Clinical Study Protocol	
Drug Substance	AZD7594
Study Code	D3741C00007
Version	2.0
Date	26 April 2019

A Phase 2b Randomised, Double-Blind, Placebo-Controlled, Parallel Arm, Multi-Centre Study to Assess Efficacy and Safety of Multiple Dose Levels of AZD7594 DPI Given Once Daily for Twelve Weeks, Compared to Placebo, in Asthmatics Symptomatic on Low Dose ICS

Sponsor:

AstraZeneca AB

151 85 Södertälje

Sweden

EudraCT number: 2017-002483-40

VERSION HISTORY

Version 2.0, 26 April 2019

The primary reasons for amending this protocol are to:

- Delete peak Forced Expiratory Volume in 1 Second (FEV_1) from the secondary efficacy endpoints as it was added in error and this endpoint is not measured.
- Update the study period.
- Update the inclusion criteria to include only patients with body mass index (BMI) ≤35.
- Delete the expected number of patients in the United States (US) versus non-US sites as the number of patients in the US sites might be less than originally planned.
- Remove interim futility analysis as it is determined no interim futility analysis is to be conducted. Patient recruitment into the study has been faster than planned and all patients are expected to be enrolled before the time point at which the interim analysis was planned to be completed. Many patients will also have completed treatment at that timepoint. The value of the futility analysis has therefore been determined to be limited.
- Incorporate the updated Hy's Law (Version 2.0, dated 10 January 2019) in the Clinical Study Protocol Appendix D.

All changes made to specific sections in the protocol were also implemented elsewhere in the protocol and in the synopsis, where applicable. Major changes to the protocol are summarised below:

Section 1.4 (Study design), Section 3.1 (Inclusion criteria), Section 4.1.3 (Visit 3 [Randomisation Visit] [Day 1, within 21 to 28 days after Visit 1]), and Section 7.2.2 (Run-in Period):
Specified the inclusion criterion #7 (pre-bronchodilator FEV_1 at Visit 3 between 40% and 90% predicted) only needs to be fulfilled at either −45 or −15 minutes pre-dose.

Section 2.1 (Primary objective) and Section 8.5.3.2 (Secondary efficacy variables):
Deleted "change from baseline in peak FEV_1 at Weeks 2, 4, 8, 12 and average over the Treatment Period" from the secondary efficacy endpoints. The Peak FEV_1 endpoint has been removed from the study protocol as it was added in error and this endpoint is not measured.

Section 2.2 (Secondary objectives), Section 5.2.3 (ECG), and Section 8.5.6 (Analysis of safety outcomes):

Deleted QT interval corrected using Bazett's formula (QTcB) as it will no longer be presented as part of summary and analysis of electrocardiogram (ECG). Added appropriate ECG parameters as described in Section 5.2.3.

Section 3.1 (Inclusion criteria):
Updated the inclusion criteria #2 to include only patients with BMI ≤35, considering obesity may impact asthma symptoms and asthma control and also could be a confounding factor in efficacy endpoints and patient safety assessment.

Section 3.2 (Exclusion criteria):
Clarified the exclusion criterion #3 that patients with current sleep apnea are excluded.
Clarified the exclusion criterion #21 for alcohol and drug abuse.

Section 3.6 (Methods for assigning treatment groups):
Deleted the expected number of patients in the US versus non-US sites as the number of patients in the US sites might be less than originally planned.
Updated the personnel who receive the randomisation list as the interim analysis will not be conducted.

Section 3.9 (Restrictions):
Clarified the required treatments for postmenopausal patients.

Section 3.10 (Discontinuation of Investigational Product):
Clarified that the patients will be discontinued when specified criteria are met.

Section 4 (Study plan and timing of procedures), Table 2 (Study plan detailing the procedures):
Updated table footnote to clarify that Visit 3 baseline data will be collected before finishing cortisol collection within -2 and 0 h pre-dose.
Updated table footnote a to add the restriction for performing Visit 2 related procedures.
Updated table footnote m to add the allowed time window for performing reversibility testing.
Updated table footnote n to clarify the number of measurements and the timing along with the allowed time windows for performing spirometry tests at specified visits.
Added table footnote to clarify that peak expiratory flow will be measured by the patient at home after completing the morning and evening diary using a peak flow meter.

Section 4.1.1 (Visit 1 [Screening Visit] [within 21 to 28 days before Visit 3]):
Deleted measure peak expiratory flow as it will be measured by the patient at home.

Section 4.1.3 (Visit 3 [Randomisation Visit] [Day 1, within 21 to 28 days after Visit 1]), Section 4.2.1 (Visits 4, 5 and 6 [Days 15, 29, and 57 ± 1 day]), Section 4.2.2 (Visit 7 [Day 85± 1 day], End of treatment), Section 4.2.3 (Early Termination Visit), and Section 5.1.1.1 (Pulmonary function test [spirometry]):
Clarified the number of measurement and timing of spirometry.

Section 5.1.2 (Secondary efficacy assessments) and Section 7.5 (Compliance):
Clarified the compliance rate in the Run-in Period and the expected compliance rate in the Treatment Period.

Section 5.1.2.3 (Peak expiratory flow):
Clarified that peak expiratory flow will be measured at home after completing the morning and evening diary.

Section 5.8 (Exploratory objectives: Forced oscillation technique):
Clarified that Forced Oscillation Technique (FOT) evaluation and training will take place at Visit 1, instead of Visit 2.

Section 5.9 (Exploratory objectives: Real-time occurrence of CompEx events [voluntary US-specific sub-study]):
Specified that only English-language version of the application is provided for the US-specific sub-study.

Section 7.7 (Concomitant and other treatments):
Deleted the description that rescue medication should be recorded as concomitant medication, to avoid misunderstanding that it should be recorded in eCRF; rescue medication will be recorded in the eDiary as described in Section 7.7.1.

Section 8.4.7 (Interim futility analysis):
Removed the interim futility analysis as it is determined no interim futility analysis is to be conducted. Patient recruitment into the study has been faster than planned and all patients are expected to be enrolled before the time point at which the interim analysis was planned to be completed. Many patients will also have completed treatment at that timepoint. The value of the futility analysis has therefore been determined to be limited.

Section 8.5.1 (Demographic and baseline characteristics):
Clarified that the analysis set used for demographic and baseline characteristics is Full Analysis Set (FAS).
Clarified the baseline asthma severity is assessed using the pre- Short-Acting $Beta_2$ Agonists (SABA) value at Visit 2, instead of pre-bronchodilator value at Visit 1.
The number of patients who met the reversibility criteria was deleted.

Section 8.5.4.2 (Statistical analysis of the Pharmacokinetic Parameters) and Section 8.5.6 (Analysis of safety outcomes):
“Individual plasma concentrations versus time on Week 12 (Day 84) plotted on linear and semi-logarithmic scale with all treatments overlaid on the same plot and separate plots for each patient” will no longer be provided as part of pharmacokinetics (PK) analysis.
Geometric standard deviation (SD) will no longer be presented on figures of geometric mean for concentration-time data as part of the PK analysis.

Section 8.5.7.1 (Additional analysis)
Clarified the definition of ACQ-5 responder: a patient with ACQ-5 score decrease from

baseline of ≥0.5 in ACQ-5, instead of a patient with a change from baseline of ≥0.5 in ACQ-5. Section 9.3 (Study timetable and end of study): Deleted the description on the futility criteria as it is determined no interim futility analysis is to be conducted. Appendix D (Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law): Incorporated the updated Hy's Law (Version 2.0, dated 10 January 2019) in the Clinical Study Protocol Appendix D. Minor changes included: Updated the list of abbreviation accordingly. Added ethnicity and country to demographic and baseline characteristics, and region to subgroup analysis.
Version 1.0, 25 May 2018
Initial creation

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

CLINICAL STUDY PROTOCOL SYNOPSIS

A Phase 2b Randomised, Double-Blind, Placebo-Controlled, Parallel Arm, Multi-Centre Study to Assess Efficacy and Safety of Multiple Dose Levels of AZD7594 DPI Given Once Daily for Twelve Weeks, Compared to Placebo, in Asthmatics Symptomatic on Low Dose ICS

International Co-ordinating Investigator

PPD

Study centre(s) and number of patients planned

It is planned that approximately 714 patients with asthma symptomatic on low dose inhaled corticosteroid (ICS) will be randomised into the study, 102 patients per arm.

The study will be conducted in approximately 100 centres in 8 countries in Europe, United States (US), South Africa, and Japan.

Study period		Phase of development
Estimated date of first patient enrolled	Q1 2019	Phase 2b
Estimated date of last patient completed	Q3 2019	Phase 2b

Study design

This is a randomised, placebo-controlled, double-blind study with an open-label active comparator ICS (fluticasone furoate [FF]) arm to assess the efficacy and safety of AZD7594 administered once daily (QD) by inhalation at multiple dose levels over a 12-week treatment period to patients with asthma symptomatic on low dose ICS.

The primary objective is to determine the efficacy of AZD7594 as assessed by change from baseline in trough forced expiratory volume in 1 second (FEV_1) at Week 12, when compared to placebo, with the aim of selecting doses to advance to Phase 3 studies. Secondary efficacy assessments include asthma control questionnaire (ACQ-5), fractional exhaled nitric oxide (F_ENO), forced vital capacity (FVC), peak expiratory flow (PEF), rescue medication use, night-time awakenings, daily asthma symptoms as recorded in an electronic diary (eDiary), and "CompEx", a composite endpoint for severe exacerbations of asthma which combines severe exacerbations and diary events (ie, combination of eDiary variables).

Other secondary objectives of the study include the description of the (steady state) pharmacokinetics (PK) and the pharmacodynamics (assessment of cortisol suppression) of AZD7594 in a subset of patients. Only selected sites that are capable of doing quality PK (and

cortisol) sampling will participate in the PK subset. The safety and tolerability of AZD7594 will also be evaluated in relation to placebo.

Exploratory objectives will include the use of Forced Oscillation Technique (FOT) (as a measure of small airways involvement) for patients in the US and Europe, a genomics (Gx) analysis [redacted].

The study will consist of a Run-in Period (Visits 1 to 3), a Treatment Period (Visits 4 to 7) and a Follow-up Contact (Visit 8).

In addition, all patients will be provided a short-acting $beta_2$ agonist (SABA) (salbutamol/albuterol) as rescue medication for use throughout the run-in and treatment periods.

All patients will sign informed consent form (ICF) prior to participating in any study-specific procedures.

The **Run-in Period** will typically last 21-28 days (up to a maximum of 35 days, if Visit 3 is repeated) and will consist of 3 visits: a Screening Visit (Visit 1), a Reversibility Visit (Visit 2) and a Randomisation Visit (Visit 3). Patients found to be eligible at Visit 1 (Screening Visit) will discontinue all asthma medications and switch to low dose budesonide (200 µg twice a day [BID] in Europe and 180 µg BID in US) and rescue medication will be taken as needed. Visit 1 (Screening Visit) and Visit 2 can occur the same day, unless the patient is taking a long-acting beta agonist (LABA), fixed dose combination ICS/LABA treatment or a long-acting muscarinic antagonist (LAMA), in which case the patient will return for Visit 2 between 2 to 7 days after Visit 1 to allow sufficient time to wash-out their asthma medications.

Visit 2 will occur within 7 days of Visit 1 and will assess reversibility (increase of FEV_1 ≥12% and ≥200 mL after administration of a short-acting bronchodilator). All patients should refrain from taking SABA for 6 hours prior to reversibility testing. If a patient does not meet reversibility criteria, Visit 2 can be repeated once within 1 week. If reversibility criteria are not achieved at the repeat attempt, the patient will be discontinued from the study.

If reversibility criteria are met at Visit 2, patients will proceed to Visit 3. Randomisation will occur at Visit 3, within 21 to 28 days of Visit 1. At Visit 3, patients who remain symptomatic while on low dose budesonide (as assessed by asthma mean symptom score >1 over the previous 7 days or use of a SABA on ≥3 days of the previous 7 days) and meet FEV_1 criteria (≥40% to ≤90% predicted at either −45 or −15 minutes pre-dose) will be randomised to one of 7 possible treatment arms (see below). If patients do not meet eligibility (especially symptom criteria or lung function criteria), Visit 3 can be repeated once within 1 week. If this occurs, additional budesonide may need to be provided to the patient to ensure that the patient has run-in medication (budesonide) available throughout the run-in period.

Patients who are uncontrolled during the Run-in Period (as per an ACQ-5 score of ≥3 or daily rescue medication (SABA) use of ≥12 puffs for ≥3 consecutive days) or those with <80%

eDiary compliance during Run-in Period will be discontinued from the study. Once a patient has failed screening, re-screening will not be allowed.

The **Treatment Period** will include 4 more visits (Visit 4 to Visit 7) and will last 12 weeks. At Visit 7, patients will stop investigational treatment and change back to their regular asthma therapy. Each patient will receive one of the following 7 possible treatments (for AZD7594, nominal strength and delivered dose have been included below):

- AZD7594 DPI 55µg [nominal strength]/50 µg [delivered dose] (QD)
- AZD7594 DPI 99 µg/90 µg QD
- AZD7594 DPI 198 µg/180 µg QD
- AZD7594 DPI 396 µg/360 µg QD
- AZD7594 DPI 792 µg/720 µg QD
- Placebo for AZD7594 QD
- FF 100 µg QD (open-label)

During the follow-up period, there will be a follow-up telephone contact (Visit 8) 1 week after Visit 7. A complete listing of assessments and timing is included in the Study Plan in the main body of the Clinical Study Protocol.

The “end of study” is the date when all patients randomised in the study perform the last contact (either Visit 7 or Visit 8) and will be communicated to Regulatory Authorities and Ethics Committees on due time according to local regulations.

Study objectives

Primary Objective:	Outcome Measure:
To investigate the clinical efficacy of AZD7594 at different dose levels in asthmatics symptomatic on low dose ICS	**Primary efficacy endpoint:** • Change from baseline in trough FEV_1 at Week 12 **Secondary efficacy endpoints:** • Change from baseline in trough FEV_1 at Weeks 2, 4, 8, and average over the treatment period • Change from baseline in F_ENO at Weeks 2, 4, 8, 12, and average over the treatment period (analysis to be done on natural log-scale and results back-transformed to linear scale) • Change from baseline in trough FVC at Week 12 and average over the treatment period • Change from baseline in ACQ-5 at Week 12 and average over the treatment period • Change from baseline in average morning PEF over the treatment period • Change from baseline in average evening PEF over the treatment period • Change from baseline in average daily use of rescue medication over the treatment period • Change from baseline in percent night-time awakening days over the treatment period • Change from baseline in average daily asthma symptom score over the treatment period • Change from baseline in percent asthma control days over the treatment period • Change from baseline in percent rescue-free days over the treatment period • Change from baseline in percent symptom-free days over the treatment period • Time to first CompEx event, time to recurrent CompEx event, and CompEx event rate

Secondary Objectives:	Outcome Measure:
To describe the (steady state) pharmacokinetics (PK) of AZD7594 in a subset of asthmatics symptomatic on low dose ICS	AZD7594 plasma concentration and (steady state) PK parameters ($C_{ss,max}$, $C_{ss,min}$, $t_{ss,max}$, AUC_{last}, AUC_{τ}, $C_{ss,avg}$, $C_{ss,max}/D$, and AUC_{τ}/D and %Fluctuation) will be derived
To describe the pharmacodynamics of AZD7594 by measuring cortisol suppression in a subset of asthmatics symptomatic on low dose ICS	Area under the plasma cortisol concentration-time curve from zero to 24 hours after dosing ($AUEC_{(0-24)}$), compared to placebo
To evaluate the safety and tolerability of AZD7594 in relation to placebo in asthmatics symptomatic on low dose ICS	Adverse events (AEs)/Serious adverse events (SAEs)/Discontinuation of IP due to AE (DAEs) Vital signs Clinical chemistry/haematology parameters Electrocardiogram (ECG)[a]

[a] The following parameters will be recorded for each ECG: date and time, HR (beats/min), RR interval, PR interval, QRS interval, QT interval (ms), QT interval corrected using Fridericia's formula (QTcF) (ms), and overall evaluation.

AUC_{τ}, Area under the plasma concentration-curve within a dosing interval; AUCτ/D, Dose normalised AUCτ; AUC_{last}, area under the plasma concentration-curve from time zero to the time of last quantifiable analyte concentration; CompEx, Composite endpoint for severe exacerbations of asthma; $C_{ss,avg}$, Average plasma concentration during a dosing interval at steady state, estimated as AUCτ/24; $C_{ss,max}$, observed maximum concentration at steady state, taken directly from the individual concentration-time curve; $C_{ss,max}/D$, Dose normalised $C_{ss,max}$; $C_{ss,min}$, observed minimum concentration at the end of the dosing interval; $t_{ss,max}$, time to maximum concentration at steady state, taken directly from the individual concentration-time curve.

Exploratory Objectives:	Outcome Measure:
To obtain (optional) blood samples for future Gx research aiming to identify/explore biomarkers or genetic variations that may affect the efficacy, pharmacodynamics, safety and tolerability profile related to AZD7594 treatment in asthmatics symptomatic on low dose ICS	DNA from whole blood
To evaluate the effect of AZD7594 on small airways obstruction in asthmatics symptomatic on low dose ICS	Change from baseline up to Week 12 in measures of airway resistance and reactance, including R5-R20, as evaluated by FOT
[redacted] CCI	[redacted]

FOT, forced oscillation technique; Gx, genomics; ICS, inhaled corticosteroid

Target patient population

This study will be performed in men and non-pregnant, non-lactating women, all between 18 and 85 years of age with body mass index (BMI) ≤35 with asthma symptomatic on low dose ICS and bronchodilator reversibility (increase of FEV_1 ≥12% and ≥200 mL after administration of a short-acting bronchodilator).

Duration of treatment

The study will consist of a 21-28 days (3-4-week and no longer than 5 weeks) Run-in Period (Visits 1 to 3) followed by a 12-week Treatment Period (Visits 4 to 7) and a 1-week follow-up contact (Visit 8).

The total duration of study will be between 113 - 135 days for each individual patient and is planned to run approximately 12 months (it should not exceed 18 months).

Investigational product, dosage and mode of administration

Investigational product	Dosage form and strength (nominal dose/delivered dose)	Administration route and dosing frequency
AZD7594	Inhalation powder (55 µg/50 µg) Inhalation powder (99 µg/90 µg) Inhalation powder (198 µg/180 µg) Inhalation powder (396 µg/360 µg) Inhalation powder (792 µg/720 µg)	Oral inhalation (by SD3FL inhaler, DPI) QD
Placebo to AZD7594	Inhalation powder	Oral inhalation (by SD3FL inhaler, DPI) QD
Fluticasone furoate	Inhalation powder (100 µg per nominal dose)	Oral inhalation (by ELLIPTA inhaler, DPI) QD

DPI, dry powder inhaler; IP, investigational product; QD, once a day
AstraZeneca will provide the test IPs, ie, AZD7594, fluticasone furoate, and placebo

Non-Investigational products

Product name	Dosage form and strength	Administration route and dosing frequency
Budesonide (run-in medication)	Inhalation powder 200 µg per nominal dose (ex-US) 180 µg per nominal dose (US)	Oral inhalation by DPI, BID, eg, Pulmicort® Turbohaler® 200 µg (AstraZeneca)
SABA (salbutamol/albuterol), rescue medication	Inhalation aerosol 100 µg per nominal dose 90 µg per nominal dose (US)	Oral inhalation by MDI, PRN, eg, Sultanol® Dosier-Aerosol 100 µg (GlaxoSmithKline), Ventolin® Evohaler® 100 µg (GlaxoSmithKline)

DPI, dry powder inhaler; BID, twice a day; ex-US, excluding United States; MDI, metered-dose inhaler; PRN, as needed; SABA, short-acting beta agonist; US, United States
PAREXEL will source and provide budesonide and salbutamol/albuterol.

Statistical methods

Sample Size Determination

Approximately 102 patients will be randomised to each arm (overall randomisation ratio 1:1:1:1:1:1:1) in order to ensure at least 86 evaluable patients per arm. This sample size will provide at least 80% power to detect a difference in the primary endpoint, ie, a difference of 175 mL in change from baseline in trough FEV_1 at Week 12 between each dose of AZD7594 and placebo, assuming an inter-patient standard deviation of 405 mL, using a 2-sided test with a significance level of 0.05 and with an estimated 15% dropout rate. The targeted total number of patients to be randomised is approximately 714 patients.

Interim futility analysis

Not applicable.

Primary efficacy analysis

The primary variable is the change from baseline in trough FEV_1 at Week 12. Baseline for FEV_1 will be defined as the mean of the 2 measured values for the corresponding variable (2 measurements 30 minutes apart, at −45 minutes and −15 minutes, before IP administration), on Day 1. Trough will be defined as the mean of the 2 FEV_1 measurements 30 minutes apart (23 hours after last dose).

The change from baseline in trough FEV_1 will be analysed using a MMRM with treatment, visit, treatment by visit interaction and region (US, Japan, and Rest of the World [RoW]) as fixed effects, and baseline FEV_1 and baseline FEV_1 by visit interaction as continuous covariates. The within-patient correlation will be modelled using the unstructured covariance matrix. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom. The main comparisons will be between each AZD7594 dose and placebo at Week 12. The comparison between active comparator (FF) and placebo will be used for bench marking.

To control type I error rate for the primary efficacy endpoint comparisons at Week 12, a sequential hierarchical step-down approach will be used. This approach starts from testing the highest dose versus placebo first, using a two-sided alpha of 0.05. If this p-value is ≤ 0.05 for the comparison, then the next highest dose versus placebo will be tested using the same two-sided alpha of 0.05. This process continues until the first p-value >0.05 occurs or the lowest dose versus placebo is tested.

The primary analysis will be based on the full analysis set (FAS) population and additionally for sensitivity purposes on the per protocol (PP) population. Further subgroup analyses will be done to evaluate treatment effects for trough FEV_1 at Week 12.

Secondary efficacy analysis

The following variables are secondary efficacy variables:

- Change from baseline in trough FEV_1 at Weeks 2, 4, 8, and average over the treatment period
- Change from baseline in F_ENO at Weeks 2, 4, 8, 12, and average over the treatment period (analysis to be done on natural log-scale and results back-transformed to linear scale)
- Change from baseline in trough FVC at Week 12 and average over the treatment period
- Change from baseline in ACQ-5 at Week 12 and average over the treatment period
- Change from baseline in average morning PEF over the treatment period
- Change from baseline in average evening PEF over the treatment period
- Change from baseline in average daily use of rescue medication over the treatment period
- Change from baseline in percent night-time awakening days over the treatment period
- Change from baseline in average daily asthma symptom score over the treatment period
- Change from baseline in percent asthma control days over the treatment period
- Change from baseline in percent rescue-free days over the treatment period
- Change from baseline in percent symptom-free days over the treatment period
- Time to first CompEx event, time to recurrent CompEx event, and CompEx event rate

Similar mixed models for repeated measures as for the primary variable will be used for the analysis at specified visit week. Analysis of covariance (ANCOVA) with treatment and region (ie, US, Japan, and RoW) as fixed effects, and baseline as covariate will be used for the analysis of average over the treatment period. No multiplicity adjustments will be applied for the secondary variables.

CompEx will be analysed with a Cox proportional hazards model, a marginal means/rates model, and a negative binomial model for time to first event, time to recurrent event, and event rate (due to observation time per patient) respectively, with region and treatment included as covariates in all models.

PK analysis

Sampling for PK analysis will be done in a subset of patients. Steady state PK parameters of AZD7594 will be derived using non-compartmental methods with Phoenix® WinNonlin® Version 6.3 or higher.

A listing of PK blood sample collection times, as well as derived sampling time deviations will be provided.

Plasma concentrations will be listed and summarised by treatment using appropriate descriptive statistics. Where possible, the following descriptive statistics will be presented: n, geometric mean, geometric coefficient of variation, arithmetic mean, arithmetic standard deviation (SD), median, minimum and maximum based on the PK analysis set. Plasma concentrations that are below lower limit of quantification will be handled as described in the Statistical Analysis Plan (SAP).

Combined individual plasma concentration per dose level (spaghetti plots) will be presented in linear and semi-logarithmic scale with separate plots for each dose level.

Figures for the geometric mean concentration-time data will be presented for all doses overlaid on the same plot, in both a linear and semi-logarithmic scale.

Additional graphical presentations of PK data may be added at the discretion of the PK scientist. More details will be provided in the SAP.

All plasma PK parameters will be listed for each patient and summarised by treatment using similar descriptive statistics. For t_{max} only n, median, minimum and maximum will be reported.

Data from patients excluded from the PK analysis set will be included in the data listings, but not in the descriptive statistics or in the inferential statistics.

Dose proportionality of AZD7594 on Week 12 (Day 84) will be assessed graphically and analysed using the power model approach with the natural logarithm of PK parameters ($C_{ss,max}$ and AUC_{τ}) as the dependent variable and the logarithm of the dose as the independent variable.

Further details regarding the model specifications will be provided in the SAP.

Pharmacodynamic analysis

As a measure of cortisol suppression, 24-hour plasma cortisol measurements will be performed in the same subset of patients as PK sampling and a selected subset of FF treated patients. Plasma cortisol will be measured just before and at the end of the Treatment Period. Measurement before the first dose will serve as a baseline value. Patients will be required to stay overnight for 24 hours before IP administration on Day 1 and for 24 hours after the last dose on Day 84.

The change from baseline in log-transformed $AUEC_{(0-24)}$ (area under the plasma cortisol concentration-time curve from zero to 24 hours after dose) will be analysed by ANCOVA approach with treatment as a fixed effect, baseline log AUEC as a covariate, and patient as a random effect. The estimated ratio for each AZD7594 arm versus placebo and FF versus placebo, and their associated 95% confidence intervals will be presented.

Exploratory analyses

An ACQ-5 responder analysis will be explored based on the percentage of ACQ-5 responders at Weeks 2, 4, 8, and 12. An ACQ-5 responder is defined as a patient with a decrease from baseline of ≥0.5 in their ACQ-5 score.

Measures of airway resistance and reactance via FOT, [redacted] and Gx variables will be analysed at Week 12 by using mixed models for repeated measures as for the primary variable.

In addition, dose-response modelling for trough FEV_1 and the relationship between AZD7594 exposure and plasma cortisol $AUEC_{(0-24)}$ may be explored.

Safety analysis

Safety will be assessed by descriptive analysis of vital signs, ECGs, laboratory assessments and AEs reported.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

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

Abbreviation or special term	Explanation
ACQ-5	Asthma Control Questionnaire
AE	Adverse Event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AM3	Asthma Monitor 3
ANCOVA	Analysis of covariance
AO	Airwave Oscillometry
AST	Aspartate aminotransferase
ATS	American Thoracic Society
AUCτ	Area under the plasma concentration-curve within a dosing interval;
AUCτ/D	Dose normalised AUCτ
AUC_{last}	Area under the plasma concentration-curve from time zero to the time of last quantifiable analyte concentration
$AUEC_{(0-24)}$	Area under the plasma cortisol concentration-time curve from 0 to 24 hours after dosing
AV	Atrial-ventricular
AZRand	AZ Randomisation
BDRM	Blind Data Review Meeting
BID	Twice a Day
BLQ	Below lower limit of quantification
BMI	Body Mass Index
CFC	Chlorofluorocarbon (propellant)
CI	Confidence Interval
C_{max}	maximum plasma concentration-time curve
CompEx	Composite endpoint for severe exacerbations of asthma
COPD	Chronic Obstructive Pulmonary Disease
CPKA	Covance Clinical Pharmacokinetic Alliance
CPMP	Committee for Proprietary Medicinal Products
CRP	C-reactive protein

Abbreviation or special term	Explanation
CSR	Clinical Study Report
CSA	Clinical Study Agreement
$C_{ss,avg,}$	Average plasma concentration during a dosing interval at steady state, estimated as AUCτ/24
$C_{ss,max}$	Observed maximum concentration at steady state, taken directly from the individual concentration-time curve
$C_{ss,max}/D$	Dose normalised $C_{ss,max}$
$C_{ss,min}$	Observed minimum concentration at the end of the dosing interval
DAE	Discontinuation of IP due to adverse event
DES	Data Entry Site
DILI	Drug-Induced Liver Injury
DMP	Data Management Plan
DNA	Deoxyribonucleic acid
DPI	Dry Powder Inhaler
DVS	Data Validation Specification
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eDiary	Electronic Diary
EDC	Electronic Data Capture
CCI	CCI
EMA	European Medicines Agency
EOT	End of treatment
ERS	European Respiratory Society
ERT	e-Research Technology
ETV	Early termination visit
FAS	Full Analysis Set
FDA	Food and Drug Administration
F_ENO	Fractional Exhaled Nitric Oxide
FEV_1	Forced Expiratory Volume in 1 Second
FF	Fluticasone Furoate
FOT	Forced Oscillation Technique
FSH	Follicle-Stimulating Hormone

Abbreviation or special term	Explanation
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GINA	Global Initiative for Asthma
GLIMMIX	Generalized Linear Mixed Effect Model
GMP	Good Manufacturing Practice
GR	Glucocorticoid Receptor
Gx	Genomics
H	Hour
HBsAg	Hepatitis B Surface Antigen
HCV	Hepatitis C Virus
HFA	Hydrofluoroalkane (propellant)
HIV	Human Immunodeficiency Virus
HL	Hy's Law
HPA	Hypothalamic-pituitary-adrenal
HR	Heart Rate
HRT	Hormone Replacement Therapy
IATA	International Airline Transportation Association
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
ICS	Inhaled Corticosteroid
IEC	Independent Ethics Committee
INR	International normalised ratio
International Co-ordinating Investigator	If a study is conducted in several countries the International Co-ordinating Investigator is the Investigator co-ordinating the Investigators and/or activities internationally
IP	Investigational Product
IRB	Institutional Review Board
IUD	Intrauterine Device
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
LABA	Long-Acting Beta Agonist

Abbreviation or special term	Explanation
LAMA	Long-acting Muscarinic Antagonist
LH	Luteinizing Hormone
LS	Least square
MCH	Mean corpuscular haemoglobin
MCV	Mean corpuscular volume
MDI	Metered-dose Inhaler
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Model for Repeated Measures
NCA	Non-compartmental Analysis
PEF	Peak Expiratory Flow
PHL	Potential Hy's Law
PI	Principal Investigator
PK	Pharmacokinetics
PP	Per protocol
PRN	As Needed
QCP	Quantitative Clinical Pharmacology
QD	Once Daily
QTc	QT interval corrected
QTcF	QT interval corrected using Fridericia's formula
RoW	Rest of the World
RTSM	Randomization and Trial Supply Management
SABA	Short-Acting Beta Agonist
SAE	Serious Adverse Event
SAMA	Short-acting muscarinic antagonist
SAP	Statistical Analysis Plan
SD	Standard deviation
SDTM	Study Data Tabulation Model
SDV	Source Data Verification
SE	Standard Error
SGRM	Selective GR modulator
SOP	Standard Operating Procedure
TBL	Total bilirubin

Abbreviation or special term	Explanation
TEAE	Treatment-emergent adverse event
TC	Telephone call
TSH	Thyroid stimulating hormone
$t_{ss,max}$	Time to maximum concentration at steady state, taken directly from the individual concentration-time curve
T4	Thyroxine
ULN	Upper limit of normal
US	United States
WHO	World Health Organisation
WOCBP	Women Of Child-Bearing Potential

1. INTRODUCTION

1.1 Background and rationale for conducting this study

AZD7594 is a non-steroidal, potent and selective modulator of the glucocorticoid receptor (GR) under development for once daily (QD) inhaled treatment of chronic obstructive pulmonary disease (COPD) and asthma.

Inhaled corticosteroids (ICSs) are the cornerstone of therapy for asthma patients of all severity levels. The Global Initiative for Asthma (GINA) 2018 guidelines (GINA, 2018), as well as the European Medicines Agency (EMA) guideline on the clinical investigation of medicinal products for the treatment of asthma (CHMP/EWP/2922/01 Rev.1, 2015) recommend ICS as first-line treatment for all asthmatic patients requiring regular anti-inflammatory therapy. ICS have been shown to improve symptom control, lung function and quality of life; reduce exacerbations, asthma-related hospitalisations and death. However, ICS have known side-effects with long-term use. Therefore, a GR agonist with a better therapeutic index (balance between desired and undesired effects) than currently available ICSs could improve the available treatment options for asthma patients.

The GR is a well-known target and there is extensive clinical experience with GR agonists used as ICSs. Besides common local adverse reactions such as hoarseness and oral candidiasis, which are inconvenient for the patient but not of a serious nature, GR agonists have the potential to cause systemic side-effects such as effects on the hypothalamic-pituitary-adrenal (HPA) axis and effects on bone mineral density and (in children) growth velocity. These systemic effects are rare, and generally related to long-term treatment with high doses (Christensson, 2008).

AZD7594 is a non-steroidal GR modulator and may have several potential benefits over conventional ICS. Non-clinical pharmacology studies in the Sephadex rat model, known to provide reasonable estimates of the relative potency of GR agonists in humans, indicate that the therapeutic index may be improved for AZD7594 compared with currently marketed inhaled steroidal GR agonists such as fluticasone propionate. The high selectivity of AZD7594 for the GR over other steroid nuclear hormone receptors and the high degree of plasma protein binding (>99%) could also theoretically be beneficial.

AZD7594 has a predicted 24-hour duration of its effect that could improve convenience, and, potentially adherence to prescribed treatment, an acknowledged challenge in current COPD and asthma management.

The aim is to develop AZD7594 as a once daily inhaled non-steroidal selective GR modulator (SGRM), which may ultimately lead to better disease control of both COPD and asthma through improved efficacy and compliance. The overall rationale for developing a once daily AZD7594 in a dry powder inhaler (DPI) is to provide a safe and effective future treatment option for both asthma and COPD patients.

1.2 Rationale for study design, doses and control groups

The objective of the study is to assess the efficacy and safety of multiple dose levels of AZD7594 as compared to placebo after a 12-week treatment period in patients with asthma symptomatic on low dose ICS. The comparison between placebo and an active comparator (fluticasone furoate [FF]) will be used for bench marking. AZD7594 (steady state) pharmacokinetics (PK) of the multiple dose levels of AZD7594 will be assessed in a subset of patients. In addition, 24-hour plasma cortisol sampling will be carried out to assess cortisol suppression as a measure of HPA axis suppression, a well-known class-effect of inhaled ICS (Dahl, 2006; Wlodarczyk et al, 2008). The target population includes male and female patients, aged 18 to 85 years with body mass index (BMI) ≤35, with a clinical diagnosis of asthma as per the criteria of the GINA 2018 and EMA guidelines (GINA, 2018) (CHMP/EWP/2922/01 Rev.1, 2015) who are symptomatic on low dose ICS and demonstrate bronchodilator reversibility (increase of trough forced expiratory volume in 1 second [FEV_1] ≥12% and ≥200 mL after administration of a short-acting bronchodilator).

A placebo-controlled, double-blinded design has been chosen to limit the occurrence of conscious and unconscious bias in the conduct and interpretation of the clinical study arising from the influence that the knowledge of treatment may have on the recruitment and allocation of patients. It is considered the optimal approach according to International Council for Harmonisation (ICH) E9 “Statistical principles in clinical studies”. The active comparator (FF) will be open-label. An overall 1:1:1:1:1:1:1 randomisation ratio has been selected to avoid any possible bias.

Matching placebo will be used as a negative control and FF will be used as a positive control for assessing AZD7594 characteristics. An open-label active comparator has been chosen over a double-dummy design because of the difficulties to produce a placebo of the active comparator. The DPI device containing AZD7594 or placebo will have the same external appearance to ensure the double-blinded nature of the study. Neither the active compound nor the placebo has perceptible taste, appearance, odour or colour that could unmask their identity. By randomly assigning treatments, differences in baseline characteristics of the treatment groups will be minimised. FF was chosen as an active comparator at the recommendation of the Food and Drug Administration (FDA) because of the once daily dosing, and the need to demonstrate efficacy.

The inclusion of a placebo arm is considered the most reliable method to minimise patient and Investigator bias according to ICH E10 “Choice of control group in clinical trials”, ICH/364/96 guideline adopted by the Committee for Proprietary Medicinal Products (CPMP), CPMP/EWP/562/98 and the FDA. The use of placebo is also recommended by the EMA regulatory guidance in the design of dose-finding studies for moderate-severe asthma.

The proposed dose levels of AZD7594 in this study range from 50 µg to 720 µg QD (delivered dose). Doses have been selected based on the safety, tolerability, PK, and pharmacodynamics information generated in previous AZD7594 clinical studies. Three AZD7594 dose levels (58 µg, 250 µg and 800 µg [delivered doses]) have been tested in a 2 week incomplete block crossover study in asthmatic patients. There was a clear dose

ordering of the response as measured by primary endpoint of trough FEV_1 on Day 15, with the highest effect observed in the 800 µg dose group. All dose levels were found to be safe and well tolerated. The cortisol suppression at the highest dose (720 µg) is predicted to be <10%. The proposed dose levels should adequately cover the therapeutic dose range.

For further details, refer to the Investigator's Brochure (IB).

1.3 Benefit/risk and ethical assessment

Patients participating in the early clinical studies of AZD7594 will obtain no individual benefit from their participation in the studies. The aim of the early studies is to enable further investigations in patients to evaluate and develop AZD7594 as a once daily selective inhaled GR modulator for treatment for COPD and asthma, with an acceptable side-effect profile compared to inhaled GR agonists already on the market.

Data have been gathered from previous clinical experience with GR agonists, non-clinical safety pharmacology and toxicology studies and clinical studies with AZD7594. The GR is a well-known target and there is extensive clinical experience with GR agonists use as ICSs. The side-effect profile of inhaled GR agonists is well-known and consists of local effects including oropharyngeal candidiasis, dysphonia and cough, as well as systemic effects such as skin thinning and bruising, endocrine/metabolic effects (including HPA suppression), osteoporosis and (in children) reduced growth velocity (Dahl, 2006). Pneumonia has also been noted with ICS use, especially in patients with severe COPD (GOLD, 2017). Although AZD7594 is not a steroid, given the shared target, the side-effect profile is potentially similar. In preclinical studies, AZD7594 displayed features typical of a potent GR agonist. Findings in humans can be monitored and are expected to be reversible. In the clinical studies conducted to date, AZD7594 was generally safe and well tolerated, though HPA suppression was seen at inhaled delivered doses higher than 1248 µg. Overall, the data generated suggest no findings of concern that would preclude proposed clinical studies with inhaled administration of AZD7594. Intravenous and oral dosing of AZD7594 (single doses) are also supported by the available data.

The development of any AE, abnormality in laboratory variables or any other safety variables will be closely monitored and evaluated on an ongoing basis during the clinical studies. Data from patients and healthy volunteers involved in the current and future AZD7594 clinical studies will be monitored for electrocardiogram (ECG), spirometry (only in patients with asthma or COPD), clinical chemistry, vital signs, adverse events (AEs) and PK. To further investigate the effect of AZD7594 on cortisol suppression, 24-hour plasma cortisol levels will be measured in a subset of patients in the current, as well as future clinical studies. Systemic absorption can occur directly through the lung surface or by swallowing the drug. In accordance with standard practice, patients will be instructed to wash their mouth after drug inhalation to reduce local and systemic side effects.

This study will include a placebo arm. The use of the placebo arm may increase the risk of asthma exacerbation among enrolled patients randomised to this treatment. However, the inclusion of a placebo arm is in accordance with EMA (CHMP/EWP/2922/01 Rev.1, 2015),

which recommends randomised, double-blind, placebo-controlled trials for dose-finding studies. This approach has previously been used safely in moderate-to-severe asthma populations to study the efficacy of FF (Bleeker et al, 2012 and Busse et al, 2012).

Patients enrolled in the trial will be requested to take protocol-defined asthma medications only. All patients will be provided with a short-acting beta$_2$ agonist (SABA) (salbutamol/albuterol) to be used as rescue medication throughout the run-in and treatment periods. Although some patient may have an increased risk of deterioration based on a decrease in their total inhaled steroid dose, this risk will be minimised by frequent study visits, symptom reporting, and contact with medical personnel. The Investigators will carefully monitor the patients throughout the study, and evidence of asthma progression (through study visits and eDiary recordings of lung function, symptom score, and rescue inhaler use), will trigger an alert to the local clinician as well as the medical monitor. Patients whose asthma is not controlled on low dose ICS during the Run-in Period will be discontinued from the study, and patients are free to withdraw from participation in the study at any time. Upon completion of the study, patients are not restricted in the choice of medical therapies.

For further details, refer to the IB.

1.4 Study design

This is a randomised, placebo-controlled, double-blind study with an open-label active comparator ICS (FF) arm to assess the efficacy and safety of AZD7594 administered QD by inhalation at multiple dose levels over a 12-week treatment period to patients with asthma symptomatic on low dose ICS.

The study will be conducted in approximately 100 centres in 8 countries in Europe, United States (US), South Africa, and Japan. It is planned that approximately 714 patients will be randomised into the study, 102 patients per arm. The total duration of the study will be between 113 to 135 days for each individual patient and is planned to run approximately 12 months (it should not exceed 18 months).

The primary objective of the study is to determine the efficacy of AZD7594 as assessed by change in trough forced expiratory volume in 1 second (FEV_1) at Week 12, when compared to placebo, with the aim of selecting doses to advance to Phase 3 studies.

All patients will sign an informed consent form (ICF) prior to participating in any study-specific procedures.

The study will consist of a Run-in Period (Visits 1 to 3), a Treatment Period (Visits 4 to 7) and a Follow-up Contact (Visit 8) (Figure 1). All patients will be provided budesonide for the run-in period, a SABA (salbutamol/albuterol) as rescue medication for use throughout the run-in and treatment periods and will be randomly assigned to AZD7594, FF, or placebo during the treatment period. Patients will record daily symptoms, peak flow, and rescue medication use in eDiaries.

Run-in Period: This period will typically last 21 to 28 days (up to a maximum of 35 days, if Visit 3 is repeated) and consist of 3 visits: a Screening Visit (Visit 1), a Reversibility Visit within 7 days of Visit 1 (Visit 2) and, if reversibility criteria are met (increase of FEV_1 ≥12% and ≥200 mL after administration of a short-acting bronchodilator), a Randomisation Visit within 21 to 28 days of Visit 1 (Visit 3).

Patients found to be eligible at Visit 1 will discontinue all asthma medications and switch to low dose budesonide (200 µg twice a day [BID] in Europe and 180 µg BID in US) and rescue medication will be taken as needed. Visit 1 (Screening Visit) and Visit 2 can occur the same day, unless the patient is taking medication that precludes reversibility testing, including long-acting beta agonist (LABA), fixed dose combination ICS/LABA treatment or long-acting muscarinic antagonist (LAMA), in which case the patient will return for Visit 2 between 2 to 7 days after Visit 1, to allow sufficient time to wash-out their asthma medications.

All patients should refrain from taking SABA 6 hours prior to reversibility testing. If a patient does not meet reversibility criteria, Visit 2 can be repeated once within 1 week. If reversibility criteria are not achieved at the repeat attempt, the patient will be discontinued from the study.

Randomisation Visit (Visit 3): Patients who remain symptomatic while on low dose budesonide (as assessed by asthma mean symptom score >1 over the previous 7 days or use of a SABA on ≥3 days of the previous 7 days) and meet FEV_1 criteria (≥40% to ≤90% predicted at either −45 or −15 minutes pre-dose) will be randomised to one of 7 possible treatment arms (see below). If patients do not meet eligibility (especially symptom criteria or lung function criteria), Visit 3 can be repeated once within 1 week. If this occurs, additional budesonide may need to be provided to the patient to ensure that the patient has run-in medication (budesonide) available throughout the run-in period.

If at any point during the study, patient's asthma becomes uncontrolled (as per Asthma Control Questionnaire [ACQ-5] score of ≥3 or daily rescue (SABA) use of ≥12 puffs for ≥3 consecutive days) they will be discontinued from the study. Patients who demonstrate <80% eDiary compliance during Run-in Period, will not be randomised. Once a patient has failed screening, re-screening will not be allowed.

Treatment Period: This period will include 4 visits (Visit 4 to Visit 7) and will last 12 weeks. At Visit 3, each patient will receive one of the following 7 possible treatments:

- AZD7594 DPI 55µg [nominal strength]/50 µg [delivered dose] (QD)
- AZD7594 DPI 99 µg/90 µg QD
- AZD7594 DPI 198 µg/180 µg QD
- AZD7594 DPI 396 µg/360 µg QD
- AZD7594 DPI 792 µg/720 µg QD

- Placebo for AZD7594 QD

- FF 100 µg QD (open-label)

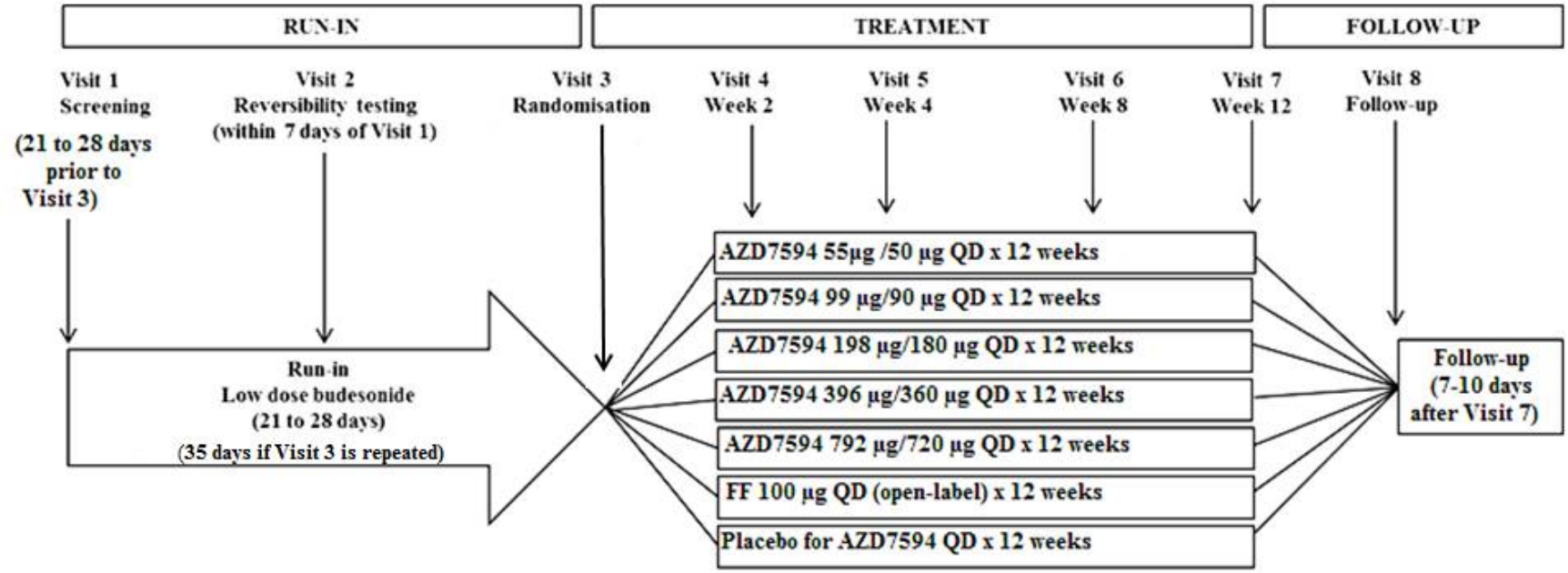
Throughout the treatment period, patients will record their daily symptoms including peak flow and medication use in eDiaries. At each treatment visit, patients will have their eDiaries reviewed, will complete the ACQ-5, will have an ECG and spirometry. At Visit 7, patients will stop investigational product (IP) and change back to their regular asthma therapy.

Follow-up Period: There will be a Follow-up telephone contact (Visit 8), 1 week after Visit 7.

The "end of study" is defined as the date when all patients randomised in the study perform the last contact (either Visit 7 or Visit 8). This date will be communicated to Regulatory Authorities and Independent Ethics Committees (IECs) in due time according to local regulations.

The study design is driven by the EMA guidance on length of treatment required (CHMP/EWP/2922/01 Rev.1, 2015); precedence for new chemical entity (FF); regulatory advice (both FDA & CHMP in 2015).

Figure 1 Study flow chart



FF, fluticasone furoate; QD, once a day.
Note: AZD7594 DPI [nominal strength]/[delivered dose]

2. STUDY OBJECTIVES

2.1 Primary objective

Primary Objective:	Outcome Measure:
To investigate the clinical efficacy of AZD7594 at different dose levels in asthmatics symptomatic on low dose ICS	**Primary efficacy endpoint:** • Change from baseline in trough FEV_1 at Week 12 **Secondary efficacy endpoints:** • Change from baseline in trough FEV_1 at Weeks 2, 4, 8, and average over the treatment period • Change from baseline in F_ENO at Weeks 2, 4, 8, 12, and average over the treatment period (analysis to be done on natural log-scale and results back-transformed to linear scale) • Change from baseline in trough FVC at Week 12 and average over the treatment period • Change from baseline in ACQ-5 at Week 12 and average over the treatment period • Change from baseline in average morning PEF over the treatment period • Change from baseline in average evening PEF over the treatment period • Change from baseline in average daily use of rescue medication over the treatment period • Change from baseline in percent night-time awakening days over the treatment period • Change from baseline in average daily asthma symptom score over the treatment period • Change from baseline in percent asthma control days over the treatment period • Change from baseline in percent rescue-free days over the treatment period • Change from baseline in percent symptom-free days over the treatment period • Time to first CompEx event, time to recurrent CompEx event, and CompEx event rate

CompEx, Composite endpoint for severe exacerbations of asthma; F_ENO, fractional exhaled nitric oxide; FVC, forced vital capacity; PEF, Peak Expiratory Flow

2.2 Secondary objectives

Secondary Objectives:	Outcome Measure:
To describe the (steady state) pharmacokinetics (PK) of AZD7594 in a subset of asthmatics symptomatic on low dose ICS	AZD7594 plasma concentration and (steady state) PK parameters ($C_{ss,max}$, $C_{ss,min}$, $t_{ss,max}$, AUC_{last}, AUC_{τ}, $C_{ss,avg}$, $C_{ss,max}$ /D, and AUC_{τ}/D and %Fluctuation) will be derived
To describe the pharmacodynamics of AZD7594 by measuring cortisol suppression in a subset of asthmatics symptomatic on low dose ICS	Area under the plasma cortisol concentration-time curve from zero to 24 hours after dosing ($AUEC_{(0-24)}$), compared to placebo
To evaluate the safety and tolerability of AZD7594 in relation to placebo in asthmatics symptomatic on low dose ICS	Adverse events (AEs)/Serious adverse events (SAEs)/Discontinuation of IP due to AE (DAEs) Vital signs Clinical chemistry/haematology parameters Electrocardiogram (ECG)[a]

[a] The following parameters will be recorded for each ECG: date and time, HR (beats/min), RR interval, PR interval, QRS interval, QT interval (ms), QT interval corrected using Fridericia's formula (QTcF) (ms), and overall evaluation.

AUC_{τ}, Area under the plasma concentration-curve within a dosing interval; AUCτ/D, Dose normalised AUCτ; AUC_{last}, area under the plasma concentration-curve from time zero to the time of last quantifiable analyte concentration; $C_{ss,avg}$, Average plasma concentration during a dosing interval at steady state, estimated as AUCτ/24; $C_{ss,max}$, observed maximum concentration at steady state, taken directly from the individual concentration-time curve; $C_{ss,max}$/D, Dose normalised $C_{ss,max}$; $C_{ss,min}$, observed minimum concentration at the end of the dosing interval; $t_{ss,max}$, time to maximum concentration at steady state, taken directly from the individual concentration-time curve.

2.3 Exploratory objectives

Exploratory Objectives:	Outcome Measure:
To obtain (optional) blood samples for future genomics (Gx) research aiming to identify/explore biomarkers or genetic variations that may affect the efficacy, pharmacodynamics, safety and tolerability profile related to AZD7594 treatment in asthmatics symptomatic on low dose ICS	DNA from whole blood
To evaluate the effect of AZD7594 on small airways obstruction in asthmatics symptomatic on low dose ICS	Change from baseline up to Week 12 in measures of airway resistance and reactance, including R5-R20, as evaluated by Forced Oscillation Technique (FOT)
[redacted] CCI	[redacted]

FOT, forced oscillation technique; Gx, genomics; ICS, inhaled corticosteroid

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

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

3.1 Inclusion criteria

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

1. Provision of informed consent prior to any study-specific procedures

2. Men and women 18 to 85 years of age, inclusive, with body mass index (BMI) ≤35

3. Patients need to be non-smokers or ex-smokers (have quit e-cigarettes or other inhaled tobacco products ≥6 months before Visit 1) with a total smoking history of less than 10 pack-years (not applicable for e-cigarettes)

4. Documented clinical diagnosis of asthma for ≥6 months before Visit 1

5. Patients on stable medium to high dose ICS (equivalent of budesonide >400 µg/day) or low to medium dose ICS/LABA for at least 4 weeks prior to screening (Visit 1) (Appendix A, GINA, 2018)

6. Patients must demonstrate reversibility to inhaled bronchodilators at Visit 2 (a ≥12% and ≥200 mL improvement in FEV_1 after administration of a 4 puffs of salbutamol/albuterol)

7. Pre-bronchodilator FEV_1 at Visit 3 between 40% and 90% predicted at either −45 or −15 minutes pre-dose

8. At Visit 3, patients need to be symptomatic on low dose ICS as evidenced by combined daily asthma mean symptom score of >1 over the previous 7 days-or SABA use on ≥3 of the last 7 days during the Run-in Period

9. Demonstrate the ability to use the study inhalation device properly

10. Patient able to perform acceptable pulmonary function testing for FEV_1 according to American Thoracic Society/European Respiratory Society (ATS/ERS) acceptability criteria

11. Patient is willing and able to follow study procedures and restrictions. Women of child-bearing potential (WOCBP) should be stable on their chosen method of highly effective birth control for a minimum of 3 months prior to Visit 1, and willing to

use that for the entire duration of the study (from the time they sign the informed consent), and for 1 month after the last dose of IP

12. For optional inclusion in the Gx component of the study, patients must provide separate informed consent for the genomic sampling and analysis

3.2 Exclusion criteria

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

1. Known or suspected hypersensitivity to any of the IPs, including budesonide, or excipients, including lactose

2. Systemic steroid use within the 6 weeks before Visit 1

3. Concomitant chronic respiratory disease (including current sleep apnea)

4. History or clinical suspicion of any clinically relevant or active disease or disorder which, in the opinion of the Investigator, may either put the patient at risk because of participation in the study, or influence the results or the patient's ability to participate in the study, or any other safety concerns in the opinion of the Investigator

5. Use of prohibited medications that cannot be stopped during the entire period of the study (starting Visit 1), see Table 5 and Table 6

6. Patients with <80% eDiary compliance during Run-in Period at Visit 3

7. ACQ-5 of ≥3 at Visit 1, Visit 2, or Visit 3

8. Daily rescue use of SABA ≥12 puffs for ≥3 consecutive days at any time during Run-in Period, before randomisation

9. Any clinically important abnormalities in rhythm, conduction or morphology of the digital ECG at rest and any abnormalities in the digital ECG (at Visit 1 or Visit 3) that, as considered by the Investigator, may interfere with the interpretation of QT interval corrected (QTc) interval changes

10. Prolonged QT interval corrected using Fridericia's formula (QTcF) ≥450 msec based on ECG at Visit 1 or Visit 3; or family history of long QT syndrome

11. PR (PQ) interval prolongation (>240 msec), intermittent second or third degree atrial-ventricular (AV) block or AV dissociation at Visit 1 or Visit 3

12. Patients with implantable cardiac defibrillator and patients with sustained symptomatic ventricular and/or atrial tachyarrhythmia

13. Patients with unstable angina pectoris or stable angina pectoris classified higher than Canadian Cardiovascular Society Class II, or a myocardial infarction or stroke within 6 months before Visit 1

14. History of hospitalisation within 12 months before Visit 1 caused by heart failure or a diagnosis of heart failure higher than New York Heart Association Class II

15. Patients who are positive for hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV) antibody or human immunodeficiency virus (HIV) at Visit 1

16. Donation of blood (≥ 450 mL) within 3 months or donation of plasma within 14 days before Visit 1

17. Suspected poor capability to follow instructions of the study, as judged by the Investigator

18. Previous participation or prior screen failure in the current study, or participation in any other research study within 1 month prior to Visit 1

19. Patient under treatment with biologicals such as monoclonal antibodies or chimeric biomolecules including omalizumab, mepolizumab, and reslizumab within 6 months or 5 half-lives before Visit 1, whichever is longer

20. Patient treated with any investigational drug within 30 days (or 5 half-lives, whichever is longer) prior to Visit 1

21. Positive drug screening result that cannot be justified by patient's medical history and its relevant treatment (over-the-counter product or a valid prescription), or history of or current alcohol or drug abuse (including marijuana and marijuana-containing valid prescriptions), as judged by the Investigator

22. Planned in-patient surgery, major dental procedure or hospitalisation during the study

23. Pregnant woman or lactating woman

24. Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff, contract research organisation staff and/or staff at the study centre)

25. Suspicion of Gilbert's syndrome

26. Vulnerable persons (eg, persons kept in detention)

Procedures for withdrawal of incorrectly enrolled patients see Section 3.5.

3.3 Exclusion criteria for the pharmacogenomic part of the study

If a patient agrees to participate in the optional Gx investigation of the study, the following exclusion criteria will apply:

- Previous allogeneic bone marrow transplant
- Non-leukocyte depleted whole blood transfusion within 120 days of the date of the genomic sample collection

3.4 Patient enrolment and randomisation

Investigator(s) should keep a record, the patient Screening and Enrolment log, of all patients who entered the study, including those who failed the screening.

At Visit 3, approximately 714 patients will be randomly assigned to one of the 7 possible treatments using an overall balanced 1:1:1:1:1:1:1 randomisation ratio. Thus, approximately 102 patients will be assigned to each treatment arm. There will be a stratification factor for US, Japan, and Rest of the World (RoW), with different allocation ratios.

The Randomization and Trial Supply Management (RTSM) specification will have stratification by region (US versus Japan versus RoW) and PK sub study participation (Yes versus No) in RoW countries excluding South Africa. PK sub study will only take place in RoW countries excluding South Africa and is not permitted in US and Japan.

Prior to initiating the study, a computer-generated randomisation schedule will be prepared to assign a treatment to a randomisation number by PAREXEL through AZRand according to the relevant Standard Operating Procedure (SOP). The randomisation schedule will describe the link between the randomly assigned treatments to each randomisation number. The block size will be determined in agreement with the Clinical Study Manager and the Statistician, and will not be communicated to the Investigators. Further details will be included in the user requirement specification document.

The Investigator(s) will:

1. Obtain signed informed consent from the patient before any study-specific procedures are performed
2. Call/access the Interactive Voice Response System (IVRS)/Interactive Web Response System (IWRS) to assign potential patients a unique identification number. This number will be composed of 2 parts: the first part will have 4 digits (fixed) representing the site identifier. The second part will have 3 digits (ascending) which will be assigned sequentially within each site, starting with 001
3. Determine patient eligibility at Visits 1 to 3. See Sections 3.1, 3.2, and 3.3

4. For patients fulfilling the eligibility criteria at Visit 3, the Investigator will call/access IVRS/IWRS to assign a unique randomisation number and medication kit number

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

Randomisation data will be kept strictly confidential, accessible only to authorised persons, until the time of unblinding of the allocated treatment of all study patients after locking the database upon termination of the study. When the study is completed and the data verified and locked and the populations defined, the randomisation list will be made available for data analysis.

Randomisation codes will be assigned in strict sequential order, as eligible patients are identified for randomisation.

3.5 Procedures for handling incorrectly enrolled or randomised patients

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

Where a patient does not meet all eligibility criteria but is randomised in error, or incorrectly started on treatment, the Investigator should inform the PAREXEL Medical Monitor immediately, and a discussion should occur between the PAREXEL Medical Monitor and the Investigator regarding whether to continue or discontinue the patient from treatment. The AstraZeneca Study Physician will also be informed and PAREXEL must ensure all decisions are appropriately documented.

3.6 Methods for assigning treatment groups

PAREXEL will be responsible for generating the randomisation scheme through AZRand. The choice of treatment group is balanced. The approximate randomisation ratio is shown in Table 1. Patients will be allocated to the 7 treatment groups in an overall 1:1:1:1:1:1:1 ratio. For sites in the US, no patients will be randomised to the AZD7594 DPI 792 µg/720 µg QD group.

Table 1 Randomisation Ratio by Region

Region	Randomisation Ratio
	AZD7594 DPI 55µg/50 µg QD AZD7594 DPI 99 µg/90 µg QD AZD7594 DPI 198 µg/180 µg QD AZD7594 DPI 396 µg/360 µg QD AZD7594 DPI 792 µg/720 µg QD* Placebo for AZD7594 QD FF 100 µg QD (open-label)
US	1:1:1:1:0:1:1
Non-US	2:2:2:2:3:2:2
Total	1:1:1:1:1:1:1

FF, Fluticasone Furoate; QD, once daily; US, United States; * US excluded.

Randomisation will be performed using the centralised IVRS/IWRS at Visit 3 (Day 1). Specific information concerning the use of the IVRS/IWRS will be provided in a separate manual. Randomised patients who discontinue from treatment will not be replaced. At randomisation, the IVRS/IWRS will inform the site about the medication kit numbers to be administered and dispensed to each particular patient.

The randomisation list will only be provided to the following personnel:

- AstraZeneca personnel responsible for study medication preparation
- Covance Bioanalytical group responsible for PK analyses

3.7 Methods for ensuring blinding

All double-blind medication kits will have similar appearance regardless of the IP (AZD7594 or placebo) contained in a DPI device and will be labelled using a unique medication identification number (Kit ID) that is linked to a treatment arm. IVRS/IWRS will assign the study medication to be dispensed to each patient at Visit 3.

Supplies of budesonide, FF and SABA (salbutamol/albuterol) will be open-label.

3.8 Methods for unblinding

Individual treatment codes, indicating the treatment randomisation for each randomised patient, will be available to the Investigator(s) or pharmacists from the IVRS/IWRS. Only authorised personnel at the research site will receive unblinding permits in IVRS/IWRS. Patients will be immediately withdrawn from the study once treatment has been unblinded.

Routines for this will be described in the IVRS/IWRS user manual that will be provided to each centre.

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

Personnel responsible for analysing PK samples will be unblinded as to the exact content of investigational treatments (ie, the randomisation code). AstraZeneca retains the right to break the code for serious adverse events (SAEs) that are unexpected and are suspected to be causally related to an IP and that potentially require expedited reporting to Regulatory Authorities. Treatment codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual patient have been made and documented.

3.9 Restrictions

Patients enrolled in the study should adhere to the following restrictions for the duration of the study. Any event likely to interfere with the objectives of the study will be communicated to the Investigator and reported without delay to AstraZeneca.

- Patient should keep regular night/day shifts
- Blood donation is not allowed throughout the study
- The following activities should preferably be avoided prior to lung function testing:
  - Consuming alcohol within 4 hours before testing
  - Consuming caffeine within 6 hours before testing
  - Performing vigorous exercise within 30 minutes before testing
  - Wearing clothing that substantially restricts full chest and abdominal expansion
  - Eating a large meal within 2 hours before testing
- Patients should avoid taking inhaled bronchodilators prior to spirometry (see Section 7.7). A SABA should be withheld for at least 6 hours before each visit up to the last procedure on that visit. If the patient has taken a SABA within 6 hours prior to the visit, the visit should be rescheduled within 1 to 2 days as possible. However, patients are permitted to use a SABA if its use is absolutely necessary during the visit, and with the approval of the Investigator.
- Restrictions on medications (prescribed or over-the-counter products) are defined in Section 7.7.

- WOCBP will require a highly effective method of birth control during the study. WOCBP should be stable on their chosen method of highly effective birth control for a minimum of 3 months prior to Visit 1, and willing to use this for the entire duration of the study (from the time they sign the informed consent), and for 1 month after the last dose of IP. With the exception of abstinence, it is recommended that male partners of enrolled women additionally use a condom during the duration of the study. Highly effective methods of birth control are defined as those which result in a low failure rate (ie, less than 1% per year) when used consistently and correctly. These include:

  - Female sterilisation (ie, documented bilateral tubal ligation)

  - Hormonal methods of contraception associated with inhibition of ovulation (including levonorgestrel intrauterine system [eg, Mirena™], medroxyprogesterone injections [eg, Depo Provera™], etonogestrel implants [eg, Implanon™, Norplan™], normal and low dose combined oral pills, norelgestromin/ethinylestradiol transdermal system, intravaginal device [eg, ethinylestradiol and etonogestrel], and desogestrel [eg, Cerazette™])

  - An intrauterine device (IUD) (provided coils are copper-banded)

  - True abstinence (when this is in line with the preferred and usual lifestyle of the patient) and male sterilisation (if only one sexual partner, with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate). Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

- Women will be considered postmenopausal if the following age-specific requirements apply:

  - Women under 50 years of age would be considered postmenopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatments AND with luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels in the postmenopausal range.

  - Women over 50 years of age would be considered postmenopausal if they have been amenorrheic for 12 months or more following cessation of all exogenous hormonal treatments.

  Women who are considered to be postmenopausal without documentation of 12-month amenorrhea and receiving hormone replacement therapy (HRT), will have to use one of the non-hormonal highly-effective contraception methods in addition to HRT, or discontinue HRT and to use hormonal highly-effective method for at least 3 months prior to Visit 1.

- Male patients will be advised in the informed consent of the potential risk to embryofoetal development observed in non-clinical studies. Male patients must be

willing to use a condom during the study and for 90 days after the study, unless their partner is over 50 years of age and have been amenorrheic for 12 months or more following cessation of all exogenous hormonal treatments or are surgically sterile. Male patients must refrain from donating sperm from the first day of dosing until 90 days after the last dose of IP.

3.10 Discontinuation of investigational product

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

- Patient withdrawal: The patient is free to discontinue treatment at any time, without prejudice to further treatment. A patient who decides to discontinue the IP will always be asked about the reason(s) and the presence of any AEs. If possible, they will be seen and assessed by an Investigator(s). AEs will be followed up (See Section 6.3) and all study drugs should be returned by the patient.

- AE (including asthma exacerbations): If a patient experiences an AE, their premature discontinuation will be considered at the discretion of either the Investigator or the patient regardless of the causal relationship to the IP. AE should be indicated as the reason for discontinuation.

- Development of protocol-specific criteria; In these cases, patients must be discontinued from the IP:

  – Patient with any asthma-specific withdrawal criteria described below:

    (a) ≥12 puffs of rescue medication for ≥3 consecutive days

    (b) Decrease from baseline in morning peak expiratory flow (PEF) by ≥30% for ≥3 consecutive days (baseline defined as mean peak flow over the last week of Run-in Period)

    (c) Decrease from baseline in evening PEF by ≥30% for ≥3 consecutive days (baseline defined as mean peak flow over the last week of Run-in Period)

    (d) ACQ-5 ≥3.0 at any time during the study

    (e) Clinical asthma exacerbation requiring increased dose of ICS or systemic steroids or hospitalisation for asthma exacerbation

  – Patient with prolonged QTcF >450 ms or an increase from baseline (Visit 3 pre-dose) of >60 ms, confirmed (persistent for at least 5 min)

    Note: If any of these conditions have been reported as AE, then this AE should be the primary reason for discontinuation reported into the electronic Case Report Form (eCRF).

- Protocol deviation: After randomisation, any protocol deviations detected should be corrected when possible and the patient should be allowed to continue. The following will lead to discontinuation of treatment: protocol deviations that could affect patient's safety (eg, illness requiring treatment(s) which in the clinical judgement of the Investigator [or after discussion with the study medical monitor] might invalidate the study by interfering with the IP); deviations due to patient non-compliance with the study protocol.

- Failure to meet randomisation criteria: Violations of inclusion and/or exclusion criteria detected after randomisation. See Section 3.5 for patients not fulfilling inclusion/exclusion criteria but detected after randomisation.

- Lost to follow-up/Non-attendance: In these cases, every effort should be made by the Investigator to ascertain the reason and to assure the patient's attendance as soon as possible. Every effort (at least 3 documented attempts) should be made to contact the patient and will be documented in the medical records. If the patient cannot be reached after that, a registered mail letter will be sent to the patient and will be documented in the medical records.

- Pregnancy: In case of pregnancy, the patient will be immediately discontinued from the study (see Section 6.6.1).

- Patient withdrawal due to death.

- Other: Study cancellation or any other reason not described above.

Generally before discontinuation of a patient from the study, a discussion between the PAREXEL Medical Monitor and the Investigator is encouraged, as much as feasible.

3.10.1 Procedures for discontinuation of a patient from investigational product

At any time, patients are free to discontinue the IP or withdraw from the study (ie, IP and assessments – see Section 3.12), without prejudice to further treatment. A patient that decides to discontinue IP will always be asked about the reason(s) and the presence of any AEs. If possible, they will be seen and assessed by an Investigator(s) in an Early Termination Visit. AEs will be followed up (See Section 6.3.2); eDiary and study drugs should be returned by the patient.

3.11 Criteria for withdrawal

3.11.1 Screen failures

Screening failures are patients who do not fulfil the eligibility criteria for the study, and therefore must not be randomised. For these patients, the reason for study withdrawal should be recorded as 'Screen failure' (ie, the patient does not meet the required inclusion/exclusion criteria). This reason for study withdrawal is only valid for screen failures (not randomised patients).

3.11.2 Withdrawal of the informed consent

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

If a patient withdraws consent to the use of donated biological samples, the patient is withdrawn from further study participation, as collection of the biological samples is an integral part of the study. This does not apply for withdrawal of consent for Gx sample.

A patient who withdraws consent will always be asked about the reason(s) and the presence of any AE. The Investigator will follow-up AEs outside of the clinical study. The patient will return the eDiary as well as the IP.

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

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

3.12 Discontinuation of the study

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

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

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

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

4. STUDY PLAN AND TIMING OF PROCEDURES

The Study Plan detailing the procedures during in the Run-in Period, the Treatment Period and during Follow-up Contact is presented in Table 2.

Table 2 Study plan detailing the procedures

	RUN-IN			TREATMENT					F/UP
	Visit 1[a] (Screening)	**Visit 2[a] (Reversibility)**	**Visit 3[a] (Randomisation)**	**Visit 4 (Wk 2)**	**Visit 5 (Wk 4)**	**Visit 6 (Wk 8)**	**Visit 7 (Wk 12) (EOT)**	**ETV**	**Visit 8 (TC)**
Day	**Within 21-28 days before Visit 3**	**Within 0-7 days after Visit 1**	**Day 1**	**Day 15 ±2 days**	**Day 29 ±1[b] days**	**Day 57 ±1[b] days**	**Day 85 ±1[b] days**		**7-10 days after Visit 7**
Signed Informed Consent	X								
Inclusion/Exclusion criteria	X	X	X						
Demography	X								
Medical/Surgical history	X								
Smoking history	X								
Asthma history	X								
Concomitant medication and procedures	X	X	X	X	X	X	X	X	X
Height/Weight	X						X[c]		
Physical examination	X[d]		X[e]				X[d]	X[d]	
Vital signs	X	X	X	X	X	X	X	X	
Inhalation training	X[f]		X[f]						
Run-in medication (budesonide)	X								
Rescue medication (SABA)[g]	X	X	X	X	X	X			
Blood sample for Gx (optional)			X[h]						

	RUN-IN			TREATMENT					F/UP
	Visit 1[a] (Screening)	**Visit 2[a] (Reversibility)**	**Visit 3[a] (Randomisation)**	**Visit 4 (Wk 2)**	**Visit 5 (Wk 4)**	**Visit 6 (Wk 8)**	**Visit 7 (Wk 12) (EOT)**	**ETV**	**Visit 8 (TC)**
Day	**Within 21-28 days before Visit 3**	**Within 0-7 days after Visit 1**	**Day 1**	**Day 15 ±2 days**	**Day 29 ±1[b] days**	**Day 57 ±1[b] days**	**Day 85 ±1[b] days**		**7-10 days after Visit 7**
[redacted]			[redacted]				[redacted]	[redacted]	
Safety laboratory[j]	X		X		X		X	X	
Digital ECG[k]	X		X	X			X	X	
Forced Oscillation Technique[l]	X		X	X	X	X	X	X	
Reversibility test[m]		X							
Spirometry (FEV_1 and FVC)[n]		X	X	X	X	X	X	X	
Peak flow meter dispensing and training	X								
Peak expiratory flow[o]	←	—	—	—	—	—	→		
F_ENO test	X	X	X	X	X	X	X	X	
[redacted]			[redacted]		[redacted]		[redacted]	[redacted]	
ACQ-5	X	X	X	X	X	X	X	X	
Dispense eDiary and training	X								
Check eDiary		X	X	X	X	X	X	X	
Collect eDiary							X	X	
Pregnancy test for females[q]	X		X		X	X	X	X	

	RUN-IN			TREATMENT					F/UP
	Visit 1[a] (Screening)	**Visit 2[a] (Reversibility)**	**Visit 3[a] (Randomisation)**	**Visit 4 (Wk 2)**	**Visit 5 (Wk 4)**	**Visit 6 (Wk 8)**	**Visit 7 (Wk 12) (EOT)**	**ETV**	**Visit 8 (TC)**
Day	**Within 21-28 days before Visit 3**	**Within 0-7 days after Visit 1**	**Day 1**	**Day 15 ±2 days**	**Day 29 ±1[b] days**	**Day 57 ±1[b] days**	**Day 85 ±1[b] days**		**7-10 days after Visit 7**
LH and FSH, only in women <50 years with amenorrhea for 12 months without an alternative medical cause	X								
Urine drug screen	X								
Serology (HBsAg, HCV, HIV)	X								
PK sampling[r]					X		X		
24-h plasma cortisol measurement[s]			X*				X		
IP dispensing[t]			X		X	X			
Return unused study medication and inhaler					X	X	X	X	
Return of budesonide used during Run-in			X						
Adverse events[u]	X	X	X	X	X	X	X	X	X

*The patients having 24-hour cortisol sampling will present to clinic 24 hours prior to Day 1 to initiate cortisol sampling. Visit 3 baseline data will be collected before finishing cortisol collection within -2 and 0 h pre-dose.

[a] Visit 1 (Screening Visit) and Visit 2 can occur the same day, unless the patient is taking a LABA, fixed dose combination ICS/LABA treatment or a LAMA, in which case the patient will return for Visit 2 within 2 to 7 days to allow sufficient time to wash-out their asthma medications. Visit 2 and Visit 3 (Randomisation Visit) can be repeated once within 7 days. It is recommended that patients should have a minimum of 21 days and maximum 28 days between Visit 1 and Visit 3. Visit 2 related procedures (e-diary check, ACQ-5 collection, FeNO) should not be performed if Visit 2 occurs on the same day as Visit 1.

[b] The length between Visit 3 and Visit 5 must not exceed 30 days in order to accommodate the 30-day drug supply. From Visit 5 to Visit 7, length between two consecutive scheduled visits must not exceed 30 days.

[c] Weight only.

[d] A complete physical examination including an assessment of the general appearance, respiratory, cardiovascular, abdomen, skin, head and neck (including ears, eyes, nose, mouth, teeth, and throat), lymph nodes, thyroid, musculoskeletal and neurological systems will be performed.

[e] A brief physical examination including an assessment of the general appearance, lung, cardiovascular system, lymphatic nodes, abdomen, musculoskeletal system, neurological system, skin, mouth, and throat will be performed.

[f] Inhalation training for budesonide will happen at Visit 1 (Screening Visit) for all patients including those switching from ICS/LABA, LABA or LAMA medications. Inhalation training for the IP (AZD7594/placebo/FF) will happen at Visit 3 after randomisation (never before Visit 3).

[g] Check if patient has enough rescue medication until the next visit (during run- in and the treatment periods) and refill if necessary, collect rescue medication at Visit 7.

[h] A blood sample will be collected for Gx analysis before IP administration at Visit 3 only from randomised patients who have signed the informed consent form for the Gx sub-study.

[i] [redacted]

[j] Safety laboratory assessments require patients to fast for 8 hours (see laboratory safety assessments table) and will be done at all visits marked; thyroid function only at baseline and at EOT (Visit 7).

[k] During treatment period, digital ECG will be measured before IP administration (prior to spirometry) and 1 h (±10 minutes) after administration as indicated.

[l] Forced Oscillation Technique will be performed in patients in the US and Europe only and must be conducted prior to spirometry.

[m] Reversibility testing will be performed 15 to 30 minutes after inhalation of 4 puffs of salbutamol/albuterol (allowed time window: 15 to 45 minutes). If the reversibility criterion is not fulfilled, spirometry measurements can be repeated one time, within 30 to 60 minutes post-SABA administration. A repeat Visit 2 may be done within 1 week of the original visit.

[n] Spirometry will be performed at all listed visits. On the days with IP dosing, it should be pre-dose spirometry. Visit 3 to Visit 7 must be started between 6:00 AM and 12:00 AM at the latest and within ±2 hours relative to the baseline assessment. During the treatment visits (Visit 3 to Visit 6), 2 spirometry measurements 30 minutes apart from each other should be done at 45 minutes (allowed time window: 35 to 55 minutes) and 15 minutes before IP administration (allowed time window: 5 to 30 minutes) at each treatment visit.

[o] Peak expiratory flow will be measured by the patient at home after completing the morning and evening diary using a peak flow meter.

[p] [redacted]

[q] To be performed in all women. At Visits 1 and 3, serum and urine pregnancy tests to be done; only a urine pregnancy test is to be done thereafter at visits marked in the table above.

[r] PK blood samples will be collected in a subset of patients (AZD7594 or placebo) at Visits 5 and 7. At Visit 5 (Day 29) pre-dose blood sample will be taken immediately after spirometry. Visit 7 PK samples will be started 24 hours prior to Visit 7 assessments: (Day 84) (pre-dose and 0.25, 0.5, 1.0, 2.0, 4.0, 8.0, 12.0, 16.0 and 24h post-dose). The exact time of sampling and dosing (the day before, and the dose in the clinic) should be noted in the eCRF.

[s] Twenty-four hour plasma cortisol measurements will be performed in the same subset of patients as PK sampling and a selected subset of FF treated patients. Plasma cortisol will be measured just before and at the end of the Treatment Period. Measurement before the first dose will serve as a baseline value (patients will be required to stay overnight for 24 h before IP administration on Day 1 and for 24 h after the last dose on Day 84). Blood sampling

will occur on Day -1 (at -24, -22, -20, -18, -16, -14, -12, -8, -4, and -2 hours), on Day 1 (0 hour pre-dose) and on Day 84 (at 0 [pre-dose], 2, 4, 6, 8, 10, 12, 16, 20, 22 and 24 hours relative to IP administration). Visit 7 assessments on Day 85.

[t] IP will be administered once daily for 84 ± 2 days (Days 1 to 84). Patients will record their intake of IP daily in their eDiary.

[u] AEs will be collected from the time of informed consent.

ACQ-5, Asthma Control Questionnaire-5; AE, adverse event; ECG, electrocardiogram; eCRF, electronic case report form, eDiary, electronic diary; CCI [redacted]; EOT, end of treatment; ETV, Early Termination Visit; FEV_1, forced expiratory volume in 1 second; F_ENO, fractional exhaled nitric oxide; FSH, follicle-stimulating hormone; F/UP, follow-up; FVC, forced vital capacity; Gx, genomics; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; HIV, human immunodeficiency virus; ICS, inhaled corticosteroids; IP, investigational product; LABA, long-acting $beta_2$ agonists; LAMA, long-acting anti-muscarinic antagonists; LH, luteinizing hormone; PK, pharmacokinetics; SABA; short-acting beta agonist; TC, telephone call; US, United States; Wk, week.

4.1 Run-in Period

Procedures will be performed according to the Study Plan (Table 2).

This period will typically last 21-28 days (up to a maximum of 35 days, if Visit 3 is repeated) and will consist of 3 visits: a Screening Visit (Visit 1), a Reversibility Visit (Visit 2) and a Randomisation Visit (Visit 3). There should be a minimum of 21 days between Visit 1 and Visit 3 to allow wash-out of all prior medications and evaluation of symptoms on a stable dose of budesonide before Visit 3.

At screening, consenting patients will be assessed to ensure that they meet eligibility criteria. Patients who do not meet these criteria must not be enrolled in the study. No study-specific procedures, including any wash-out, will be performed prior to signing the ICF.

The procedures to be performed at Visits 1 to 3 are as follows:

4.1.1 Visit 1 (Screening Visit) (within 21 to 28 days before Visit 3)

- Obtain signed informed consent
- Assess inclusion and exclusion criteria
- Record demography (age, sex, race, ethnicity, country), medical/surgical history, smoking history (date of smoking initiation, date of smoking cessation, and total pack-years), asthma history and concomitant medications and procedures
- Record body weight (in light indoor clothes, without shoes) and height, perform complete physical examination and collect vital signs (prior to dosing budesonide)
- Perform digital ECG (prior to F_ENO test)
- Dispense eDiary to patient and provide training on eDiary
- ACQ-5 to be completed by the patient
- Carry out F_ENO test
- Carry out FOT tests (FOT will be performed in patients in the US and Europe only)
- Dispense peak flow meter and provide training on peak flow monitoring
- Carry out serum and urine pregnancy tests (all women)
- Carry out LH and FSH tests (only in women <50 years with amenorrhea for 12 months without an alternative medical cause)
- Urine drug screen and serology (HBsAg, HCV, HIV)

- Budesonide inhalation training
- Dispense budesonide
- Dispense rescue medication (salbutamol/albuterol)
- Record AEs (AEs will be collected from the time of Informed Consent to Follow-up Contact)

4.1.2 Visit 2 (Reversibility Visit) (within 0 to7 days after Visit 1)

Visit 2 can occur the same day as Visit 1, unless the patient is taking a LABA, fixed dose combination ICS/LABA treatment or a LAMA, in which case the patient will return for Visit 2 within 2 to 7 days after Visit 1, to allow sufficient time to wash-out their asthma medications. Patients for whom Visit 1 and Visit 2 will be done at the same day, ECG and FOT are to be done prior to spirometry; and spirometry is to be done before budesonide.

- Collect concomitant medications and procedures information
- Collect vital signs (prior to dosing of SABA for reversibility test)
- Dispense SABA rescue medication (salbutamol/albuterol), if applicable
- ACQ-5 to be completed by patient
- Check eDiary, evaluate ACQ-5
- Record any AEs and any changes in concomitant medication since Visit 1
- Confirm the patient has not taken SABA rescue medication (salbutamol/albuterol) within the 6 hours prior to reversibility testing
- Carry out F_ENO testing
- Carry out spirometry (FEV_1 and forced vital capacity [FVC] and reversibility testing)

If a patient does not meet reversibility criteria, reversibility testing can be repeated once within 1 week. If reversibility criteria are not achieved at the repeat attempt, the patient will be discontinued from the study.

4.1.3 Visit 3 (Randomisation Visit) (Day 1, within 21 to 28 days after Visit 1)

- In the subset of patients who will have cortisol sampling, 24-hour plasma cortisol sampling will be initiated 24 hours prior to Visit 3, (at −24, −22, −20, −18, −16, −14, −12, −8, -4, −2 and 0 hours before IP administration) (patients will need to attend the clinic before Visit 3 and stay for 24 hours before IP administration on Day 1). Note the exact time of sampling in the eCRF.

- Check inclusion/exclusion criteria (see Section 3)
- Collect concomitant medications and procedures information
- Collect budesonide from the patient
- Collect vital signs (prior to dosing)
- Perform a brief physical examination
- Perform digital ECG (prior to spirometry) before and 1 hour after IP administration
- ACQ-5 to be completed by patient
- Check eDiary, evaluate ACQ-5
- Record AEs since previous visit
- F_ENO testing
- Carry out FOT tests prior to spirometry (FOT will be performed in patients in the US and Europe only)
- Carry out spirometry (FEV_1 and FVC); 2 measurements 30 minutes apart, at −45 and −15 minutes before IP administration
- Review inclusion/exclusion criteria for randomisation eligibility (daily asthma mean symptom score of >1 over the previous 7 days or SABA use on ≥3 of the last 7 days; pre-bronchodilator FEV_1 between 40-90 percent predicted at either −45 or −15 minutes pre-dose) and ECG results
- Dispense SABA rescue medication (salbutamol/albuterol), if applicable
- Collect a blood sample for Gx (in those patients who have consented)
- Collect sample for exploratory biomarkers
- Carry out safety laboratory assessments
- Carry out serum and urine pregnancy tests (all women)
- [redacted]

Only patients who meet all inclusion/exclusion criteria, remain symptomatic (as assessed by asthma mean symptom score >1 over the previous 7 days or use of a SABA on ≥3 days of the previous 7 days) and meet FEV_1 criteria (≥40% to ≤90% predicted at either −45 or −15 minutes pre-dose) at this point will be allowed to continue. If patients do not meet

criteria, Visit 3 can be repeated once within 1 week (up to a maximum of 35 days after Visit 1). Otherwise the screening failure will be recorded in the IVRS/IWRS and Electronic Data Capture (EDC) system. Investigator should ensure that patient has run-in medication (budesonide) available throughout the run in period, and **if the run in period lasts >30 days, budesonide may need to be given again to the patient when asking the patient to return for a repeat Visit 3.**

- Randomise the eligible patient via IWRS/IVRS, and obtain kit number assignment. Document the randomisation date on the medical notes
- Carry out inhalation training for IP (AZD7594/placebo/FF)
- Dispense IP to the patient

4.2 Treatment period

Descriptions of the procedures for this period are included in the Study Plan (Table 2). The Treatment Period will extend for 12 weeks, and comprise of Visits 4 to 7. During this period, the patients will take the study treatment assigned at randomisation at home with the exception of doses on study visit days (Visits 4 to 6), which will be taken at the study centre.

4.2.1 Visits 4, 5 and 6 (Days 15, 29, and 57 ± 1 day)

The length between Visit 3 and Visit 5 must not exceed 30 days in order to accommodate the 30-day drug supply. From Visit 5 to Visit 7, length between two consecutive scheduled visits must not exceed 30 days.

- Collect any unused medication and inhalers from the patient (at Visit 5 and Visit 6 only)
- Collect concomitant medications and procedures information
- Collect vital signs (prior to dosing)
- Dispense SABA rescue medication (salbutamol/albuterol), if applicable
- Perform digital ECG (only at Visit 4) (pre-dose [prior to spirometry] and 1 hour after IP administration)
- ACQ-5 to be completed by patient
- Check eDiary
- Record AEs since previous Visit
- F_ENO testing

- Carry out FOT tests prior to spirometry (FOT will be performed in patients in the US and Europe only)
- Carry out spirometry (FEV_1 and FVC); 2 measurements 30 minutes apart, at −45 and −15 minutes before IP administration and at least 23 hours after last dose
- At Visit 5 (Day 29) only: Collect PK blood samples (pre-dose) immediately after spirometry in patients who consented to participate in the PK subset. Note the exact time of sampling and dosing (the day before, and the dose in the clinic) in the eCRF.
- Carry out safety laboratory assessments (only at Visit 5)
- [redacted]
- Carry out urine pregnancy test (all women) at Visit 5 and Visit 6
- Dispense IP to the patient (Visit 5 and Visit 6)

4.2.2 Visit 7 (Day 85± 1 day), End of treatment

- The subset of patients who will have PK and/or cortisol sampling will present to the clinic for sample collection 24 hours prior to Visit 7
- PK subset: Collect PK blood samples on Day 84 (pre-dose, and 0.25, 0.5, 1.0, 2.0, 4.0, 8.0, 12.0, 16.0 and 24h post-dose) (patients need to stay at the clinic for 24 hours) in the subset of consented patients only. Note the exact time of dosing (the day before, and the dose in the clinic) and the exact time of sampling in the eCRF.
- Cortisol subset: Twenty-four hour plasma cortisol measurements will be performed in the same subset of patients as PK sampling and a selected subset of FF treated patients. Blood sampling on Day 84 (pre-dose and 2, 4, 6, 8, 10, 12, 16, 20, 22 and 24 hours post-dose) (patients need to stay for 24 hours). Note the exact time of sampling in the eCRF.
- Collect any unused medication and inhalers from the patient
- Collect SABA rescue medication (salbutamol/albuterol)
- Collect concomitant medications and procedures information
- Record body weight (in light indoor clothes, without shoes)
- Perform complete physical examination and collect vital signs
- Perform digital ECG (prior to spirometry)
- ACQ-5 to be completed by patient

- Check and collect eDiary
- Record AEs since previous Visit
- F_ENO testing
- Carry out FOT tests prior to spirometry (FOT will be performed in patients in the US and Europe only)
- Carry out spirometry (FEV_1 and FVC); 2 measurements 30 minutes apart, at least 23 hours after last dose
- Collect sample for exploratory biomarkers
- Carry out safety laboratory assessments, including thyroid function
- Carry out urine pregnancy test (all women)
- [redacted]
- Patients will resume their regular asthma treatment as per the investigator's recommendation

4.2.3 Early Termination Visit

If patient discontinues prematurely from the IP for any reason, the following procedures will be performed as soon as possible after last IP intake:

- Collect any unused medication and inhalers from the patient
- Record concomitant medication and procedures since previous visit
- Perform complete physical examination and collect vital signs
- Perform digital ECG (prior to spirometry)
- ACQ-5 to be completed by patient. Collect and evaluate ACQ-5 from patients
- Collect eDiary from the patients
- Record AEs since previous Visit; follow-up on any previous reported and ongoing AE
- F_ENO testing
- Carry out FOT tests prior to spirometry (FOT will be performed in patients in the US and Europe only)

- Carry out spirometry (FEV_1 and FVC); 2 measurements 30 minutes apart, at least 23 hours after last dose
- Collect sample for exploratory biomarkers
- Perform safety laboratory tests
- Carry out urine pregnancy test (all women)
- [redacted]
- Patients will resume their regular asthma treatment as per the investigator's recommendation

4.3 Follow-up period

Descriptions of the procedures for this period are included in the Study Plan (Table 2). The Follow-up Contact will comprise of Visit 8 (telephone contact) that will be scheduled within 7 to 10 days after Visit 7 or last IP intake.

The procedures to be performed are the following:

1. Record the concomitant medication and procedures information since previous Visit
2. Record AEs since previous Visit and follow-up on any previous reported and ongoing AE

5. STUDY ASSESSMENTS

An EDC system will be used for data collection and query handling. The Investigator will ensure that data are recorded in the eCRFs as specified in the study protocol and in accordance with the instructions provided.

The Investigator will ensure the accuracy, completeness, and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement (CSA). The Investigator will sign the completed eCRFs. A copy of the completed eCRFs will be archived at the study centre.

5.1 Efficacy assessments

Efficacy measurements will be made at the time indicated in the Study Plan (Table 2).

5.1.1 Primary efficacy assessments

5.1.1.1 Pulmonary function test (spirometry)

A centralised spirometry company, e-Research Technology (ERT) will provide the spirometers and all necessary equipment (computer, calibration syringe, printer, paper, ink,

etc.), a detailed study manual and training to the technicians and PI (as needed) in charge of conducting the spirometry for this clinical study. SABA rescue medication (salbutamol/albuterol) should be withheld at least 6 hours before any pulmonary function tests.

The spirometry measurements are:

- FEV_1 (volume of air expressed in litres exhaled during the first second of performance of the FVC)

- FVC (maximal volume of air exhaled in litres with maximally forced expiratory effort from a position of maximal inspiration)

The circumstances around a patient's tests should be similar in all occasions with respect to time of the day, temperature as well as the technician, as much as possible.

Spirometry testing should be completed within a consistent time window relative to the time of the baseline assessment ±2 hours to avoid the influence of diurnal variability. 2 spirometry measurements 30 minutes apart from each other should be done at 45 minutes (allowed time window: 35 to 55 minutes) and 15 minutes before IP administration (allowed time window: 5 to 30 minutes) at each treatment visit.

The ATS and ERS guidelines (American Thoracic Society Official Documents, 2005) should be followed to provide accurate and comparable spirometry data. The spirometer will be configured to meet ATS/ERS recommendations for accuracy and precision (Miller et al, 2005). The computerised spirometer will check the consistency between tests and some of the requirements set out in the ATS/ERS spirometry guidelines, and will automatically alert the technician to the presence of some deviations from ATS/ERS requirements. However, technicians must ensure that the tests are performed with the correct technique. Technicians must use their judgement to ensure that the optimum spirometry data is gained from the patient at each test session.

These data will be electronically transmitted by the Investigator to ERT typically at the end of each patient's protocol visit. Throughout the study, a centralised reading of spirometry values will be performed by independent spirometry experts at ERT, blinded to patient's IP allocation and identity. A 2-step quality control will be done, as follows:

- "Over-Read" process: The first review of the spirometry data (including review of tests rejected by the technician) to verify that spirometry curves are according to ATS/ERS criteria. No changes will be made to the patient's data.

- "Best Test Review" process: During this procedure, the acceptability of the "best effort" is assessed first, followed by repeatability. If quality problems are encountered on the spirometry curve pre-identified as the "best effort", ERT will check if there is another curve that is acceptable within the measurement. If another spirometry curve is available that meets the acceptability standards, the current "best effort" will be deselected and the

curve with the highest value specified according to the parameter will become the "best effort" for the measurement. This new "best effort" will represent the "best test" in all analysis and reporting for the patient. A report will be sent to the Investigator indicating the change in "best test" with the reasons for the change. The Investigator will sign the report and store it along with their source documentation. The Investigator can contest the "best test" change by contacting the study medical monitor and following the rejection process.

Prior to the first spirometry, a trained technician should demonstrate the procedure to the patient by using a detached mouthpiece and allow practice attempts. Demonstration should be repeated and the patient should practise the procedure as many times during the study course as deemed necessary. Care should be taken to allow the patient sufficient time to rest between efforts so that they do not become excessively fatigued so that spirometry data quality is impacted.

Patients who are unable to produce acceptable spirometry tests must not be included in the study. The patient should be comfortable before the test; tight clothing should be loosened to allow the thorax to move freely. Each manoeuvre comprises 1 "set of tests": at least 3 measurements (curves) that are technically adequate are needed according to the acceptability and repeatability criteria of the ATS/ERS spirometry guidelines. If both the acceptability and repeatability criteria are met, and the data are considered optimal for the specific patient, the manoeuvre session can conclude after 3 measurements. If 1 or both of these criteria are not met, or the data generated are not consistent with the patients normal optimal efforts with no potential to improve then, a maximum of 5 additional tests (up to a total of 8 tests) should be performed until either both criteria are met, unless the patient is tired and cannot provide any further useful data.

The operator performing the spirometry must print every spirometry test. The responsible Investigator will need to review, sign and date the printouts.

Details on restrictions prior to lung function testing are available in Section 3.9.

5.1.2 Secondary efficacy assessments

Use of eDiary: At Visit 1, patients will receive an eDiary (AM3 Diary provided by ERT) to complete during the study. Patients will be provided training on the use of eDiary. During the Run-in and Treatment Period, patients will report their daily asthma symptoms, rescue medication intake (number of puffs/day), budesonide intake, PEF flow (morning and evening), and night-time awakening (morning, on a daily basis). During the Treatment Period, patients will report their intake of IP on a daily basis. Compliance as measured by eDiary should be ≥80% in the Run-in Period and is expected to be ≥80% during the Treatment Period.

While at the study centre at Visits 1, 2, 3, 4, 5, 6, and 7, patients will complete the ACQ-5 within the AM3.

5.1.2.1 Asthma Control Questionnaire-5

The validated ACQ-5 measures both the adequacy of asthma control and changes in asthma control. Patients are asked to recall how their asthma was during the previous week and to evaluate their symptoms. The questionnaire has 5 items (Appendix B); each item is scored on a scale of 0 to 6, where higher scores represent more severe impairment/symptoms. The overall ACQ-5 score is the average of the scores for each of the questions included in the questionnaire.

The ACQ-5 will be filled in by the patient on site (ACQ-5 is included in the eDiary and can be activated on site via a password).

5.1.2.2 Fractional exhaled nitric oxide

To investigate the effect of AZD7594 on airway inflammation, the measurement of F_ENO will be performed in accordance with ATS/ERS guidelines (American Thoracic Society Official Documents, 2005). Standardised conditions with regard to exhalation flow rate and duration of exhalation will be followed such that plateau definition can be evaluated over a minimum of 3 seconds. The concentration of F_ENO will be measured in units of ppb.

5.1.2.3 Peak expiratory flow

Peak expiratory flow will be measured by the patient at home after completing morning and evening diary using a peak flow meter (AM3 device will be provided by ERT) during the Run-in and Treatment Period. Patients will be provided with a device at Visit 1 and receive training on peak flow monitoring at that time.

The PEF measurement must be done immediately upon waking up, after the patient has cleared out mucus and before inhaling the IP and any rescue medication. The evening measurement should be done just before going to bed. The measurements should be made while standing and the best of 3 attempts should be recorded in eDiary. Patients will have peak flow reviewed at study visits, and can be offered re-training if there are any concerns with the technique.

5.1.2.4 Rescue medication use

Patients will be provided with a SABA (salbutamol/albuterol), as rescue medication, to be used as needed, starting from Visit 1. Patients will be provided with an eDiary at Visit 1 and asked to record their daily use of rescue medication during the Run-in and Treatment Period.

SABA rescue medication (salbutamol/albuterol) should be withheld at least 6 hours before any pulmonary function tests.

5.1.2.5 Asthma symptom score

During the Run-in and Treatment Periods, patients will record the severity of their asthma symptoms during night-time and day-time each morning and evening, using the eDiary. More details are available in Appendix C.

5.1.2.6 Night-time awakening

Patients will record every morning if they had any awakening because of asthma during the last night in their eDiary during the Run-in and Treatment Period.

5.2 Secondary objectives: Safety assessments

5.2.1 Laboratory safety assessments

Blood and urine samples for determination of clinical chemistry, haematology, and urinalysis will be taken at the times indicated in the Study Plan (see Section 4). Blood samples should be collected after at least 8h-fasting. The results of tests performed at Visit 3 will be regarded as baseline data. Additional safety samples may be collected if clinically indicated at the discretion of the Investigator.

The date and time of collection will be recorded in the EDC.

Clinical chemistry, haematology, thyroid function, and urinalyses will be analysed by Covance. A specific manual will be distributed by Covance.

The laboratory variables to be measured are presented in Table 3.

Table 3 Laboratory safety variables

Haematology	Haematocrit, haemoglobin, erythrocytes (red blood cells), thrombocytes (platelets) count, reticulocytes, leucocytes (white blood cells) count, leucocytes differential blood count (neutrophils, lymphocytes, monocytes, eosinophils and basophils), MCV and MCH	
Clinical chemistry	Electrolytes	Sodium, potassium, calcium, phosphate and dehydroepiandrosterone sulphate
	Enzymes	AST, ALT and ALP
	Substrates	Glucose, cholesterol, triglycerides, creatinine, bilirubin, albumin, CRP and osteocalcin
	Endocrinology	T4, free T4 and TSH (Visit 1 and Visit 7 only)
	Coagulation parameters	INR
	Other	HIV, HBsAg and antibodies to HCV (at Visit 1)
Urinalysis[a]	Dipstick analysis will be performed at the centre and includes: blood/erythrocytes/haemoglobin, protein/albumin, and glucose. If clinically relevant abnormalities are detected (positive result in dipstick), the urine sample will be sent to the central laboratory for analysis of the sediment. All patients will undergo a urine drug screen[b].	

Reproductive hormone status and pregnancy testing	In all women, at Visits 1 and 3 serum and urine pregnancy tests are to be done. Only a urine pregnancy test thereafter as marked in Table 2. LH and FSH (only in women <50 years with amenorrhea for 12 months without an alternative medical cause) at Visit 1 only.

[a] A midstream urine sample (~30 mL) will be obtained in order to avoid contamination and allow proper assessment.

[b] The urine drug screen is to include amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine and opiates.

ALP, Alkaline phosphatase; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; CRP, C-reactive protein; FSH, follicle-stimulating hormone; HBsAg, Hepatitis B surface antigen; HCV, Hepatitis C virus; HIV, Human immunodeficiency virus; INR, International normalised ratio; LH, luteinizing hormone; MCH, Mean corpuscular haemoglobin; MCV, Mean corpuscular volume; TSH, Thyroid stimulating hormone; T4, Thyroxine.

The central laboratory will provide the centre with the necessary material and instructions for the sampling. Laboratory data generated will be transmitted to the company in charge of Data Management activities.

Urine sediment analysis will be performed by Covance, only when a positive result in dipstick is obtained. The central laboratory will provide the centres with the necessary material and instructions for urine sampling collection in case sediment analysis is required. Data from the sediment analysis will also be transferred to the company in charge of Data Management activities.

In addition, details on the collection, processing, shipment of samples and reporting of the results by Covance will be provided to Investigators in the Laboratory Manual.

Safety results will be communicated to the Investigators after each study visit. Investigators must review the lab reports upon receipt, write down the assessment for the abnormal parameters, sign and date them.

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

Note: If a patient shows an aspartate aminotransferase (AST) **or** alanine aminotransferase (ALT) ≥3×upper limit of normal (ULN) **or** total bilirubin (TBL) ≥2×ULN please refer to Appendix D, for further instructions.

As per AstraZeneca standards, during the course of the study the Investigator will remain vigilant for increases in liver biochemistry. The Investigator is responsible for determining whether a patient meets potential Hy's Law (PHL) criteria at any point during the study. Hy's Law (HL) guidance for the Investigator is included in Appendix D.

5.2.2 Physical examination

A complete physical examination will be performed at Screening (Visit 1), at Visit 7, and at the time of an Early Termination Visit. It and will include an assessment of the following: general appearance, respiratory, cardiovascular, abdomen, skin, head and neck (including ears, eyes, nose, mouth, teeth, and throat), lymph nodes, thyroid, musculoskeletal and neurological systems.

A brief physical examination will be performed at Visit 3 and will include an assessment of the following: general appearance, lung, cardiovascular system, lymphatic nodes, abdomen, musculoskeletal system, neurological system, skin, mouth, and throat will be performed.

Body weight and height will be measured at Visit 1 (Screening) for calculation of BMI. Patients should be in light indoor clothes without shoes. Body weight will be measured again at Visit 7.

Throughout the study, clinically relevant new findings or worsening of a pre-existing condition from the medical history/physical examination must be considered an AE and must be recorded on the AE form of the eCRF.

5.2.3 ECG

Standard digital ECG evaluations will be recorded after approximately 5 minutes resting in supine position and before any blood sampling and spirometry test. Digital ECGs will be recorded preferably always by the same technician for each patient.

ERT, as the responsible company for the centralised electrocardiographic assessments, will provide the research sites with the MasterScope equipment and supplies, specific training and written instructions.

Following an acquisition of a quality ECG tracing, the Investigator or designee will electronically transfer the data to ERT.

ECGs will be performed at the times presented in the Study Plan (Table 2).

Individual ECG analysis will be performed by the Investigator at each site. Results will be available on the ECG report printed from the MasterScope. The responsible Investigator will need to print, date and sign the printed ECG report.

The Investigator will review the reports to assess the clinical relevance of any abnormal findings and/or to decide if the patient is or remains eligible for the study. The Investigator assessment will be recorded in the eCRF.

The digital ECG will be recorded at 25 mm/sec and will consist of a recording of leads I, II, III, aVR, aVL, aVF and V1 to V6 and 10 seconds recording of lead II (rhythm strip). At least 3 complete evaluable complexes per lead will be recorded. The following ECG parameters will be determined:

- Heart rate (HR)
- RR interval: Duration in milliseconds between 2 R peaks of 2 consecutive QRS complexes
- PR interval: Duration in milliseconds from the beginning of wave P to onset of ventricular depolarisation (Q and R)
- QRS interval: Duration in milliseconds of the QRS complex
- QT interval: Duration in milliseconds from the beginning of Q wave to the end of the T-wave
- QTc interval: QT interval corrected by HR:
  - QTcF interval: QT interval corrected using Fridericia's formula ($QT[msec]/RR[sec]^{1/3}$)

Investigators will assess patients' eligibility according to the ECG report of Visit 1 and Visit 3.

Any abnormal finding in the ECG tracing will be evaluated by the Investigator and will be specifically documented and registered in the eCRF.

Throughout the study, clinically relevant new findings or worsening of a pre-existing finding in the ECGs (parameters or abnormal findings in the tracing) must be considered an AE and must be recorded in the AE eCRF form. For information on how AEs based on ECG results should be recorded and reported, see Section 6.3.

In case of technical problems, the Investigator considers any result is clinically relevant or doubtful, additional digital ECGs may be performed, using the same equipment, within a reasonable time.

5.2.4 Vital signs

The vital signs to be assessed (prior to IP administration) are blood pressure and pulse rate measurements.

For information on how AEs based on vital signs should be recorded and reported, see Section 6.3.

5.2.4.1 Blood pressure

Systolic and diastolic blood pressure (in mm Hg) will be measured after at least 5 minutes resting, and before taking any blood sample and conducting any spirometry. Measurements will be carried out with the patient in a seated position and preferably always on the same arm. Data will be recorded on the eCRF.

If there is any suspicion of unreliable measurement, blood pressure will be measured again. The value obtained on the second measurement will be considered as definitive and will be the one recorded on the eCRF.

5.2.5 Adverse events

Procedures for recording and assessing AEs are included in Section 6.3.

5.2.6 Unscheduled tests

As deemed necessary by the Investigator, additional safety test(s) can be performed at any time during the study in order to follow-up the progress of any clinically relevant abnormal finding, or to investigate any potential new AE. These additional tests out of the initial schedule of the study will not be associated with any study visit.

5.2.7 Repeated tests

Any safety test may be repeated at the Investigator's discretion when there is any kind of problem with the first test (ie, technical problem with the ECG machine, blood sample haemolysed, presence of artefacts, etc.). The Investigator should repeat the individual test as soon as possible, prior to the next visit.

The repeated tests will be associated with the same visit as the first attempt.

5.3 Reversibility testing

Airflow reversibility is not an outcome variable. Baseline reversibility testing will be performed at Visit 2, which can sometimes coincide with Visit 1 (for more details see Section 1.4).

Reversibility testing will include a pre-SABA spirometry, followed by administration of 4 puffs of SABA by oral inhalation (salbutamol/albuterol) and spirometry testing approximately 15 to 30 minutes after inhalation SABA. If the reversibility criterion is not fulfilled, spirometry measurements can be repeated one time, within 30 to 60 minutes post-SABA administration.

The reversibility test will be considered positive if patients show increase of FEV_1 ≥12% and ≥200 mL after administration of SABA.

Details on restrictions prior to lung function testing are available in Section 3.9.

5.4 Secondary objectives: Pharmacokinetics

Only selected sites that are capable of doing quality PK (and cortisol) sampling will participate in the PK subset. PK subset will include only patients who are assigned to AZD7594 or placebo treatment arms. Only patients who sign a separate ICF (PK and PD ICF) will participate in the PK subset. Approximately 20 patients per treatment arm (AZD7594 or placebo) are planned to participate in PK sampling from the selected sites.

Details of the PK parameters and analysis are given in Sections 8.4.3 and 8.5.4, respectively.

5.4.1 Collection of samples

Blood samples for PK analysis will be collected from patients participating in the PK subset at the time points (3 mL at each time point) detailed in Table 2.

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

5.4.2 Determination of drug concentration

Samples for the determination of AZD7594 concentration in plasma will be analysed by Covance on behalf of AstraZeneca, using a validated bioanalytical method. Full details of the analytical method used will be described in a Bioanalytical Report separate from the clinical study report (CSR).

Results will only be reported for samples shipped within a timeframe for which the stability of AZD7594 in the samples has been validated and shown to be acceptable.

Samples from patients assigned to placebo will only be analysed if there is cause to expect incorrect study drug administration.

5.4.3 Storage and destruction of pharmacokinetic samples

Pharmacokinetic (PK) samples will be disposed of after the Bioanalytical Report finalisation or 6 months after issuance of the draft Bioanalytical Report (whichever is earlier), unless requested for future analyses.

Pharmacokinetic samples may be disposed of or destroyed and anonymised by pooling. Additional analyses may be conducted on the anonymised, pooled PK samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately from the CSR.

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples. The results from the evaluation will not be reported in the CSR but separately in a Bioanalytical Report.

5.5 Secondary objectives: Pharmacodynamics

24-hour cortisol measurement: As a measure of cortisol suppression, 24-hour plasma cortisol measurements will be performed in the same subset of patients as PK sampling and a selected subset of FF treated patients. Only patients who sign a separate ICF (PK and PD ICF) will participate in this subset. The targeted sample size for cortisol sampling is approximately 20 patients per arm. Plasma cortisol will be measured just before and at the end of the Treatment Period. Measurement before the first dose will serve as a baseline value (patients will be required to stay overnight for 24 hours before IP administration on Day 1 and for 24 hours after the last dose on Day 84). Blood sampling will occur on Day −1 (at −24, −22,

−20, −18, −16, −14, −12, −8, −4, and −2 hours), on Day 1 (0 hour pre-dose), and on Day 84 (at 0 [pre-dose], 2, 4, 6, 8, 10, 12, 16, 20, 22 and 24 hours relative to IP administration).

2 mL of blood at each sampling time point will be collected for the plasma cortisol bioanalysis.

Samples for determination of cortisol concentration in plasma will be analysed by Covance on behalf AstraZeneca using appropriate bioanalytical methods. Full details of the analytical methods will be described in a separate Bioanalytical Report.

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

5.6 Exploratory objectives: Pharmacogenomics sub-study

5.6.1 Collection of optional genomic samples

The patient's consent to participate in the genomic research components of the study is optional.

A blood sample for genomic research will be obtained from the patients at Visit 3, ie, after randomisation, but prior to IP administration, and only after patients agree and sign the additional genomics ICF. Although DNA variants are stable parameters, early sample collection is preferred to avoid introducing bias through excluding patients who may withdraw due to an AE, such patient would be important to include in any genomic analysis. If for any reason the sample is not drawn at Visit 3, it may be taken at any visit until the last study visit. Only one sample should be collected per patient for genomics during the study.

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

5.6.2 Storage and destruction of genomic samples

The processes adopted for the coding and storage of samples for genomic analysis are important to maintain patient confidentiality. Samples will be stored for a maximum of 15 years or as per local regulations from the date of the Last Subject's Last Visit, after which they will be destroyed. DNA is a finite resource that may be used up during analyses. The results of any possible future analyses will not be reported in the CSR, but separately in a scientific report or publication.

No personal details identifying the individual will be available to AstraZeneca or designated organisations working with the DNA.

For more information on the conduct of genomic research, please refer to Appendix E.

5.7 Exploratory objectives: Biomarker analysis

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

Biomarker testing will be performed to assess response to the study drug AZD7594 and to use in patient segmentation.

The effect of AZD7594 will be investigated on the following exploratory biomarkers:

The results of such analyses will be listed and summarised by treatment, as appropriate and will be reported outside the CSR, in a separate report.

5.7.1 Storage, re-use and destruction of biological samples

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

5.7.2 Labelling and shipment of biological samples

The PI will ensure that samples are labelled and shipped in accordance with the Laboratory Manual and the Biological Substance, Category B Regulations (materials containing or suspected to contain infectious substances that do not meet Category A criteria), see Appendix F '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.

5.7.3 Chain of custody of biological samples

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

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

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

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

Samples retained for further use will be registered in the AstraZeneca Biobank during the entire life cycle.

5.7.4 Withdrawal of informed consent for donated biological samples

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

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

The PI:

- Will ensure a patient's withdrawal of informed consent to the use of donated samples is notified immediately to AstraZeneca
- Will ensure that biological samples from that patient, if stored at the study site, are immediately identified, disposed of /destroyed, and the action documented
- Will ensure the organisation(s) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed, the action documented and the signed document returned to the study site
- Will ensure that the patient and AstraZeneca are informed about the sample disposal
- Will ensure that the patient is withdrawn from the study and a follow-up visit is completed (this does not apply for withdrawal of consent for Gx sample)

5.8 Exploratory objectives: Forced oscillation technique

FOT is a non-invasive, lung function test included in this study to evaluate the study treatment effect on small airway physiology. A calibrated system will be used for measurements. Detailed procedures for performing, recording and analysing FOT data will be described in a separate manual. FOT evaluation will be performed in accordance with the schedule provided

in Table 2 and prior to spirometry. The assessment at Visit 1 will consist of a training manoeuvre for patients. All patients at selected sites will undergo FOT.

Based on pressure and flow data measured in response to a gentle, subsonic oscillatory wave (also known as airwave oscillometry [AO]) being superimposed onto the patient's quiet breathing, frequency-dependent resistance and reactance will be calculated by the AO system software. A signed and dated copy of the results printout from the equipment must be kept at the study site for SDV. The printout must be marked with the study code, patient enrolment code, date and time of measurement, and visit number. A number of parameters, including but not limited to R5-R20, will be recorded and analysed.

6. SAFETY REPORTING AND MEDICAL MANAGEMENT

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

The Investigator will closely monitor any AE and will adopt the necessary clinical measures to ensure the safety of the patients until the resolution of the AEs.

6.1 Definition of adverse events

An AE 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, ECG). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including Run-in or wash-out periods, even if no study treatment has been administered.

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

6.2 Definitions of serious adverse event

A SAE is an AE occurring during any study phase (ie, screening, treatment, follow-up), that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital abnormality or birth defect

- Is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above

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

6.3 Recording of adverse events

6.3.1 Time period for collection of adverse events

AEs will be collected from the time of signature of informed consent throughout the Run-in, as well as the Treatment period and including the follow-up period (Follow-up Contact or Early Termination Visit).

6.3.2 Follow-up of unresolved adverse events

Any AEs that are unresolved at the patient's last AE assessment in the study will be 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.

6.3.3 Variables

The following variables will be collected for each AE:

- AE (verbatim)
- The date when the AE started and stopped
- Maximum intensity
- Whether the AE is serious or not
- Investigator causality rating against the IP (yes or no)
- Action taken with regard to IP
- 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 SAE
- Date Investigator became aware of SAE
- AE is serious due to (ie, seriousness criteria)
- 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

For grading the intensity of an AE, the following intensity rating scale will be used:

1. Mild: awareness of sign or symptom, but easily tolerated (acceptable)
2. Moderate: discomfort sufficient to cause interference with normal activities (disturbing)
3. Severe: incapacitating, with inability to perform normal activities (unacceptable)

AEs will be recorded only once with their maximum intensity.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 6.2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE unless it meets the criteria shown in Section 6.2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE when it satisfies the criteria shown in Section 6.2.

6.3.4 Causality collection

The Investigator will assess causal relationship between IP administration and each AE, 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 IP?’

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 G.

6.3.5 Adverse events based on signs and symptoms

All AEs spontaneously reported by the patient or their care provider 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.

6.3.6 Adverse events based on examinations and tests

The results from the Clinical Study Protocol-mandated laboratory tests and vital signs will be summarised in the CSR. Deterioration as compared to baseline in protocol-mandated laboratory test values and vital signs should therefore only be reported as AEs if they fulfil any of the SAE criteria or are the reason for discontinuation of treatment with the IP.

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting Investigator uses the clinical, rather than the laboratory term (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).

Deterioration of a laboratory value, which is unequivocally due to disease progression, should not be reported as an AE/SAE.

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

6.3.7 Hy's Law

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

6.3.8 Disease under study

Asthma symptoms or signs, such as wheeze, cough, chest tightness, dyspnoea, breathlessness and phlegm, will be recorded as AEs when:

- The sign or symptom is serious according to definitions, 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 asthma history (defined as within 1 year of Visit 1) as judged by the Investigator

Events, which are unequivocally due to the disease under study should not be reported as an AE during the study unless they meet SAE criteria or lead to discontinuation of the IP.

6.4 Reporting of serious adverse events

All SAEs have to be reported, whether or not considered causally related to the IP, or to the study procedure(s). All SAEs will be recorded in the eCRF. A paper SAE form will be available at the study centres in case the EDC is temporarily unavailable.

If any SAE occurs in the course of the study, then Investigators or other site personnel will inform the appropriate AstraZeneca representatives or designee within one day ie, immediately but **no later than 24 hours** of when they become aware of it.

The designated AstraZeneca representative or designee will work with the Investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site (DES) **within 1 calendar day** of initial receipt for fatal and life-threatening events **and within 5 calendar days** of initial receipt for all other SAEs. Therefore all information relevant to the SAEs should be collected and entered as soon as possible.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up will be undertaken immediately. Investigators or other site personnel will inform AstraZeneca representatives or designee of any follow-up information on a previously reported fatal or life-threatening SAE within 1 calendar day ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

Once the Investigators or other site personnel indicate an AE is serious in the EDC system, an automated e-mail alert will be sent to the designated AstraZeneca representative or designee.

If the EDC system is not available, then the Investigator or other study centre personnel will report a SAE to the appropriate AstraZeneca representative or designee by e-mail/fax using the study-specific paper form, within one calendar day.

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

In Europe, the reference document for definition of expectedness/listedness is the IB for the AstraZeneca drug and for the active comparator product FF.

6.5 Overdose

Any dose above the investigated dose should be considered an overdose. There is no experience with overdose and no data regarding overdose with AZD7594 are available from clinical studies. However, overdose would likely lead to effects that are typical of GR agonists.

There is no known antidote to AZD7594. In cases of known or suspected overdose, symptomatic treatment and monitoring of vital functions should be performed according to

routine clinical practice. Immediate discontinuation of the drug should be performed, and appropriate symptomatic therapy should be instituted.

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

The designated AstraZeneca representative will work with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety DES.

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

6.6 Pregnancy

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

6.6.1 Maternal exposure

If a patient becomes pregnant during the course of the study, the IP should be discontinued immediately. If a female patient, or the female partner of a male patient, who has received IP becomes pregnant, the pregnancy will be recorded.

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

If any pregnancy occurs during the course of the study, then the Investigator or other site personnel will inform the appropriate AstraZeneca representatives within 1 calendar day ie, immediately but **no later than 24 hours** of when he or she becomes aware of it according to the safety reporting procedure stated in Section 6.4.

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

The same timelines apply when outcome information is available. In case of pregnancy, this will be reported in a specific form in the eCRF and the outcome of pregnancy will be reported through a paper form (or eCRF, if available).

6.6.2 Paternal exposure

In case of pregnancy of the patient's partner, the participant will not be necessarily discontinued from the study but the partner's pregnancy should be reported on the pregnancy form (consent from the partner must be obtained before the pregnancy form is completed) following the same timeframe and routing as described for any participant's pregnancy. Pregnancy of the patient's partner is not considered to be an AE. These pregnancies will also be followed up, and the outcome of the pregnancy (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should, if possible, be obtained and documented.

6.6.3 Time period for the collection of pregnancy information

All pregnancies in female patients or the female partners of male patients, receiving at least one administration of the IP will be recorded from first dose to 1 month after the final IP administration. Pregnancies of the female partner of male participants are only required to be recorded when the male patient received the AZD7594/placebo double-blind treatment.

6.7 Medication error

For the purposes of this clinical study, a medication error is an unintended failure or mistake in the treatment process for an AstraZeneca study drug that either causes harm to the patient or has the potential to cause harm to the patient.

A medication error is not lack of efficacy of the drug, but rather a human or process related failure while the drug is under control of the study centre staff or patient.

Medication errors include situations where an error:

- Occurred
- Was identified and intercepted before the patient received the drug
- Did not occur, but circumstances were recognised that could have led to an error

Examples of events to be reported in clinical studies as medication errors:

- Drug name confusion
- Dispensing error eg, medication prepared incorrectly, even if it was not actually given to the patient
- Drug not administered as indicated, for example, wrong route or wrong site of administration

- Drug not taken as indicated eg, tablet dissolved in water when it should be taken as a solid tablet
- Drug not stored as instructed eg, kept in the fridge when it should be at room temperature
- Wrong patient received the medication (excluding IVRS/IWRS errors)
- Wrong drug administered to patient (excluding IVRS/IWRS errors)

Examples of events that do not require reporting as medication errors in clinical studies:

- Errors related to or resulting from IVRS/IWRS - including those which lead to one of the above listed events that would otherwise have been a medication error
- Patient accidentally missed drug dose(s) eg, forgot to take medication
- Accidental overdose (will be captured as an overdose)
- Patient failed to return unused medication or empty packaging
- Errors related to background and rescue medication, or standard of care medication in open-label studies, even if an AZ product

Medication errors are not regarded as AEs but AEs may occur as a consequence of the medication error.

If a medication error occurs in the course of the study, then the Investigator or other site personnel will inform the appropriate AstraZeneca representatives within 1 day ie, immediately but no later than 24 hours of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is completed within 1 or 5 calendar days if there is a SAE associated with the medication error (see Section 6.4) and within 30 days for all other medication errors.

6.8 Management of IP related toxicities

Not applicable.

6.9 Study governance and oversight

There will be no steering committee, data monitoring committee or scientific advisory committee.

7. INVESTIGATIONAL PRODUCT AND OTHER TREATMENTS

7.1 Identity of investigational product(s)

Table 4 Investigational product

Investigational product	Dosage form and strength (nominal dose/delivered dose)	Administration route and dosing frequency
AZD7594	Inhalation powder (55 µg/50 µg)	Oral inhalation (by SD3FL inhaler, DPI) QD
	Inhalation powder (99 µg/90 µg)	
	Inhalation powder (198 µg/180 µg)	
	Inhalation powder (396 µg/360 µg)	
	Inhalation powder (792 µg/720 µg)	
Placebo to AZD7594	Inhalation powder	Oral inhalation (by SD3FL inhaler, DPI) QD
Fluticasone furoate	Inhalation powder (100 µg per nominal dose)	Oral inhalation (by ELLIPTA inhaler, DPI) QD

DPI, dry powder inhaler; IP, investigational product; QD, once a day
AstraZeneca will provide the test IPs, ie, AZD7594, fluticasone furoate, and placebo

The manufacturing, labelling, packaging and release of AZD7594 and placebo to AZD7594 will be conducted following Good Manufacturing Practices (GMPs) by AstraZeneca. Each DPI will be individually packed in an Aluminium Pouch in a box. Further information will be provided in the Investigator's drug manual.

Patients on ICS monotherapy will receive training for using the budesonide inhaler at Visit 1. At Visit 3, patients will receive training for AZD7594 or placebo and the comparator (FF) using appropriate empty inhalers for that purpose. For FF, patients will be instructed to follow the approved patient information leaflet.

Patients will record their intake of IP daily in their eDiary.

7.2 Dose and treatment regimens

7.2.1 Throughout the study

In addition to study treatment, all patients will be provided with a SABA as rescue medication (salbutamol/albuterol), to be used throughout the run-in and treatment periods. All patients should refrain from taking a SABA as rescue medication 6 hours prior to pulmonary function tests.

7.2.2 Run-in Period

This period will typically last 21-28 days (up to a maximum of 35 days, if Visit 3 is repeated) and consist of 3 visits: a Screening Visit (Visit 1), a Reversibility Visit within 7 days of Visit 1 (Visit 2) and, if reversibility criteria are met (increase of FEV_1 ≥12% and ≥200 mL after

administration of a short-acting bronchodilator), a Randomisation Visit within 21-28 days of Visit 1 (Visit 3).

Patients found to be eligible at Visit 1 will discontinue all asthma medications and switch to low dose budesonide (200 µg BID in Europe and 180 µg BID in US). Visit 1 and Visit 2 can occur the same day, unless the patient is taking a medication that precludes reversibility testing, including LABA, fixed dose combination ICS/LABA treatment or a LAMA, in which case the patient will return for Visit 2 within 2-7 days after Visit 1 to allow sufficient time to wash-out their asthma medications.

Reversibility will be assessed at Visit 2. If reversibility criteria are met at Visit 2, patients will proceed to Visit 3. Randomisation will occur at Visit 3, within 21 to 28 days of Visit 1. At Visit 3, patients who remain symptomatic while on low dose budesonide (as assessed by asthma mean symptom score >1 over the previous 7 days or use of a SABA on ≥3 days of the previous 7 days) and meet FEV_1 criteria (≥40% to ≤90% predicted at either −45 or −15 minutes pre-dose) will be randomised to one of 7 possible treatment arms (see below). If patients do not meet eligibility (especially symptom criteria or lung function criteria), Visit 3 can be repeated once within 1 week. If this occurs, additional budesonide may need to be provided to the patient to ensure that the patient has run-in medication (budesonide) available throughout the run-in period.

7.2.3 Treatment period

This period will include 4 visits (Visit 4 to Visit 7) and will last 12 weeks. Each patient will start treatment with AZD7594, placebo to AZD7594 or FF. Treatment will start after the pre-dose specified procedures and randomisation. Subsequent doses (after Visit 3) of IP will be taken at home at approximately the same time of the day, with the exception of doses on study visit days (Visits 4 to 6), which will be taken at the study centre. Patients assigned to FF arm will take this medication once a day at a daily dose of 100 µg. Patients will take the last dose of the IP the day prior to Visit 7, and resume their regular asthma therapy at the completion of Visit 7.

Further information regarding the IP kit will be provided in the Investigator drug manual.

7.3 Labelling

Labels will be prepared in accordance with GMP and local regulatory guidelines. The labels will fulfil GMP Annex 13 requirements for labelling. The label text will be translated into local language, except for the empty training and demo inhalers, which will have a label in English only.

The IP will be provided to the patient in an individual kit labelled with a study-specific label.

To allow drug reconciliation and dispensation control, research personnel will record the patient ID on the labels of the patient kit, as well as on the aluminium bag labels and inhaler labels.

Patients participating in the study will be provided with an identification card where Investigator's details, including telephone number, are included and will be instructed to keep this identification card with them at all times.

7.4 Storage

All study drugs should be kept in a secure place under appropriate storage conditions. The IP label on the study drug specifies the appropriate storage.

Further information regarding IP storage at the site will be provided in the Investigator drug manual.

7.5 Compliance

The administration of all study drugs (including IPs taken at the clinic) should be recorded in the appropriate sections of the eCRF (date and time)/MasterScope (date).

Patients will be provided with an eDiary to record their intake of the IP on a daily basis.

Compliance as measured by the eDiary should be ≥80% in the Run-in Period and is expected to be ≥80% during the Treatment Period. Re-training is to be performed for those patients who demonstrate lower compliance.

7.6 Accountability

The study drug provided for this study will be used only as directed in the Clinical Study Protocol.

The study site staff will account for all study drugs dispensed to and returned from the patient.

Study site staff and the monitor will account for all study drugs received at the site, unused study drugs and for appropriate destruction. Certificates of delivery, destruction and return should be signed.

7.7 Concomitant and other treatments

Any treatment taken during the 15 days prior to signing of the ICF must be recorded in the Previous and Concomitant Medication eCRF page to ensure proper wash-out of prohibited medications.

Patients will be withdrawn from their usual asthma therapy after signing the ICF. During the Run-in Period (typically 21-28 days and no longer than 35 days), patients will discontinue all current asthma medications and switch to budesonide (200 µg BID in Europe and 180 µg BID in US). In addition, a SABA will be provided as rescue medication for the duration of the run-in and treatment periods.

Any new treatments taken or any change in ongoing medications during the participation in the study, apart from the IP, will be transcribed onto the corresponding eCRF page by the Investigator or designee.

Patients must be instructed to inform the Investigator of plans to take any new treatment during the participation in the study, including over-the-counter medicinal and herbal products.

In the interest of patient safety and acceptable standards of medical care, patients may be allowed to take any medications not listed as either permitted or not permitted (see Table 5 and Table 6) at the discretion of the Investigator. All treatments must be recorded in the patients' eCRF. Any medication taken for medical reasons deemed acceptable by the Investigator prior to study entry will be continued at the same dose and conditions during the entire experimental phase of the study.

The tables below summarise different possible treatments for asthma and other indications, which are allowed and prohibited during the study, with examples of medication and applicable restrictions.

For more details on the restrictions that apply during the study, see Section 3.9.

Patients starting any prohibited medications during the study (after Visit 2) should be withdrawn from the study.

Table 5 Medications allowed as concomitant medications

Class of drug:
Mucolytics and expectorants not containing bronchodilators
Antihistamines (other than terfenadine, astemizole, mizolastine)
Topical, nasal and/or ocular formulations of glucocorticosteroids, disodium chromoglycate and/or nedocromil sodium
Patients on allergen specific immunotherapy must have been on a maintenance regimen for at least 3 months prior to Visit 1 and remain on a maintenance regimen during the study

Table 6 Medications prohibited as concomitant medications[a]

Class of drug:
LABA
Inhaled short- and long-acting anticholinergics
Combination of SABA and SAMA
ICS other than budesonide in the Run-in Period
Xanthines
Oral and inhaled beta$_2$ agonists (except salbutamol/albuterol used as rescue medication)
Leukotriene antagonists
Parenteral, oral or rectal steroids
Inhaled disodium cromoglycate, inhaled nedocromil sodium or 5-lipoxygenase inhibitors
Beta-adrenergic blocker, including eye-drops
Xolair® or any other monoclonal or polyclonal antibody therapy taken for any reason
Moderate and strong cytochrome P450 3A4 inhibitors (eg, ketoconazole)[b]

ICS, Inhaled corticosteroid; LABA, Long-acting beta agonist; SABA, Short-acting beta agonist; SAMA, Short-acting muscarinic antagonist

[a] Medications prohibited from Visit 1 onwards till the end of treatment (Visit 7) or early termination visit

[b] For details see Appendix H.

7.7.1 Other treatment

Other medication, which is considered necessary for the patient's safety and well-being may be given at the discretion of the Investigator(s). The administration of the first dose of Run-in budesonide and of all concomitant medication (excluding IPs and rescue medications) must be recorded in the appropriate sections of the eCRF. Administration of all the remaining doses of budesonide should be recorded in the eDiary. Administration of rescue medication should be recorded in the eDiary. Use of rescue medication will not be allowed 6 hours prior to any spirometry procedure during the study.

Written informed consent must be obtained prior to discontinuation of any asthma treatments at Visit 1. At the end of the Treatment Period, patients will resume appropriate asthma maintenance therapy.

Non-Investigational products

Product name	Dosage form and strength	Administration route and dosing frequency
Budesonide (run-in medication)	Inhalation powder 200 µg per nominal dose (ex-US) 180 µg per nominal dose (US)	Oral inhalation by DPI, BID, eg, Pulmicort® Turbohaler® 200 µg (AstraZeneca)

Product name	Dosage form and strength	Administration route and dosing frequency
SABA (salbutamol/albuterol), rescue medication	Inhalation aerosol 100 µg per nominal dose 90 µg per nominal dose (US)	Oral inhalation by MDI, PRN, eg, Sultanol® Dosier-Aerosol 100 µg (GlaxoSmithKline), Ventolin® Evohaler® 100 µg (GlaxoSmithKline)

DPI, dry powder inhaler; BID, twice a day; ex-US, excluding United States; MDI, metered-dose inhaler; PRN, as needed; SABA, short-acting beta agonist; US, United States
PAREXEL will source and provide budesonide and salbutamol/albuterol.

7.8 Post study access to study treatment

There are no plans to provide study treatment after termination of the study. Patients can return to their usual medication after completion of the study.

8. STATISTICAL ANALYSES

8.1 Statistical considerations

A fully detailed Statistical Analysis Plan (SAP) will be prepared by the Global Study Statistician from PAREXEL before database lock.

All results will be presented by treatment with descriptive statistics appropriate to the nature of the variables. Demographic and baseline characteristics will be presented as follows; for continuous variables, the number of non-missing observations, mean, standard deviation (SD), standard error (SE) of the mean, 95% confidence interval (CI) of the mean (except safety data), median, first and third quartiles, minimum and maximum, will be presented; for categorical variables: counts (n) and percentages (%) (where specified) will be presented. These summaries will be provided by time point of assessment as appropriate.

The SAS® version 9.3 or higher will be used for the data analysis. A complete set of raw data listings will be appended to the final CSR. All tables, figures and listings will be presented in portable document format (PDF) documents without any manual editing, ie, they will appear unmodified as programmed by means of the statistical package.

Details on the handling of missing data for the safety or efficacy analyses will be provided in the SAP.

8.2 Sample size estimate

Approximately 102 patients will be randomised to each arm (overall randomisation ratio 1:1:1:1:1:1:1) in order to ensure at least 86 evaluable patients per arm. This sample size will

provide 80% power to detect a difference in the primary endpoint, ie, a difference of 175 mL in change from baseline in trough FEV_1 at Week 12 between each dose of AZD7594 and placebo, assuming an inter-patient SD of 405 mL, using a 2-sided test with a significance level of 0.05 and with an estimated 15% dropout rate.

The targeted total number of patients to be randomised is approximately 714 patients. Additional patients will be screened to account for any ineligibility rate prior to randomisation. From previous studies, the screening failure rate is estimated to be approximately 50%, therefore approximately 1400-1500 screened patients will be required to achieve the goal of approximately 714 randomised patients.

8.3 Definitions of analysis sets

8.3.1 Full analysis set

The Full Analysis Set (FAS) population is defined as all patients randomised and receiving at least 1 dose of randomised IP, irrespective of their protocol adherence and continued participation in the study. Patients will be analysed as randomised, irrespective of whether or not they have prematurely discontinued. Patients who withdraw consent to participate in the study will be included up to the date of their study termination. All efficacy analyses will be based on the FAS.

8.3.2 Safety analysis set

The Safety analysis set consists of all randomised patients who received at least one dose of IP and for whom any post-dose data are available. Patients will be analysed as treated. Any important deviations from the randomised treatment assignment will be listed and considered when interpreting the safety data. All safety analyses will be based on the Safety analysis set.

8.3.3 Pharmacokinetic analysis set

The PK analysis set is defined as all randomised patients participating in the PK subset, who took at least one dose of IP and for whom at least one of the primary PK parameters can be calculated, and who have no major protocol deviations considered to impact on the analysis of the PK data (eg, disallowed medication, or incorrect study medication received). All protocol deviations that occur during the study will be considered for their severity/impact and will be taken into consideration when patients are assigned to the PK analysis set.

The exclusion of any patients or time points from the calculation of the PK parameters will be documented by the PK scientist including the reason(s) for exclusion. The available concentration data and PK parameter data for any patients excluded from the PK analysis set will be listed only, and presented in the individual figures of concentration-time plots.

8.3.4 Pharmacodynamic analysis set

The pharmacodynamic analysis set is defined as all randomised patients who took at least one dose of IP and for whom 24-hour cortisol sampling was performed and baseline and

post-baseline $AUEC_{(0-24)}$ can be calculated, and who have no major protocol deviations considered to impact on the analysis of the PD data.

8.3.5 Per Protocol set

The Per Protocol (PP) population is defined as a subset of the FAS population constituted by those patients who did not present important deviations of the protocol that may affect efficacy (eg, met all inclusion/exclusion criteria liable to affect the efficacy assessment).

8.3.6 Protocol deviations

Deviations from the protocol will be assessed as "important" by PAREXEL in conjunction with AstraZeneca. Important deviations from the protocol may lead to the exclusion of patients from the PP set and/or other analysis sets. Deviations will be defined before database hard lock and unblinding. Important deviations will include the following:

- Violation of inclusion and/or exclusion criteria
- Patients who developed withdrawal criteria during the study but were not withdrawn
- Wrong study treatment or incorrect dose administered
- Administration of prohibited concomitant medications that are expected to influence the measurement of the primary endpoint

All important protocol deviations will be listed by patient for all randomised patients. Further details will be described in the SAP.

A Blind Data Review Meeting (BDRM) will be held before database hard lock and unblinding, in order to assign the patients to each of the analysis sets according to the specified definitions. The precise reasons for excluding patients from the study populations will be defined in the protocol deviation specification and documented in the BDRM minutes.

8.4 Outcome measures for analyses

8.4.1 Primary efficacy variable

The primary variable is the change from baseline in trough FEV_1 at Week 12.

Efficacy analysis will be based on the FAS population that includes all randomised patients who received at least 1 dose of randomised study drug. Patients will be included in the analysis according to the treatment to which they were randomised.

Baseline for FEV_1 will be defined as the mean of the 2 measured values before first IP administration (30 minutes apart, at −45 minutes and −15 minutes, before IP administration) on Day 1 (Visit 3). If 1 of those 2 measurements is missing, the remaining one will be used instead. If both are missing, the screening value will be used. Trough will be defined as the mean of the 2 FEV_1 measurements 30 minutes apart (23 hours after last dose) pre-dose for

every visit throughout treatment period (Visit 4/Week 2 – Visit 7/Week 12). If 1 of these 2 measurements is missing, the remaining one will be used as trough FEV_1 instead.

8.4.2 Secondary efficacy variables

The secondary efficacy variables are ACQ-5, F_ENO, morning and evening PEF, rescue medication use, asthma symptom score, night-time awakenings and daily symptoms as recorded in an eDiary.

In addition, secondary efficacy assessment includes evaluating CompEx, a combination of severe exacerbations of asthma and diary events (ie, combination of eDiary variables). CompEx is a composite surrogate endpoint for severe exacerbations of asthma, recently developed by AstraZeneca (it is not yet a regulatory-approved clinical endpoint). Severe exacerbations are defined as those episodes that lead to hospitalisation, emergency room visit and/or treatment with oral corticosteroids. Diary events are defined by threshold and slope criteria using the following Morning/Evening (am/pm) diary variables:

- PEF
- Symptom score (0–3)
- Rescue use

CompEx can predict treatment efficacy on severe exacerbations in early development before running traditional long-term severe exacerbation trials. CompEx can be used broadly in the design of new therapeutic interventions for asthma.

8.4.3 Pharmacokinetic variables

Where possible, the following (steady state) PK parameters will be assessed for AZD7594 in a subset of patients participating in the PK subset and derived by standard non-compartmental analysis (NCA):

$C_{ss,max}$	Observed maximum concentration at steady state, taken directly from the individual concentration-time curve
$C_{ss,min}$	Observed minimum concentration at the end of the dosing interval
$t_{ss,max}$	Time to maximum concentration at steady state, taken directly from the individual concentration-time curve
AUC_{last}	Area under the plasma concentration-curve from time zero to the time of last quantifiable analyte concentration
AUC_τ	Area under the plasma concentration-curve within a dosing interval
$C_{ss,avg}$	Average plasma concentration during a dosing interval at steady state, estimated as $AUC_\tau/24$
$C_{ss,max}/D$	Dose normalised $C_{ss\ max}$

AUC_{τ}/D	Dose normalised AUC_{τ}
%Fluctuation	Fluctuation index during a dosing interval estimated as $100*(C_{ss,max} - C_{ss,min})/C_{ss,avg}$ (%), where $C_{ss,min}$ is the minimum concentration at the end of the dosing interval

Additional parameters may be determined as appropriate.

The plasma concentration-time data from patients participating in the PK subset may be pooled with other PK data to build a population PK model. PK modelling will be the responsibility of AstraZeneca and will be described in a separate Data Analysis Plan. The results of any such modelling will be reported outside the CSR.

8.4.4 Pharmacodynamic variables

The pharmacodynamics of AZD7594 will be assessed by measuring cortisol suppression in the same subset of patients as PK sampling and a selected subset of FF treated patients. Cortisol suppression will imply the measurement of the area under the plasma cortisol concentration-time curve from zero to 24 hours after dosing ($AUEC_{(0-24)}$) as compared to placebo.

8.4.5 Exploratory variables

Exploratory outcomes will include the use of FOT as a measure of small airways involvement, biomarker analysis and a Gx analysis.

No multiplicity adjustments will be done for secondary or other efficacy variables.

8.4.6 Safety outcomes

Safety will be assessed by descriptive analysis of vital signs, ECGs, laboratory assessments and AEs reported.

Safety analyses will be based on Safety analysis set that includes all patients who received at least 1 dose of the IP, and for whom any post-dose data are available. Throughout the safety results sections, erroneously treated patients (eg, those randomised to AZD7594 but actually given placebo) will be accounted for in the actual treatment group.

8.4.7 Interim futility analysis

Not applicable.

8.5 Methods for statistical analyses

8.5.1 Demographic and baseline characteristics

Analyses of demographic and baseline characteristics will be performed on the FAS. Demographic characteristics to be assessed are age, sex, race, ethnicity, country, height, weight and BMI. Baseline characteristics to be assessed include:

- Smoking duration (years) and smoking consumption (total pack-years)
- Medical history (including physical findings, asthma and surgical history) classified by System Organ Class and Preferred Term
- Asthma duration (years)
- Time since last exacerbation (days)
- Asthma severity at screening according to GINA Guidelines 2018 using the pre-SABA value at Visit 2:
  - Group 1: $FEV_1 \geq 80\%$ predicted
  - Group 2: $60\% < FEV_1 < 80\%$ predicted
  - Group 3: $FEV_1 \leq 60\%$ predicted
- Absolute values of the FEV_1 and FVC (pre- and post-bronchodilator test) at screening
- Percent of predicted values of FEV_1 and FVC at screening
- Ratio FEV_1/FVC at screening
- Mean bronchodilator reversibility (FEV_1 change in mL from pre-bronchodilator test value) at Visit 2
- Percentage of bronchodilator reversibility (% FEV_1 increase over pre-bronchodilator test value) at Visit 2

Screening values for ECGs, laboratory assessments, pregnancy tests and blood pressure will not be presented in the tables corresponding to demographic and screening characteristics but together with the corresponding assessments after baseline and with the changes from baseline to ease the interpretation of these safety outcomes.

Appropriate descriptive statistics will be provided for these variables. No statistical tests will be performed.

All demographic and baseline characteristics, will be analysed using the FAS.

8.5.2 Analyses of prior and concomitant (including rescue medication)

Analyses of prior and concomitant medication will be performed on the Safety analysis set.

8.5.2.1 Prior medication

Prior medication is defined as any medication taken within 15 days before the ICF signature date and up to the first dose of IP.

The number and percentage of patients who used any prior medication (15 days before ICF signing up to IP intake) will be summarised overall by therapeutic categories. Anatomical Therapeutic Chemical Code (third level), and preferred name. Patients with multiple drug usage in the same preferred name will be counted only once.

Additionally, a subset of the previous summary will be produced presenting the number and percentage of patients who used any prior medication for asthma within 15 days before the ICF signing up to first IP intake by therapeutic categories (eg, LABA + ICS). Therapeutic categories will be defined in the SAP.

8.5.2.2 Concomitant medication

Concomitant medication is defined as any medication taken during the study treatment duration between the date of the first dose of study drug and the date of the last dose of study drug (inclusive). Any medications started after the date of the last dose of double-blind study drug (AZD7594 or placebo) will not be considered concomitant medications.

Concomitant medications will be analysed based on 2 periods: 1) medications that the patient started to take before the randomisation and continued after the first study drug administration, and 2) medications that the patient started to take during the double-blind treatment duration.

Concomitant medication will be summarised descriptively for the Safety analysis set.

8.5.3 Analysis of the efficacy variable(s)

The analysis of all the efficacy variables will be performed on the FAS. In addition, the primary efficacy variable will also be analysed using the PP set.

8.5.3.1 Primary efficacy variable

The primary efficacy variable, change from baseline in trough FEV_1 at Week 12, will be analysed by means of MMRM using all post-baseline visit trough FEV_1 data throughout the treatment period (Visit 4/Week 2 – Visit 7/Week 12). The model will include treatment, visit, treatment by visit interaction, and region (US, Japan, and RoW) as fixed effects as well as baseline FEV_1, and baseline FEV_1 by visit interaction as covariates. This analysis will be based on the FAS (primary analysis population) and the PP set (secondary analysis population, sensitivity analysis).

The within-patient correlation will be modelled using the unstructured covariance matrix. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom. The analysis will be performed using only the observed cases without imputation of missing values. If the model does not converge, then the compound symmetry covariance structure will be used. Restricted maximum likelihood method will be applied.

Each treatment effect and treatment differences between all active treatments, administered once a day, versus placebo at each visit will be estimated by the Least Square (LS) means on the correspondent treatment by visit interaction, along with their SE and 95% CI, and the

p-value corresponding to the between-treatment group difference. The comparison between active comparator (FF) and placebo is used for bench marking.

A step-down closed testing procedure will be applied to control the overall type I error rate due to multiplicity on the primary treatment comparisons for the primary endpoint using the following hierarchy for the primary comparisons:

Change from baseline in trough FEV_1 at Week 12:

- AZD7594 DPI 792 µg [nominal strength]/720 µg [delivered dose] QD versus placebo.
- AZD7594 DPI 396 µg/360 µg QD versus placebo.
- AZD7594 DPI 198 µg/180 µg QD versus placebo.
- AZD7594 DPI 99 µg/90 µg QD versus placebo.
- AZD7594 DPI 55 µg/50 µg QD versus placebo.

The previous dose will be required to be significant at the two-sided 0.05 level in order to infer on the following dose of this pre-defined hierarchy. If a given statistical test fails to reject the null hypothesis of no treatment difference at the two-sided significance level of 0.05, then all tests lower down in the hierarchy will be interpreted as descriptive only.

In addition, the overall treatment effect and treatment difference over the double-blind treatment period will be estimated by the LS means and the difference in LS means on the treatment factor, along with the SEs, and 95% CIs and the p-value corresponding to the between-treatment group difference.

Subgroup analyses

Treatment effects will be evaluated for trough FEV_1 at Week 12 in the following subgroup of patients:

- % Predicted FEV_1 ($\geq$40 to $\leq$65% or >65 to $\leq$90%) at Visit 3 (randomisation).
- Prior use of ICS (low/medium/high dose).
- Smoking status (non-smoker, former smoker).
- Region (US, Japan, and RoW).

These variables will be analysed using similar MMRM as the primary variable.

8.5.3.2 Secondary efficacy variables

These analyses will be based on the FAS set. The following variables are secondary efficacy variables:

- Change from baseline in trough FEV_1 at Weeks 2, 4, 8, and average over the treatment period.
- Change from baseline in F_ENO at Weeks 2, 4, 8, 12, and average over the treatment period (analysis to be done on natural log-scale and results back-transformed to linear scale)
- Change from baseline in trough FVC at Week 12 and average over the treatment period
- Change from baseline in ACQ-5 at Week 12 and average over the treatment period
- Change from baseline in average morning PEF over the treatment period
- Change from baseline in average evening PEF over the treatment period
- Change from baseline in average daily use of rescue medication over the treatment period
- Change from baseline in percent night-time awakening days over the treatment period
- Change from baseline in average daily asthma symptom score over the treatment period
- Change from baseline in percent asthma control days over the treatment period
- Change from baseline in percent rescue-free days over the treatment period
- Change from baseline in percent symptom-free days over the treatment period
- Time to first CompEx event, time to recurrent CompEx event, and CompEx event rate

Similar mixed models for repeated measures as for the primary variable will be used for the analysis at specified visit week. Analysis of covariance (ANCOVA) with treatment and region (ie, US, Japan, and RoW) as fixed effects, and baseline as covariate will be used for the analysis of average over the treatment period.

CompEx is a composite endpoint combining severe exacerbation and diary events. Severe exacerbations are defined as those episodes that lead to hospitalisation, emergency room visit and/or treatment with oral corticosteroids.

Diary events are defined by threshold and slope criteria using the following Morning/Evening (am/pm) diary variables:

- PEF
- Symptom score (0–3)
- Rescue use

CompEx will be analysed with a Cox proportional hazards model, a marginal means/rates model, and a negative binomial model for time to first event, time to recurrent event, and event rate respectively, with region and treatment included as covariates in all models. Further details on the derivation and analysis of this variable will be given in the SAP.

No multiplicity adjustments will be applied for the secondary variables.

8.5.4 Analysis of pharmacokinetic variables

8.5.4.1 Calculation or derivation of the pharmacokinetic parameters

Pharmacokinetic analyses will be performed by Covance Clinical Pharmacokinetic Alliance (CPKA) on behalf of AstraZeneca R&D. (Steady state) PK parameters will be derived using standard non-compartmental methods with Phoenix® Winnonlin®, version 6.3 or higher. The PK analysis will be carried out, where possible, using actual times recorded in the raw data. If actual times are missing, nominal times may be used.

Pharmacokinetic analyses will be conducted according to AstraZeneca guidelines for PK analyses, if not otherwise indicated.

Plasma concentrations below the lower limit of quantification (BLQ) from the time of pre-dose sampling (t=0) up to the time of the first quantifiable concentration will be set to a value of 0. After this point, BLQ plasma concentrations will be set to missing for all concentration profiles. Also, if 2 or more consecutive BLQ concentrations are followed by quantifiable concentrations in the terminal portion of the concentration-curve, the profile will be deemed to have terminated and therefore these quantifiable values will be set to missing for the calculation of the PK parameters unless there is a scientific rationale not to do so documented in the PK analysis notes.

If an entire concentration-time profile is BLQ, the profile is excluded from the PK analysis.

Area under the plasma concentration-curve will be calculated using trapezoidal methods when concentration is increasing and logarithmic trapezoidal method when concentrations are decreasing.

The minimum requirement for the calculation of AUC will be the inclusion of at least 3 consecutive plasma concentrations above the lower limit of quantitation, with at least 1 of these concentrations following C_{max}.

Further details regarding the calculation of the PK parameters will be described in the SAP.

8.5.4.2 Statistical analysis of the Pharmacokinetic Parameters

A listing of PK blood sample collection times, as well as derived sampling time deviations will be provided.

Plasma concentrations will be listed and summarised by treatment using appropriate descriptive statistics. Where possible, the following descriptive statistics will be presented: n, geometric mean, geometric coefficient of variation, arithmetic mean, arithmetic SD, median, minimum and maximum based on the PK analysis set. Plasma concentrations that are BLQ will be handled as described in the SAP.

Combined individual plasma concentration per dose level (spaghetti plots) will be presented in linear and semi-logarithmic scale with separate plots for each dose level.

Figures for the geometric mean concentration-time data will be presented for all doses overlaid on the same plot, in both a linear and semi-logarithmic scale.

Additional graphical presentations of PK data may be added at the discretion of the PK scientist. More details will be provided in the SAP.

All plasma PK parameters will be listed for each patient and summarised by treatment using similar descriptive statistics. For t_{max} only n, median, minimum and maximum will be reported.

Data from patients excluded from the PK analysis set will be included in the data listings, but not in the descriptive statistics or in the inferential statistics.

Dose proportionality of AZD7594 on Week 12 (Day 84) will be assessed graphically and analysed using the power model approach with the natural logarithm of PK parameters ($C_{ss,max}$ and AUC_{τ} on Week 12/Day 84) as the dependent variable and the logarithm of the dose as the independent variable.

All descriptive and inferential statistical computations will be performed using SAS Version 9.2, or higher. Graphics may be prepared with SAS® (Version 9.4 or higher).

Further details regarding the model specifications will be provided in the SAP.

8.5.5 Pharmacodynamic analysis

The $AUEC_{(0-24)}$ (area under the plasma cortisol concentration-time curve from zero to 24 hours after dose) will be calculated by using the linear trapezoidal rule from 0 to 24 hours. The $AUEC_{(0-24)}$ will be listed by patient and time point and summarised (n, geometric mean, geometric coefficient of variation, median, arithmetic mean, arithmetic SD, minimum and maximum) by treatment. Further details regarding the handling of missing measurements will be described in the SAP.

8.5.5.1 Statistical analysis of the pharmacodynamic parameter

The change from baseline in log-transformed $AUEC_{(0-24)}$ will be analysed by ANCOVA approach with treatment as a fixed effect, baseline log AUEC as a covariate, and patient as a random effect. The estimated ratio for each AZD7594 arm versus placebo and FF versus placebo, and their associated 95% CIs will be presented.

8.5.6 Analysis of safety outcomes

All analyses of safety and tolerability outcomes will be performed on the Safety analysis set. Individual safety and tolerability data will be provided in data listings and summarised as appropriate by treatment and overall. Continuous variables (laboratory parameters, ECG, and blood pressure) will be summarised using descriptive statistics (n, mean, SD, minimum, median, and maximum) as appropriate by scheduled assessment time point. Where applicable, data will be summarised for the observed value, and for the corresponding change from baseline/screening. Categorical variables will be summarised in frequency tables (counts and percentage) as appropriate by scheduled assessment time point too.

Change from baseline will be calculated as the differences between the post-dose value at each time point and the morning value prior to first administration of the IP.

For all variables, including blood pressure, digital ECG parameters, and laboratory tests, the baseline values will be defined as the values obtained prior to the first morning IP administration on Day 1 of Visit 3.

Any clinically relevant new physical examination findings or worsening of a pre-existing physical examination finding that were to be recorded as an AE will be presented with the AEs.

AEs: The number and percentage of patients who experienced 1 or more treatment-emergent adverse events (TEAEs), and the number of TEAE occurrences will be tabulated by treatment group. An AE will be considered a TEAE if it starts after the intake of the first dose of IP and up to and including 7 days after the last dose of IP. TEAEs will be presented in data listings with System Organ Class, Preferred Term, intensity, causality, action taken, seriousness criteria and treatment group using descriptive statistics.

ECG findings will be presented with counts and percentages by treatment.

ECG results and ECG abnormalities will also be listed.

An analysis of potentially clinically significant ECG values on QT, QTcF, QRS and PR interval, and HR will be performed. The criteria based on severity will be defined in the SAP. The number and percentage of patients with potentially clinically significant ECG values will be tabulated across time and treatment group.

Blood Pressure: Systolic blood pressure and diastolic blood pressure (mm Hg) will be analysed at each scheduled assessment time point using descriptive statistics for both observed absolute values and changes from baseline.

Additionally, the number and percentage of patient with notable changes from pre-dose at each post-dose time point for systolic and diastolic blood pressure and pulse rate will be presented by treatment group. The criteria for notable changes in blood pressure will be detailed in the SAP.

Laboratory tests: Observed absolute values and changes from baseline in haematology, serum biochemistry and urinalysis parameters will be summarised by treatment group using descriptive statistics at each scheduled assessment time point.

Out of range values will be flagged in the data listings.

Additionally, out of range values in laboratory parameters will be summarised by means of shift contingency tables comparing the values (post-dose vs screening and follow-up vs screening).

8.5.7 Exploratory analysis

Except for the model-based analyses (PK or PK-PD), all exploratory analyses will be performed on the FAS.

8.5.7.1 Additional analysis

An ACQ-5 responder analysis will be explored based on the percentage of ACQ-5 responders at Weeks 2, 4, 8, and 12. An ACQ-5 responder is defined as a patient with a decrease from baseline of ≥0.5 in their ACQ-5 score. Percentage of ACQ-5 responders will be analysed by means of a logistic regression using a Generalized Linear Mixed Effect Model (GLIMMIX) approach.

The following variables will be analysed at Week 12 by using mixed models for repeated measures (with similar models as for the primary variable):

- Change from baseline (pre-dose, Visit 3) in measures of resistance and reactance via FOT including R5-R20

CCI

The results of any exploratory Gx analyses will be reported outside the CSR.

CCI

In addition, dose-response modelling for trough FEV_1 and the relationship between AZD7594 exposure and plasma cortisol $AUEC_{(0-24)}$ may be explored. A PK-PD population modelling approach with combined clinical study data may be used to characterize the effect of

AZD7594 on cortisol suppression, as well as PK-PD and clinical efficacy and/or safety relationships. Any such PK-PD modelling will be the responsibility of AstraZeneca and will be described in a separate Data Analysis Plan. The results of any such modelling will be reported outside the CSR.

9. STUDY AND DATA MANAGEMENT

9.1 Training of study centre staff

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

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

9.2 Monitoring of the study

During the study, a PAREXEL 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 Laboratory Manual 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 direct access to all original records for each patient (eg, clinic charts)
- Ensure withdrawal of informed consent to the use of the patient's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the patient

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

9.2.1 Source data

Refer to the CSA for location of source data.

9.2.2 Study agreements

The PI at each centre should comply with all the terms, conditions, and obligations of the CSA, or equivalent, for this study. In the event of any inconsistency between this Clinical Study Protocol and the CSA, 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 CSA shall prevail.

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

9.2.3 Archiving of study documents

The Investigator follows the principles outlined in the CSA.

9.3 Study timetable and end of study

The end of the study is defined as 'the last visit of the last patient undergoing the study'. For this study, the last visit corresponds to the Follow-up Contact (Visit 8).

The study is expected to start (first patient enrolled) in Quarter 3, 2018 and to end (last patient completed) by Quarter 4, 2019.

The study may be terminated at individual centres if the study procedures are not being performed according to Good Clinical Practice (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 AZD7594 (see section 3.12).

9.4 Data management by PAREXEL

Data management will be performed by PAREXEL. Data Management processes will be detailed in the Data Management Plan.

Database and data validation

DataLabs (an EDC system) will be used to collect and manage clinical data.

The Investigators (and appropriately authorised staff) will be given access (after successful completion of training) to DataLabs for use in this study. The DataLabs eCRF is specifically designed for the collection of clinical data in an electronic format. Access and rights to the eCRF will be carefully controlled and configured according to each individual's role throughout the study.

The DataLabs eCRF should be completed for each patient included in the study and should reflect the latest observations on the patients participating in the study. Therefore, the eCRFs

are to be completed as soon as possible during or immediately after the patient's visit or assessment. The Investigator must verify that all data entries in the eCRF are accurate and correct. If some assessments cannot be done, or if certain information is unavailable, not applicable, or unknown, the Investigator should indicate this in the eCRF.

After completion, the Investigator will be required to electronically sign off the clinical data.

The Data Validation Specification (DVS) will be created by PAREXEL and will contain details of consistency and structural checks to be run against the data as well as listings required for PAREXEL data cleaning and review.

Automated edit checks within DataLabs are available once the data has been entered and saved. Additional queries will also be identified during the study via listing review by PAREXEL personnel. These include queries relating to clinical data coding, external vendor data etc. Queries for data inconsistences or clarifications will be issued within the eCRF and updates will be made by the appropriate trained site personnel.

Database, edit checks, listings (programmed for data review) and any programming implying data conversions will be appropriately validated by PAREXEL.

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

Clinical coding

AEs and medical/surgical history will be classified according to the terminology of the Medical Dictionary for Regulatory Activities (MedDRA). Medications will be classified according to the WHO-Drug Enhanced plus Herbal Dictionary. Classification coding will be performed by PAREXEL.

Serious adverse event reconciliation

SAE reconciliation reports are produced and reconciled with the Patient Safety.

Data mapping

Data will be collected during the study execution and will be mapped into Study Data Tabulation Model (SDTM) datasets in an ongoing basis.

Transfers of SDTM datasets will be periodically received at AstraZeneca during the study and after database lock. The frequency of these transfers will be agreed between AstraZeneca and PAREXEL and documented within the DMP.

Management of external data

In addition to the eCRF data, PAREXEL will receive electronic records for external data processed by vendors (Covance for safety laboratory tests and PK, and ERT for MasterScope spirometry, ECG, F_ENO, FOT, IP administration, and eDiaries). A reconciliation process will

be performed by PAREXEL of eCRF data against the rest of the data sources to ensure consistency of the common data.

Audit trail of all databases will be maintained in order to protect the authenticity and integrity of the clinical data.

When all data have been coded, validated, and electronically signed, the database will be locked. Any treatment revealing data (such as the treatment information and PK data) will be added to the set of data to be transferred after the database has been locked and the populations' definition has been completed.

9.5 Data management by AstraZeneca

Data Management of genotype data

Any genotype data generated in this study will be stored in the AstraZeneca genotyping LIMS database, or other appropriate secure system within AstraZeneca and/or any other organisation contracted to work with AstraZeneca to analyse samples. The results from this genomic research will not be reported in the CSR but in a separate report, as appropriate.

Data associated with human biological samples

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

10. ETHICAL AND REGULATORY REQUIREMENTS

10.1 Ethical conduct of the study

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

10.2 Patient data protection

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

10.3 Ethics and regulatory review

An IEC/IRB should approve the final study protocol, including the final version of the ICF 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 IEC/IRB, and to the study centre staff.

The opinion of the IEC/IRB should be given in writing. The Investigator should submit the written local approval to AstraZeneca before enrolment of any patient into the study.

The IEC/IRB should approve all advertising used to recruit patients for the study.

AstraZeneca should approve any modifications to the ICF that are needed to meet local requirements.

If required by local regulations, the protocol should be re-approved by the IEC/IRB annually.

Before enrolment of any patient into the study, the final study protocol, including the final version of the ICF, will be approved by the national Regulatory Authority or a notification to the national Regulatory Authority will be done, according to local regulations.

AstraZeneca or its representative will handle the distribution of any of these documents to the national Regulatory Authorities.

AstraZeneca or its representative will provide Regulatory Authorities, ECs and PIs with safety updates/reports according to local requirements.

Each PI is responsible for providing the local IEC/IRB with reports of any serious and unexpected adverse drug reactions from any other study conducted with the IP. AstraZeneca will provide this information to the PI so that he/she can meet these reporting requirements.

10.4 Informed consent

The PI(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 a signed and dated ICF before conducting any study procedure
- Ensure the original, signed ICF(s) is/are stored in the Investigator's Study File
- Ensure a copy of the signed ICF 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 ICF that is approved by an IEC/IRB

10.5 Changes to the clinical study protocol and informed consent form

Study procedures will not be changed without the mutual agreement of the International 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 IEC/IRB 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 PI. For distribution to IEC/IRB see Section 10.3.

If a protocol amendment requires a change to a centre's ICF, AstraZeneca and the centre's IEC/IRB are to approve the revised ICF before the revised form is used.

If local regulations require it, any administrative change will be communicated to or approved by each IEC/IRB.

10.6 Audits and inspections

Authorised representatives of AstraZeneca, a Regulatory Authority, or an IEC 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, GCP, guidelines of the ICH, and any applicable regulatory requirements. The Investigator will contact PAREXEL/AstraZeneca immediately if contacted by a Regulatory Agency about an inspection at the centre.

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Appendix A Estimated clinical comparability for low, medium, and high doses of inhaled corticosteroids

Drug	Daily dose (mcg)		
	Low	**Medium**	**High**
Beclometasone dipropionate (CFC)*	200-500	>500-1000	>1000
Beclometasone dipropionate (HFA)	100-200	>200-400	>400
Budesonide (DPI)	200-400	>400-800	>800
Ciclesonide (HFA)	80-160	>160-320	>320
Fluticasone furoate (DPI)	100	Not applicable	200
Fluticasone propionate (DPI)	100-250	>250-500	>500
Fluticasone propionate (HFA)	100-250	>250-500	>500
Mometasone furoate	110-210	>210-440	>440
Triamcinolone acetonide	400-1000	>1000-2000	>2000

CFC: Chlorofluorocarbon propellant; DPI: Dry powder inhaler; HFA: Hydrofluoroalkane propellant
*Beclometasone dipropionate (CFC) is included for comparison with old literature.
Source: Global Strategy for Asthma Management and Prevention. Updated 2018. Available from http://www.ginasthma.org/ (accessed on 24 March 2018).

Appendix B Asthma Control Questionnaire-5

ASTHMA CONTROL QUESTIONNAIRE (ACQ)

(SYMPTOMS ONLY)

For further information:

Elizabeth Juniper, MCSP, MSc
Professor
20 Marcuse Fields
Bosham, West Sussex
PO18 8NA, England
Telephone: +44 1243 572124
Fax: +44 1243 573680
E-mail: juniper@qoltech.co.uk
Web: http://www.qoltech.co.uk

DECEMBER 2002

SYMPTOMS ONLY MODIFIED JUNE 2014 NORTH AMERICAN ENGLISH

ASTHMA CONTROL QUESTIONNAIRE© Page 1 of 1

Please answer questions 1 - 5.

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

1.	On average, during the past week, how often were you **woken by your asthma** during the night?	0 Never 1 Hardly ever 2 A few times 3 Several times 4 Many times 5 A great many times 6 Unable to sleep because of asthma
2.	On average, during the past week, how **bad were your asthma symptoms when you woke up** in the morning?	0 No symptoms 1 Very mild symptoms 2 Mild symptoms 3 Moderate symptoms 4 Quite severe symptoms 5 Severe symptoms 6 Very severe symptoms
3.	In general, during the past week, how **limited were you in your activities** because of your asthma?	0 Not limited at all 1 Very slightly limited 2 Slightly limited 3 Moderately limited 4 Very limited 5 Extremely limited 6 Totally limited
4.	In general, during the past week, how much **shortness of breath** did you experience because of your asthma?	0 None 1 A very little 2 A little 3 A moderate amount 4 Quite a lot 5 A great deal 6 A very great deal
5.	In general, during the past week, how much of the time did you **wheeze**?	0 Not at all 1 Hardly any of the time 2 A little of the time 3 A moderate amount of the time 4 A lot of the time 5 Most of the time 6 All the time

SYMPTOMS ONLY MODIFIED JUNE 2014 NORTH AMERICAN ENGLISH

Appendix C Asthma Symptom Score

Severity scores for asthma symptoms will be recorded daily during Run-in and Treatment Period.

Asthma symptom scores during night-time will be assessed by the patient each morning according to the following scoring system and recorded on the eDiary:

0	No asthma symptoms
1	You were aware of your asthma symptoms but you can easily tolerate the symptoms
2	Your asthma was causing you enough discomfort to cause problems with sleep
3	You were unable to sleep because of your asthma

Asthma symptom scores during the day-time will be assessed by the patient each evening according to the following scoring system and recorded on the eDiary:

0	No asthma symptoms
1	You were aware of your asthma symptoms but you can easily tolerate the symptoms
2	Your asthma was causing you enough discomfort to cause problems with normal activities
3	You were unable to do your normal activities because of your asthma

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

1. Introduction

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

During the course of the study the Investigator will remain vigilant for increases in liver biochemistry. The Investigator is responsible for determining whether a patient meets PHL criteria at any point during the study.

All sources of laboratory data are appropriate for the determination of PHL and HL events; this includes samples taken at scheduled study visits and other visits including central and all local laboratory evaluations even if collected outside of the study visits; for example, PHL criteria could be met by an elevated alanine aminotransferase (ALT) from a central laboratory **and/or** elevated total bilirubin (TBL) from a local laboratory.

The Investigator will also review adverse event (AE) data (for example, for AEs that may indicate elevations in liver biochemistry) for possible PHL events.

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

The Investigator is responsible for recording data pertaining to PHL/HL cases and for reporting AEs and serious adverse events (SAEs) according to the outcome of the review and assessment in line with standard safety reporting processes.

2. Definitions

Potential Hy's Law (PHL)
Aspartate aminotransferase (AST) or ALT ≥ 3× upper limit of normal (ULN) **together with** TBL ≥ 2×ULN at any point during the study following the start of study medication irrespective of an increase in alkaline phosphatase (ALP).

Hy's Law (HL)
AST or ALT ≥ 3× ULN **together with** TBL ≥ 2×ULN, where no other reason, other than the IP, can be found to explain the combination of increases, eg, elevated ALP indicating cholestasis, viral hepatitis, another drug.

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

3. Identification of Potential Hy's Law Cases

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

- ALT ≥3×ULN
- AST ≥3×ULN
- TBL ≥2×ULN

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

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

- Notify the AstraZeneca representative
- Request a repeat of the test (new blood draw) by the central laboratory without delay
- Complete the appropriate unscheduled laboratory electronic Case Report Form (CRF) module(s) with the original local laboratory test result

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

- Determine whether the patient meets PHL criteria (see Section 2 within this Appendix for definition) by reviewing laboratory reports from all previous visits (including both central and local laboratory results)

4. Follow-up

4.1 Potential Hy's Law Criteria not met

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

- Inform the AstraZeneca representative that the patient has not met PHL criteria
- Perform follow-up on subsequent laboratory results according to the guidance provided in the Clinical Study Protocol

4.2 Potential Hy's Law Criteria met

If the patient does meet PHL criteria the Investigator will:

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

- Within 1 day of PHL criteria being met, the Investigator will report the case as an SAE of Potential Hy's Law; serious criteria 'Important medical event' and causality assessment 'yes/related' according to Clinical Study Protocol process for SAE reporting.

- For patients that met PHL criteria prior to starting IP, the investigator is not required to submit a PHL SAE unless there is a significant change in the patient's condition.
  Note: A 'significant' change in the patient's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST or TBL) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the Investigator, this may be in consultation with the Study Physician if there is any uncertainty.

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

- Monitor the patient until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated. Completes follow-up SAE Form as required.

- Investigate the aetiology of the event and perform diagnostic investigations as discussed with the Study Physician. This includes deciding which tests available in the Hy's Law lab kit should be used.

- Complete the 3 Liver eCRF Modules as information becomes available.

5. Review and Assessment of Potential Hy's Law Cases

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

As soon as possible after the biochemistry abnormality was initially detected, the Study Physician contacts the Investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the IP, to ensure timely analysis and reporting to health authorities within 15 calendar days from date PHL criteria was met. The AstraZeneca Global Clinical Lead or equivalent and Global Safety

Physician will also be involved in this review together with other subject matter experts as appropriate.

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

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

- If the alternative explanation is not an AE, record the alternative explanation on the appropriate eCRF.

- If the alternative explanation is an AE/SAE: update the previously submitted PHL SAE and AE eCRFs accordingly with the new information (reassessing event term; causality and seriousness criteria) following the AZ standard processes.

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

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

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

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

If, there is an unavoidable delay of over 15 calendar days in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Provides any further update to the previously submitted SAE of Potential Hy's Law, (report term now 'Hy's Law case') ensuring causality assessment is related to IP and seriousness criteria is medically important, according to Clinical Study Protocol process for SAE reporting.

- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are still met. Update the previously submitted PHL SAE report following Clinical Study Protocol process for SAE reporting, according to the outcome of the review and amending the reported term if an alternative explanation for the liver biochemistry elevations is determined.

References

FDA Guidance for Industry (issued July 2009) 'Drug-induced liver injury: Premarketing clinical evaluation'.

Appendix E Genomic Research

Rationale and Objectives

AstraZeneca intends to collect and store deoxyribonucleic acid (DNA) for genomic research to explore how genomic variations may affect clinical parameters, risk and prognosis of diseases, and the response to medications. Genomic research may lead to better understanding of diseases, better diagnosis of diseases or other improvements in health care and to the discovery of new diagnostics, treatments or medications.

In addition, collection of DNA samples from populations with well described clinical characteristics may lead to improvements in the design and interpretation of clinical trials and, possibly, to genetically guided treatment strategies.

Genomic Research Plan and Procedures

Selection of genomic research population

Study selection record

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

Inclusion criteria

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

- Provide informed consent for the genomic sampling and analyses.

Exclusion criteria

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

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

Discontinuation of patients from this genomic research

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

Withdrawal of consent for genomic research: Patients may withdraw from this genomic research at any time, independent of any decision concerning participation in other aspects of the main study. Voluntary discontinuation will not prejudice further treatment. Procedures for discontinuation are outlined in Section 7.5 of the main Clinical Study Protocol.

Collection of samples for genomic research

A blood sample for genomic research will be obtained from the patients at Visit 3. Although DNA is stable, early sample collection is preferred to avoid introducing bias through excluding patients who may withdraw due to an AE, such patients would be important to include in any genomic analysis. If for any reason the sample is not drawn at Visit 3, it may be taken at any visit until the last study visit. Only one sample should be collected per patient for genomics during the study. Samples will be collected, labelled, stored and shipped as detailed in the Laboratory Manual.

Coding and storage of DNA samples

The processes adopted for the coding and storage of samples for genetic analysis are important to maintain patient confidentiality. Samples will be stored for a maximum of 15 years, from the date of last patient last visit, after which they will be destroyed. DNA is a finite resource that is used up during analyses. Samples will be stored and used until no further analyses are possible or the maximum storage time has been reached.

An additional second code will be assigned to the blood either before or at the time of DNA extraction replacing the information on the sample tube. Thereafter, the sample will be identifiable by the second, unique number only. This number is used to identify the sample and corresponding data at the AstraZeneca genomics laboratories, or at the designated organisation. No personal details identifying the individual will be available to any person (AstraZeneca employee or designated organisations working with the DNA).

The link between the patient enrolment/randomisation code and the second number will be maintained and stored in a secure environment, with restricted access at AstraZeneca or designated organisations. The link will be used to identify the relevant DNA samples for analysis, facilitate correlation of genotypic results with clinical data, allow regulatory audit and to trace samples for destruction in the case of withdrawal of consent.

Ethical and Regulatory Requirements

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

Informed consent

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

Patient data protection

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

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

Data management

Any genotype data generated in this study will be stored at a secure system at AstraZeneca and/or designated organisations to analyse the samples.

The results from this genomic research may be reported in a separate report from the CSR or published in scientific journals.

AstraZeneca and its designated organisations may share summary results (such as genomic differences from groups of individuals with a disease) from this genomic research with other researchers, such as Hospitals, Academic Organisation or Health Insurance Companies. This can be done by placing the results in scientific databases, where they can be combined with the results of similar studies to learn even more about health and disease. The researchers can only use this information for health related research purposes. Researchers may see summary results but they will not be able to see individual patient data or any personal identifiers.

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

Statistical Methods and Determination of Sample Size

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

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

Labelling and shipment of biohazard samples

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

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

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

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

- UN 3373 – Biological Substance, Category B

- are to be packed in accordance with UN3373 and IATA 650

Exempt - all other materials with minimal risk of containing pathogens

- Clinical trial samples will fall into Category B or exempt under IATA regulations

- Clinical trial samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging

- Biological samples transported in dry ice require additional dangerous goods specification for the dry ice content

- IATA compliant courier and packaging materials should be used for packing and transportation and packing should be done by an IATA certified person, as applicable

- Samples routinely transported by road or rail are patient to local regulations which require that they are also packed and transported in a safe and appropriate way to contain any risk of infection or contamination by using approved couriers and packaging / containment materials at all times. The IATA 650 biological sample containment standards are encouraged wherever possible when road or rail transport is used.

Appendix G Additional Safety Information

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

Life threatening

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

Hospitalisation

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

Important medical event or medical intervention

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

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

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

Development of drug dependency or drug abuse

A Guide to Interpreting the Causality Question

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

- Time Course. Exposure to suspect drug. Has the patient actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?

- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?

- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?

- No alternative cause. The AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, other host or environmental factors.

- Re-challenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a re-challenge.

- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

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

- Is this a recognised feature of overdose of the drug?

- Is there a known mechanism?

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

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

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

Appendix H Classification of In Vivo Inhibitors of CYP3A4 Enzymes

Examples of CYP enzyme inhibitors

CYP enzyme	Strong inhibitors	Moderate inhibitors	Weak inhibitors
CYP3A	Boceprevir, cobicistat, conivaptan, danoprevir and ritonavir, elvitegravir and ritonavir, grapefruit juice, indinavir and ritonavir, itraconazole, ketoconazole, lopinavir and ritonavir, paritaprevir and ritonavir and (ombitasvir and/or dasabuvir), posaconazole, ritonavir, saquinavir and ritonavir, telaprevir, tipranavir and ritonavir, troleandomycin, voriconazole	Aprepitant, cimetidine, ciprofloxacin, clotrimazole, crizotinib, cyclosporine, dronedarone, erythromycin, fluconazole, fluvoxamine, imatinib, tofisopam, verapamil	Chlorzoxazone, cilostazol, fosaprepitant, istradefylline, ivacaftor, lomitapide, ranitidine, ranolazine, tacrolimus, ticagrelor

CYP, cytochrome P450
Note: Strong, moderate, and weak inhibitors are drugs that increase the AUC of sensitive index substrates of a given metabolic pathway ≥5-fold, ≥2 to <5-fold, and ≥1.25 to <2-fold, respectively.

Please note the following: This is not an exhaustive list. For an updated list, see the following link:
https://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm080499.htm (accessed on 20 July 2017).

Appendix I Signatures

Not applicable.

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