro* esterase activity lower than a pre-defined limit will be excluded from the study. The defined limit will be based on the anticipated inter individual variations of esterase activity.

Analysis of BChE activity will be performed at AstraZeneca R&D.

6.2.7 Allergen titration

An allergen titration procedure will be performed at Visit 1 to estimate an individually symptom-producing, tolerable, and repeatable dose for the seven daily nasal allergen challenges to be performed during Visit 15.

The allergen titration will be performed according to standardised procedures and increasing allergen doses will be administered in 10-minute intervals using a nasal spray device. The device delivers 100 µL per actuation, and one actuation will be sprayed into each nostril, resulting in effective doses of 100, 300, 1000, and 3000 standardized quantity units per nasal cavity. The scheme will be followed until the patient responds with at least 5 sneezes and/or a symptom score of 2 or more, on a scale from 0 to 3 in any of the 2 symptoms of nasal blockage or runny nose. The allergen dose that produced this response will be given to that patient at each daily allergen challenge during Visit 15. The allergen dose will only be recorded as source data in the Investigator study file.

6.2.7.1 Allergens

The birch and timothy grass pollen allergens to be administered during the allergen titration procedure and the allergen challenge series are Aquagen SQ (ALK), MT numbers 90032 (Birch) and 90073 (Timothy). Both allergens are approved by the Swedish Medical Products Agency and are commercially available.

Aquagen SQ is a solution for injection developed for allergen specific immunotherapy in IgE-mediated allergic diseases. Aquagen SQ will be provided by the clinic by way of the Hospital Pharmacy, Lund University Hospital, Sweden.

6.2.8 Follow-up procedures

6.2.8.1 Treatment follow-up visit (Visit 16)

A follow-up visit (Visit 16) will be performed 11 to 16 days after administration of last dose of study drug. This will consist of:

- Physical examination including clinical inspection of the nose

- Vital signs (pulse and blood pressure)
- Weight; in kg (light clothing and no shoes)
- ECG
- Haematology and clinical chemistry
- Blood samples for auto antibodies (ANA, RF, anti-dsDNA)
- Urinalysis
- Contraceptive history (WOCBP only)
- Pregnancy test (women only)
- Concomitant medication
- Collection of adverse events.

6.2.8.2 Safety follow-up (WOCBP only)

A telephone contact to be scheduled 3 months after last dose to collect contraceptive history and the result of a pregnancy test (urine dipstick to be provided in advance).

6.2.8.3 Long term safety follow-up (Visit 18 and Visit 19 (telephone contact))

Safety evaluation will be performed 5 to 7 months and 11 to 13 months after last study drug administration. Any vaccinations and, in case of SAE, any concomitant medication from start of SAE until stop of SAE should be collected. At the 5 to 7 month follow-up a blood sample for autoantibodies will be performed. Follow-up 11 to 13 months after last dose is a telephone contact.

6.3 Efficacy

6.3.1 Allergen challenge (Visit 15)

The allergen dose determined at Visit 1 will be given to the patient at each daily allergen challenge during Visit 15. The allergen dose will only be recorded as source data in the Investigator's Study File (ISF). The first allergen challenge (Day 1 Visit 15) will be performed approximately 30 minutes after the nasal lavage.

6.3.2 Reflective Total Nasal Symptom Score (TNSS)

Reflective TNSS represents symptoms over a time period and will be used during allergen challenge (Visit 15) for evaluation of study drug effect.

- Reflective TNSS (recall period 10 min): represents symptoms over the last 10 minutes, collected during clinic visits

- Reflective TNSS (recall period 12 h): represents symptoms over the last 12 hours, collected in patient diary

During Visit 15, the patient will record reflective TNSS (recall period 10 min) in a source data sheet. The patients will also record reflective TNSS (recall period 12 h) in a diary every morning and evening from the evening of the first day of challenge, Day 1, until the morning of Day 8. Recording of AEs based on nasal symptoms is described in Section 6.4.3.

For time points of reflective TNSS measurements, see Table 7.

Definition of TNSS

Each individual symptom is scored 0 to 3 and the scores of each symptom (runny nose, blocked nose and the maximum score of nasal itching or sneezing) will be added together to give a TNSS of 0 to 9. The patient will rate the severity of the symptoms runny nose, blocked nose, sneezing, itchy nose and score in a paper source data sheet them according to the following scale:

0 = Absence of symptoms: no signs or symptoms evident
1 = Mild symptoms: signs or symptoms clearly present, but minimal awareness, easily tolerated
2 = Moderate symptoms: definite awareness of signs or symptoms that are bothersome but tolerable
3 = Severe symptoms: signs or symptoms that are hard to tolerate, cause interference with activities of daily living and/or sleeping

6.3.3 Peak Nasal Inspiratory Flow (PNIF)

PNIF measurements are used to evaluate nasal obstruction and as a surrogate for disease activity in allergic rhinitis and other nasal complaints.

PNIF will be recorded immediately after TNSS scoring, according to local routines at the clinic. Briefly, the patient will breathe out as much as he can. Then a mask (Portable Inspiratory Flow Meter) will be placed over the nose and mouth and the patient will inspire forcefully through the nose while the lips remain tightly closed. The highest PNIF (L/minute) out of 3 measurements will be recorded, along with the date and time of collection.

PNIF will be collected for evaluation for study effect at the same time points as reflective TNSS is collected, see Table 7. During Visit 15, the patient will record PNIF 10 minutes after allergen challenge. The patients will also record PNIF in a diary every morning and evening from the evening of first day of challenge, Day 1, until the morning of Day 8, see Table 7.

6.4 Safety

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

6.4.1 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 (eg, nausea, chest pain), signs (eg, tachycardia, enlarged liver) or the abnormal results of an investigation (eg, 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.

The term AE is used to include both serious and non-serious AEs.

6.4.2 Definitions of serious adverse event

A serious adverse event is an AE occurring during any study phase (ie, run-in, treatment, washout, 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 or incapacity
- 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.

During the long term safety follow-up at Visits 18 and 19, autoimmune disease diagnosis or suspect symptoms or medication suggesting treatment of such disease, irrespective of severity, should be reported as an SAE.

For further guidance on the definition of a SAE, see Appendix B to the Clinical Study Protocol.

6.4.3 Recording of adverse events

Time period for collection of adverse events

Adverse Events will be collected in the eCRF from time of signature of informed consent throughout the treatment period and including the follow-up period. However, the first AE questioning will be done at Visit 2. During Visits 18 and 19 only SAEs will be collected.

Follow-up of unresolved adverse events

Any AEs that are unresolved at the patient's last AE assessment in the study are followed up by the Investigator for as long as medically indicated, but without further recording in the eCRF. 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.

Variables

The following variables will be collect for each AE;

- AE (verbatim)
- The date when the AE started and stopped (and time if starting and/or ending occurs during a study visit)
- Maximum intensity
- Whether the AE is serious or not
- Investigator causality rating against the Investigational Product (yes or no)
- Action taken with regard to investigational product
- AE caused patient's withdrawal from study *(*yes or no*)*
- 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 hospitalisation
- Date of discharge

- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to Study procedure(s)
- Causality assessment in relation to Other medication
- Description of AE.

The patient will be asked to assess the intensity of the reported AE according to the following scale:

- mild (awareness of sign or symptom, but easily tolerated)
- moderate (discomfort sufficient to cause interference with normal activities)
- severe (incapacitating, with inability to perform normal activities).

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 6.4.2. 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. 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.

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?’

Causal relationship in cases where Disease Under Study (DUS) has deteriorated due to lack of effect will be classified as no reasonable possibility.

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 B to the Clinical Study Protocol.

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 eCRF. 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.

Symptoms related to DUS will be handled as follows;

Allergic rhinitis symptoms or signs (not provoked by allergen challenge), such as blocked nose, itchy nose, runny nose and sneezing will be recorded as AEs when:

- the sign or symptom is serious according to definitions (as stated in the study protocol) and/or
- the patient discontinues the study due to the sign or symptom and/or
- the sign or symptom is new to the patient or not consistent with the patient's pre-existing allergic rhinitis history (defined as within 1 year of Visit 1) as judged by the Investigator.

Signs and symptoms clearly related to a normal allergen challenge procedure without complications are not to be reported as AEs unless they fulfil any SAE criteria or lead to discontinuation.

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, vital signs, and other safety variables (including ECG) 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 such a variable 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 (eg, 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.

The individual nasal symptoms (ie, runny nose, blocked nose, nasal itching and sneezing) captured by the TNSS scoring (see Section 6.3.2) should not be recorded on the AE form unless they fulfil any SAE criteria or lead to discontinuation. However, if the nasal symptoms are associated with a diagnosis (eg, influenza, cold) then the diagnosis should be recorded on the AE form.

Clinically relevant deterioration in non-protocol-mandated measurements will be reported as AE(s).

6.4.4 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 eCRF.

If any SAE occurs in the course of the study, then Investigators or other centre personnel inform appropriate AstraZeneca representatives within one day ie, immediately but **no later than the end of the next business day** 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 one (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 centre personnel inform AstraZeneca representatives of any follow-up information on a previously reported SAE within one calendar day ie, immediately but **no later than the end of the next business day** of when he or she becomes aware of it.

Once the Investigators or other centre 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 centre personnel reports a SAE to the appropriate AstraZeneca representative by telephone.

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

The reference document for definition of expectedness/listedness is the IB for the AstraZeneca drug.

6.4.5 Laboratory safety assessment

Blood and urine samples for determination of clinical chemistry, haematology and urinalysis parameters will be taken at the visits and time points given in Table 5, Table 6, and

Table 7. The date and time of collection will be recorded.

Samples will be collected in tubes according to standard routines at the clinic, and the samples will be destroyed after analysis. All samples will be handled and analysed by a local hospital laboratory and/or a contract laboratory, except for the urinalysis that will be analysed at the study centre according to local procedures.

For blood volume see Section 7.1

The following laboratory variables will be measured (for assessment times see Table 5, Table 6 and Table 7):

Clinical chemistry (plasma)

- Alkaline phosphatase
- Aspartate aminotransferase (AST)
- Alanine aminotransferase (ALT)
- Albumin
- Bilirubin (total)
- Creatinine
- Calcium (total)
- Potassium
- Sodium
- Glucose
- Thyroxine free (T4)
- Thyroid-stimulating hormone
- C-reactive protein (CRP)
- Activated partial thromboplastin time
- Prothrombin time (International normalized ratio, INR)
- FSH (if applicable)
- LH (if applicable).

Haematology (whole blood)

- Haemoglobin (Hb)
- Platelet count

- Leucocyte count
- Leucocyte differential count (neutrophils, eosinophils, basophils, lymphocytes, monocytes)
- Erythrocyte count
- Mean corpuscular volume
- Mean corpuscular haemoglobin
- Haematocrit
- Reticulocytes.

Urinalysis

- Hb/Erytrocytes/Blood
- Protein/Albumin
- Glucose
- Pregnancy test.

Laboratory values outside the reference limit suspected to be of any clinical significance will be repeated. Patients in whom suspected clinical significance is confirmed will either not be included or if the patient has already received the investigational product will be followed until normalisation or for as long as the Investigator considers necessary. Additional laboratory variables may be performed for safety reasons if judged appropriate by the Investigator.

Laboratory reports for haematology and clinical chemistry must be signed and dated by the Investigator and stored in the ISF

6.4.5.1 Analysis of autoantibodies

At the Visit 1, a blood sample for Anti-PR-3 autoantibody will be collected. See Table 5.

Blood samples will also be collected for analysis of ANA, RF and ds-DNA at visits indicated in Table 5. The results of these samples will not be available to the Investigator during the study. The evaluation of these autoantibodies will be performed after the last sample in the study has been drawn (these results will be reported together with the long-term safety follow-up data in a separate addendum to the CSR). The date and time of collection will be recorded. Samples will be collected, labelled and shipped as detailed in the Manual of Procedures.

6.4.5.2 Possible retrospective analysis of autoantibodies

Another blood sample will be taken at Visit 1 and Visit 18 (long-term safety follow-up) for possible retrospective analysis of autoantibodies. The date and time of collection will be

recorded and the samples will be collected, labelled and shipped as detailed in the Manual of Procedures. Autoantibody analysis will be performed in case of SAE reports of autoimmune activation or any other safety signal (a collective analysis may be performed if needed, in order to evaluate a safety signal within the AZD8848 program). Due to the broad spectrum of potential autoimmune diseases the specific autoantibodies to be analyzed can not be specified. The reported event will trigger evaluation of appropriate analysis for the individual case. A collective analysis of blood samples from all patients for the autoantibody may then be considered

6.4.6 Physical examination

A physical examination will be carried out at Visit 1 and Visit 16 (treatment follow-up) according to normal routines at the study centre. The physical examination will include: general appearance, skin, mouth, teeth and throat, lymph nodes, thyroid, musculoskeletal/ extremities, cardiovascular, lungs, abdomen, and neurological. An evaluation; Normal or Abnormal (specified), will be collected. The result from the physical examination will be interpreted by the Investigator and all new and/or aggravated findings as compared with baseline (Visit 1) must be identified and recorded as an AE in the eCRF by the Investigator.

6.4.7 Clinical inspection of the nose

Clinical inspection of the nose (visual examination using anterior rhinoscopy) will be performed at Visit 1 and at Visit 16 (treatment follow-up). An evaluation; Normal or Abnormal (specified) will be collected. Clinical inspection of the nose will also be performed upon symptoms.

Baseline inspection will be used to exclude patients with structural abnormalities of the nose or a nasal disorder that could interfere with the conduct of the study. The result from the inspection will be interpreted by the Investigator and all new and/or aggravated findings as compared with baseline must be identified and recorded as an AE in the eCRF by the Investigator.

6.4.8 Resting 12-lead ECG

A 12-lead ECG recording will be obtained after 10 minutes supine rest. A print out at paper speed 50 mm/secwith an overall evaluation; Normal or Abnormal (specified) will be collected, see Table 5 for recording time points.

6.4.9 Vital signs

Vital signs (pulse and blood pressure) will be measured at Visit 1 and Visit 16 (treatment follow-up).

Blood pressure and pulse will be measured after the patient has rested for at least 5 minutes. Blood pressure (systolic and diastolic) and pulse will be measured according to the routines at the clinic, and the date and time of collection will be recorded.

6.4.10 Instantaneous TNSS

Instantaneous TNSS represents symptoms at the moment of recording and will be collected as a safety assessment pre-dose and 15 minutes post-dose during Visits 2, 5, 8 and 11.

The patients will be asked to rate the severity of their nasal symptoms (instantaneous TNSS) and record them into a source data sheet. Recording of AEs based on nasal symptoms is described in Section 6.4.3.

For definition of TNSS see Section 6.3.2.

6.4.11 PNIF

PNIF will be collected as a safety assessment pre-dose and 15 minutes post-dose during Visits 2, 5, 8 and 11. For more information regarding PNIF see Section 6.3.3.

6.5 Patient reported outcomes (PRO)

See Section 6.3.2.

6.6 Pharmacokinetics (Not applicable)

6.7 Pharmacodynamics

6.7.1 Biomarkers

Biomarkers will be monitored in nasal lavage fluid and blood.

Samples for analysis of proof of mechanism (PoM) and exploratory biomarkers will be collected as shown in Table 9.

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

For blood volume see Section 7.1.

Table 9 Biomarkers

Proof of mechanism (PoM) biomarkers	**Medium**	**Rationale**
CXCL-10 (IP-10)	Nasal lavage, plasma	To indicate interferon production by TLR-7 agonist locally and systemic
Exploratory biomarkers e.g.		
Soluble immune/inflammatory proteins. May include but not limited to IFNγ, TNF and IL-10	Nasal lavage, plasma	To indicate changed T-cell phenotype and immuno-regulatory/inflammatory responses

Table 9 Biomarkers

mRNA expression (may include but not limited to genes related to IFNα, T-helper cell phenotypes and inflammatory functions)	Nasal lavage/Blood	Analysis of immune-regulatory/inflammatory components
Myeloperoxidase, α_2-macroglobulin, tryptase, eosinophilic cationic protein (ECP)	Nasal lavage	Activation of inflammatory cells, plasma exudation

6.7.2 Nasal Lavage biomarkers

The first nasal lavage will be performed at Visit 2, before first dose of study drug. Nasal lavage will also be collected twice during Visit 15, see Table 7.

At Visit 2 only saline nasal lavage is collected. During Visit 15 lavages are performed first with saline and thereafter with addition of histamine. After the saline lavage is collected, the nasal cavity is cleaned and then a lavage is performed with addition of histamine. Histamine will be employed to produce acute plasma exudation in order to study the possibility that histamine induced luminal entry of plasma would rinse the tissue and enrich the lavage fluid samples. Fluid will be collected after both the saline lavage and the histamine lavage. Only the myeloperoxidase (protein) α2-macroglobulin, tryptase, ECP exploratory biomarkers will be analysed in the histamine lavage fluid sample.

6.7.3 Blood/plasma biomarkers

Blood samples for analysis of biomarkers will be taken according to Table 5, Table 6, and Table 7.

6.8 Pharmacogenetics

At Visit 2 (or any other subsequent visit until Visit 16) a genetic sample will be collected from patients who have signed a separate genetic ICF. The DNA samples will be collected and stored for future exploratory genetic research on genes or genetic variation that may influence response (ie, distribution, safety, tolerability and efficacy) to AZD8848.

Further information including collection of samples, sample processing and shipping, storage and coding of DNA samples is described in detail in Appendix D.

For blood volume see Section 7.1.

6.9 Health economics (Not applicable)

7. BIOLOGICAL SAMPLING PROCEDURES

7.1 Volume of blood

The total volume of blood that will be drawn from each patient in this study is as follows:

Table 10 Volume of blood to be drawn from each patient

Assessment		Sample volume (mL)	No. of samples	Total volume (mL)
Safety	Clinical chemistry	3	6	18
	Glucose	2	6	12
	Activated partial thromboplastin time and Prothrombin time	4.5	6	27
	Haematology	2	9	18
	HIV, Hepatitis B and C	7	1	7
Auto-antibodies (anti-PR3 (only Visit 1), ANA, RF, anti-dsDNA)		3.5	4	14
Autoantibodies (non-predefined)		3.5	2	7
BChE activity		3	1	3
Soluble Immune/Inflammatory proteins and CXCL-10 (IP-10)		2.5	3	7.5
mRNA		2.5	10	25
Pharmacogenetics		10	1	10
Total				148.5

Safety samples will be repeated if needed. However, the maximum volume to be drawn from each patient will not exceed 450 mL ie, the same volume as would be drawn during a regular blood donation.

7.2 Handling, storage and destruction of biological samples

The samples will be used up or disposed of after analyses or retained for further use as described here.

7.2.1 Safety samples

All laboratory safety assessment including samples aimed for the analysis of autoantibodies will be handled and analysed according to local hospital laboratory routines. The urine analysis (dipstick) will be handled and analysed at the study centre according to local procedures.

7.2.2 Autoantibodies

Blood samples for possible retrospective analysis of autoantibodies will be stored at a AstraZeneca Biobank for a maximum of 15 years after study completion.

7.2.3 Parmacodynamic samples

Samples will be disposed of after the clinical study report has been finalised, unless retained for future analyses, see below.

Key samples for investigation of exploratory biomarkers (immune/inflammatory proteins, mRNA) will be retained at a AstraZeneca Biobank for a maximum of 15 years following the finalisation of the Clinical Study Report. The results from the investigation will not be reported in the Clinical Study Report.

7.2.4 Pharmacogenetic samples

See Appendix D of this Clinical Study Protocol.

7.3 Labelling and shipment of biohazard samples

The Principal Investigator ensures that samples are labelled and shipped in accordance with the Manual of Procedures and the Biological Substance, Category B Regulations (materials containing or suspected to contain infectious substances that do not meet Category A criteria), see Appendix C 'IATA 6.2 Guidance Document'.

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.

7.4 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 centres and auditing of external laboratory providers.

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

7.5 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 centre, 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/destroyed, the action documented and the signed document returned to the study centre
- 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 centre.

8. ETHICAL AND REGULATORY REQUIREMENTS

8.1 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.

8.2 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.

See Appendix D of this Clinical Study Protocol for additional precautions for genetic data.

8.3 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 centre 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, including SUSARs (Suspected Unexpected Serious Adverse Reactions), where relevant.

8.4 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.

8.5 Changes to the protocol and informed consent form

Study procedures will not be changed without the mutual agreement of the Co-ordinating Investigator and AstraZeneca.

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 8.3.

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

8.6 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.

9. STUDY MANAGEMENT BY ASTRAZENECA

9.1 Pre-study activities

Before the first patient is entered into the study, it is necessary for a representative of AstraZeneca to visit the investigational study centre to:

- Determine the adequacy of the facilities
- Determine availability of appropriate patients for the study
- Discuss with the Investigator(s) (and other personnel involved with the study) their responsibilities with regard to protocol adherence, and the responsibilities of AstraZeneca or its representatives. This will be documented in a Clinical Study Agreement between AstraZeneca and the Investigator.

9.2 Training of study centre 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 electronic 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).

To standardize the conduct of the study, a Manual of Procedures with detailed descriptions on all study procedures will be provided to the study centre personnel before the first patient is enrolled in the study.

9.3 Monitoring of the study

During the study, an AstraZeneca representative will have regular contacts with the study centre, 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 eCRFs, that biological samples are handled in accordance with the Manual of Procedures and that study drug accountability checks are being performed

- Perform source data verification (a comparison of the data in the eCRFs 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 access to all original records for each patient as print-outs from medical records

- 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 staffs at the centre needs information and advice about the study conduct.

9.3.1 Source data

See Source data verification plan which will be finalized before start of the study.

9.4 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.

9.4.1 Archiving of study documents

The Investigator follows the principles outlined in the Clinical Study Agreement.

9.5 Study timetable and end of study

The study is expected to start in and to be completed by .

At Clean file, data from Visit 1 to Visit 16 will be evaluated and reported in the clinical study report (CSR) including Proof of mechanism biomarkers, CXCL-10 (IP-10) in blood and nasal lavage, and myeloperoxidas, a2-macroglobulin, tryptas, and eosinophilic cationic protein in nasal lavage.

End of study is defined as final data base lock which will be performed after the last telephone contact has been completed (Visit 19).

Data from Visit 17 until Visit 19 (lon-term safety follow-up) including ANA, RF, and dsDNA results will be reported separately as an addendum to the CSR. If analysed, data from other exploratory biomarkers will be reported separately from the CSR in an exploratory biomarker summary report.

Any results from genetic research will be reported separately from the CSR.

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 AZD8848.

The study may be halted temporarily, as judged by the clinical centres and AstraZeneca R&D, for instance, parts of the study may be postponed to avoid study conduct when patients risk to be exposed to airborne birch and/or timothy grass pollen.

10. DATA MANAGEMENT BY ASTRAZENECA OR DELEGATE

Data management will be performed by AstraZeneca Data Management Centre Cognizant.

Data will be entered in the WBDC system at the study site. Trained study personnel will be responsible for entering data on the observations, tests and assessments specified in the protocol into the WBDC system and according to the eCRF Instructions. Diary data will be collected by the site and entered electronically in the WBDC system; this would be handled in the same way as the other eCRF data. The eCRF instructions will also guide the study site in performing data entry. Data entered in the WBDC system will be immediately saved to a central database and changes tracked to provide an audit trail. Site personnel will enter the data in the eCRFs. The data will then be Source Data Verified (SDV), reviewed/ queried and updated as needed. 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 principal investigator will then sign the eCRF electronically.

Planned interim clean file occurs when all required modules are received, data have been declared clean, unexpected modules been inactivated till the planned time, data been SDV, reviewed/ queried and updated as needed, all log lines been frozen (except the ongoing loglines) and data signed by the Investigator. The Investigator will sign the eCRF electronically. An interim data copy would be taken in the result database (CAVE) to show the data submitted at the interim clean file. Any treatment revealing data may thereafter be added.

At final clean file all data would be declared clean and signed by the Investigator. Any change in data declared clean during the interim clean file would require an approval and has to be documented. The final database will be locked after the same.

A copy of the eCRF will be archived at the study site when the study has been locked.

Adverse events and medical/surgical history will be classified according to the terminology of the latest version of the Medical Dictionary for Regulatory Activities (MedDRA). Medications will be classified according to the AstraZeneca Drug Dictionary.

Medical coding is done using the most current version of MedDRA and AstraZeneca Drug Dictionary.

Data Management determines the format of the data to be received from external vendors and coordinates the flow of data to an external environment or clinical database (if applicable). Data Management will ensure that the data collection tool will be tested / validated as needed. External data reconciliation will be done with the clinical database as applicable. The data reconciliation will be performed as defined in the Data Management Plan.The data will be validated as defined in the Data Management Plan. Data queries will be raised for inconsistent, impossible or missing data. All entries to the study database will be available in an audit trail.

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

SAE Reconciliation Reports are produced and reconciled with the Patient Safety database and/or the investigational centre.

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 samples.

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. The results from this genetic research will be reported separately from the clinical study report for the main study.

11. EVALUATION AND CALCULATION OF VARIABLES BY ASTRAZENECA OR DELEGATE

11.1 Calculation or derivation of efficacy variable(s)

TNSS (recall period 10 min) individual symptoms (runny nose, blocked nose, nasal itching, and sneezing) and PNIF are measured at the clinic at Visit 15 (challenge period) on Days 1 to 7. In addition, TNSS individual symptoms (recall period 12 h) and PNIF are collected by the

patient in the diary from the evening on Day 1 to the morning on Day 8. The challenge period means and means over Days 4 to 7 for TNSS, individual symptoms and PNIF will be calculated by AstraZeneca and the change over time will be evaluated.

11.2 Calculation or derivation of safety variable(s)

See Section 12.2.

11.2.1 Other significant adverse events (OAE)

During the evaluation of the AE data, an AstraZeneca medically qualified expert will review the list of AEs that were not reported as SAEs and DAEs. Based on the expert's judgment, significant adverse events of particular clinical importance may, after consultation with the Global Safety Physician, be considered Other Significant Adverse Events (OAEs) and reported as such in the CSR. Examples of these are marked haematological and other laboratory abnormalities, and certain events that lead to intervention (other than those already classified as serious), dose reduction or significant additional treatment.

11.3 Calculation or derivation of patient reported outcome variables

See Section 11.1.

11.4 Calculation or derivation of pharmacokinetic variables (not applicable)

11.5 Calculation or derivation of pharmacodynamic variable(s)

Biomarkers in nasal lavage and blood are measured at Visit 2 (pre-dose), and at Visit 15 (challenge period) on Day 1 (prior to allergen challenge) and Day 8 (post challenge). The change in biomarkers will be evaluated in three ways:

- during the challenge period calculated as the ratio between the Visit 15 Day 8 and the Visit 15 Day 1 measurements;
- during the treatment period calculated as the ratio between the Visit 15 Day 1 and Visit 2 measurements;
- from before treatment to after the challenge period calculated as the ratio between the Visit 15 Day 8 and the Visit 2 measurements

11.6 Calculation or derivation of pharmacogenetic variables

The number of patients who will agree to participate in the pharmacogenetic research is unknown. It is therefore not possible to establish whether a statistically relevant number of patients will consent to provide sufficient data to be collected to allow a formal statistical evaluation or whether only descriptive statistics will be generated.

11.7 Calculation or derivation of health economic variables (not applicable)

12. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION BY ASTRAZENECA OR DELEGATE

12.1 Description of analysis sets

12.1.1 Efficacy analysis set

For evaluation of efficacy and biomarker data, the analysis set will consist of all patients with evaluable efficacy and/or biomarker data from the challenge period (Visit 15).

12.1.2 Safety analysis set

For reporting of safety the full analysis set, as defined in the ICH E9 guideline, will be used, meaning that all randomised and treated (intake of at least 1 dose of investigational product) patients with data after randomisation will be included in the analyses. Thus, patients who were enrolled in the study but never took any dose of investigational product, will not be included in the safety reporting.

12.2 Methods of statistical analyses

All AEs will be listed for each patient and summarized by system organ class and preferred term by using MedDRA vocabulary. AEs will be analysed in terms of descriptive statistics and qualitative analysis.

Safety data will individually be listed and graphically illustrated, presented as descriptive statistics (for example median, mean, range and standard deviation) and mean value plots for each treatment and assessment time. In addition changes in safety variables over time will be presented by shift and scatter plots if existing. Values below and above AstraZeneca extended reference limits will be highlighted.

Efficacy data from this study will be pooled with the same type of data from the Tol/PoP study (D0540C00003), which was virtually identical to the present study in terms of selection criteria and study conduct. The one main difference is that in the present study, women are allowed to participate. The Tol/Pop study featured treatment arms with placebo (n 34) and 60 µg AZD8848 once weekly (n 34) respectively; efficacy data from these arms will be pooled with data from the corresponding arms in the present study.

For all comparisons between treatments the efficacy data (reflective TNSS, individual symptom scores, PNIF) and pharmacodynamic variables (biomarkers in nasal lavage and plasma) will be analysed using analysis of variance (ANOVA) models with treatment and centre as factors and, for biomarkers and clinic PNIF measurements, the baseline value as covariate. When appropriate, multiplicative models will be used.

The covariate in the respective model, the baseline value, will be the last value before first dose of the study drug. From the respective model the pairwise treatment differences between AZD8848 (once weekly and three times weekly, respectively) and placebo will be estimated and confidence intervals and p-values will be calculated. For biomarkers not reported in the CSR, appropriate statistical methods will be used.

12.3 Determination of sample size

The sample size for this study was selected to be consistent with the research hypothesis as described in Section 1.2.

From previous studies with Rhinocort® in allergic rhinitis using the same provocation model, it has been estimated that the standard deviation for TNSS (both morning and evening) is about 1.5 units. In the preceding Tol/PoP study (D0540C00003), the residual sample standard deviation in the analysis of variance (ANOVA) models was slightly higher however; about 2 units. Since the data from this study will be pooled with the data from the present one we assume a standard deviation of 2 units here too.

A planned total of 70 completed patients in proportions 1:3:1 for the treatments arms 60 µg AZD8848 once weekly, 20 µg AZD8848 three times weekly and placebo, respectively, yields 14, 42 and 14 patients respectively in these arms.

Using a one-sided test at 5 % significant level with a sample size of 42 patients in the 20 µg AZD8848 three times weekly arm and 34+14 = 48 patients in the 60 µg AZD8848 once weekly arm (obtained after pooling with the Tol/PoP study), with another 34+14 = 48 placebo patients contributing to the estimate of the standard deviation, will then give a 76 % chance to detect a difference of 1 unit between the two AZD8848 arms.

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.

12.4 Data monitoring committee (not applicable)

13. IMPORTANT MEDICAL PROCEDURES TO BE FOLLOWED BY THE INVESTIGATOR

13.1 Medical emergencies and AstraZeneca contacts

The Principal Investigator is responsible for ensuring that procedures and expertise are available to handle medical emergencies during the study. **A medical emergency usually constitutes an SAE and is to be reported as such, see Section 6.4**.

In the case of a medical emergency the Investigator may contact the Study Team Physician. If the Study Team Physician is not available, contact the Medical Science director or Study Delivery Team Leader at AstraZeneca Research and Development site in Lund.

Name	Role in the study	Address & telephone number
	Study Team Physician medically responsible for the protocol at central R&D site	AstraZeneca R&D Lund
	Medical Science Director at central R&D site	AstraZeneca R&D Lund
	Study Delivery Team Leader responsible for the protocol at central R&D site	AstraZeneca R&D Lund

13.2 Overdose

Serious intolerability resulting from drug administration cannot be excluded. There is no known antidote to AZD8848. No experience from patients who have overdosed AZD8848 is currently available. In case of known or suspected intolerability or overdose, symptomatic treatment as well as monitoring of vital functions should be performed, based on the judgment of the Investigator.

For the purpose of this study, an accidental or deliberate intake of higher doses of AZD8848 than planned according to the protocol is defined as an overdose and must be reported as such as described below;

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

If an overdose with an AstraZeneca study drug occurs in the course of the study, then Investigators or other centre personnel inform appropriate AstraZeneca representatives **within one (1) day**, ie, immediately but no later than **the end of the next business day** 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 SAE, standard reporting timelines apply, see Section 6.4. For other overdoses, reporting should be done within 30 days.

13.3 Pregnancy

All pregnancies and their subsequent outcome (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be reported to AstraZeneca using the appropriate forms.

13.3.1 Maternal exposure

WOCBP must use reliable contraception, see Section 5.1.2. In addition, pregnancy tests will be performed on WOCBP at Visits 1, 2, 8, 15, 16, and 17. For women not of childbearing potential pregnancy tests will be performed on Visits 1, 2 and 16. The tests prior to dose must be available before drug administration.

In the event of suspected pregnancy, the test should be repeated and if a pregnancy occurs, the patient must be discontinued from treatment and the pregnancy must be documented and reported as described below.

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, normal birth or congenital abnormality) must be followed up and documented even if the patient was discontinued from the study.

If any pregnancy occurs in the course of the study, the Investigator(s) or other centre personnel must inform appropriate AstraZeneca representatives immediately but not later than the end of the next business day of when he/she becomes aware of it. The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the appropriate AstraZeneca Patient safety data entry site within 30 calendar days.

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

13.3.2 Paternal exposure

Male patients should avoid unprotected intercourse with a pregnant woman from first dose until Visit 16 and avoid sperm donation and unprotected intercourse with WOCBP not using birth control from first dose until Visit 16 + 3 weeks, since the potential for chromosomal

aberrations in male gametes, and possible teratogenic effects thereof, have not yet been thoroughly investigated.

Pregnancy of patients partners is not considered to be an adverse event. If the Investigator receives information that a pregnancy has occurred during the study despite these restrictions, the Investigator should ask the patient whether this information can be forwarded to AstraZeneca. If the permission is granted, the Investigator should inform the AstraZeneca representative. The Investigator will follow up and document the outcome of the pregnancy (spontaneous miscarriage, elective termination, normal birth or congenital abnormality), as described in Section 13.3.1.

14. LIST OF REFERENCES

Dudek et al 2007
Dudek AZ, Yunis C, Harrison LI, Kumar S, Hawkinson R, Cooley S, Vasilakos JP, Gorski KS and Miller JS. First in Human Phase I Trial of 852A, a Novel Systemic Toll-like Receptor 7 Agonist, to Activate Innate Immune Responses in Patients with Advanced Cancer. Clin Cancer Res 2007;7119: 13(23)

Kawai T and Akira S 2006
Kawai T, Akira S. Innate immune recognition of viral infection. Nature Immunol 2006;7:131-137.

Newman et al 1987
Newman SP Moren F, Clarke SW. Deposition pattern of nasal sprays in man. Rhinology 1987;26:111-120

Pockros et al 2007
Pockros PJ, Guyader D, Patton H, Tong MJ, Wright T, McHutchison JG, Meng TC. Oral resiquimod in chronic HCV infection: Safety and efficacy in 2 placebo-controlled, double-blind phase IIa studies. Journal of Hepatology 2007; 47: 174–182

Schaub B et al 2006
Schaub B, Lauener R, vonMutius E. The many faces of the hygiene hypothesis. J Allergy Clin Immunol 2006;117:969-977.

Suman et al 1999
Suman JD, Laube BL and Dalby R. Comparison of nasal deposition and clearance of aerosol generated by a Nebulizer and an aqueous spray pump. Pharmaceutical Research 1999;16:1648-1652

WHO 2004

http://www.who.int/entity/reproductivehealth/publications/family_planning/9241562668index/en/index.html

http://www.who.int/entity/reproductivehealth/publications/family_planning/9241562846index/en/index.html