Parexel International

AstraZeneca

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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

Statistical Analysis Plan

Version: 3.0

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Approved by: PPD

Nov 11 2019
Date

PAREXEL SIGNATURE PAGE

Signature(s) below confirm that the Statistical Analysis Plan was developed in accordance with SOP-GDO-WW-019 and that it is approved for release.

This document has been approved and signed electronically on the final page by the following:

	Signatory
Author	PPD Project Role: Biostatistics Lead

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REVISION HISTORY

Version No.	Effective Date	Summary of Change(s)
1.0	10 Oct 18	New document
2.0	26 Jul 19	• 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. • 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. • Updated study plan as per updates in protocol • Clarified the compliance rate in the Run-in Period and the expected compliance rate in the Treatment Period. • Clarified that peak expiratory flow will be measured at home after completing the morning and evening diary. • 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. • Updated the list of abbreviation accordingly. • Add rules to clarify how missing data will be handled in derivation of secondary endpoints calculated from eDiary data • Additional PK and PD parameters requested by AZ • Corrections made to Table 9 for heart rate and RR interval • SAP template updated to latest version
3.0	08 Nov 19	• Updated list of therapeutic categories for prior asthma medications

LIST OF ABBREVIATIONS

%Fluctuation	Fluctuation index during a dosing interval
ACQ-5	Asthma Control Questionnaire-5
AE	Adverse Event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AM3	Asthma Monitor 3
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
ATC	Anatomical therapeutic chemical classification system
ATS	American Thoracic Society
AUCτ	Area under the plasma concentration-curve within a dosing interval
AUC_{0-12}	Area under the plasma concentration-curve from time 0 to 12 hours post-dose
AUCτ/D	Dose normalised AUCτ
AUC_{last}	Area under the plasma concentration-curve from time zero to the time of last quantifiable analyte concentration
$AUEC_{(0-12)}$	Area under the plasma cortisol concentration-time curve from 0 to 12 hours after dosing
$AUEC_{(0-24)}$	Area under the plasma cortisol concentration-time curve from 0 to 24 hours after dosing
AZDMC	AstraZeneca Standing Internal Data Monitoring Committee
BDRM	Blind Data Review Meeting
BLQ	Below lower Limit of Quantification
BMI	Body Mass Index
BP	Blood Pressure
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CM	Concomitant medication
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
CRP	C-reactive protein
CSP	Clinical Study Protocol
CSR	Clinical Study Report
$C_{ss,avg,}$	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
CV	Coefficient of Variation

DAE	Discontinuation of IP due to Adverse Event
DNA	DeoxyriboNucleic Acid
DPI	Dry Powder Inhaler
ECG	ElectroCardioGram
eCRF	Electronic Case Report Form
eDiary	Electronic Diary
CCI	[redacted]
EMA	European Medicines Agency
EOT	End of treatment
ERT	e-Research Technology
ETV	Early termination visit
EudraCT	European Union drug Regulating Authorities Clinical Trials
FAS	Full Analysis Set
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
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GINA	Global Initiative for Asthma
GLMM	Generalized Linear Mixed Model
GR	Glucocorticoid Receptor
Gx	Genomics
HBsAg	Hepatitis B Surface Antigen
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HL	Hy's Law
HR	Heart Rate
ICF	Informed Consent Form
ICS	Inhaled Corticosteroid
INR	International normalised ratio
IP	Investigational Product
IVRS	Interactive Voice Recognition System
LABA	Long-Acting Beta Agonist
LAMA	Long-acting Muscarinic Antagonist
LH	Luteinizing Hormone
LLOQ	Lower limit of quantification
LS	Least squares
LTRA	Leukotriene Receptor Antagonist
MCH	Mean Corpuscular Haemoglobin
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Model for Repeated Measures

NA	Not applicable
NC	Not calculable
NCA	Non-compartmental Analysis
PCS	Potentially Clinically Significant
PD	Pharmacodynamics
PDF	Portable Document Format
PEF	Peak Expiratory Flow
PHL	Potential Hy's Law
PK	Pharmacokinetics
PP	Per Protocol
PT	Preferred Term
QD	Once Daily
QTc	QT interval corrected
QTcF	QT interval corrected using Fridericia's formula
REML	Restricted maximum likelihood
RoW	Rest of the World
SABA	Short-Acting Beta Agonist
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SE	Standard Error
SGRM	Selective GR Modulator
SOC	System Organ Class
SOP	Standard Operating Procedure
TEAE	Treatment-Emergent Adverse Event
TLF	Tables, Listings & Figures
TSH	Thyroid stimulating hormone
$t_{ss,max}$	Time to maximum concentration at steady state, taken directly from the individual concentration-time curve
t_{last}	Time of last quantifiable concentration
T4	Thyroxine
ULN	Upper Limit of Normal
US	United States
WHO	World Health Organisation

1 INTRODUCTION

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. AZD7594 may have several potential benefits over conventional inhaled corticosteroids (ICSs).

Inhaled corticosteroids are the cornerstone of therapy for asthma subjects 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 subjects requiring regular anti-inflammatory therapy.

The aim is to develop AZD7594 as a QD 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 QD AZD7594 in a dry powder inhaler (DPI) is to provide a safe and effective future treatment option for both asthma and COPD subjects.

The objective of this 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 subjects with asthma symptomatic on low dose ICS. The comparison between placebo and an active comparator (fluticasone furoate [FF]) will be used for bench marking.

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, pharmacokinetics (PK), and pharmacodynamics (PD) information generated in previous AZD7594 clinical studies.

The scope of this statistical analysis plan (SAP) is to describe in detail the statistical analyses described in the clinical study protocol (CSP).

The analyses of the following variables will be reported outside the clinical study report (CSR) and therefore are outside the scope of this SAP:

- Genomic samples
- PK-PD modelling
- Anonymised pooled PK samples
- PK sample reproducibility analysis
- CCI

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- Real-time occurrence of CompEx events (United States [US] only)

An electronic Case Report Form (eCRF) will be used to capture subject data into a secure, validated database. The following data is captured outside the eCRF and will be transferred electronically into the database periodically during the study:

- Safety laboratory data
- AZD7594 concentration in plasma
- PK data
- 24-hour cortisol measurement
- MasterScope spirometry
- Electrocardiogram (ECG)
- Fractional Exhaled Nitric Oxide (F_ENO)
- Forced Oscillation Technique (FOT)
- Investigational Product (IP) administration
- eDiaries (Asthma Control Questionnaire [ACQ-5], peak expiratory flow [PEF], rescue medication, asthma symptoms, night-time awakenings)

This SAP is based upon the following study documents:

- Study Protocol, Version 2.0 (April 26, 2019)
- Study Protocol (US), Version 3.0 (April 26, 2019)
- electronic Case Report Form (eCRF), Version 4.0 (May 17, 2019)

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This study was conducted in compliance with Good Clinical Practice (GCP), the General Principles of the Declaration of Helsinki (with amendments), the AstraZeneca policy on Bioethics and Human Biological Samples, and in accordance with local legal and regulatory requirements.

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

ACQ-5, Asthma Control Questionnaire-5; CompEx, Composite endpoint for severe exacerbations of asthma; FEV_1, Forced Expiratory Volume in 1 Second; F_ENO, fractional exhaled nitric oxide; FVC, forced vital capacity; ICS, Inhaled corticosteroid; 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 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), and overall evaluation.

AUC_τ, Area under the plasma concentration-curve within a dosing interval; AUC_τ/D, Dose normalised AUC_τ; 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; ECG, Electrocardiogram; ICS, Inhaled corticosteroid; HR; Heart rate; IP, Investigational product; $t_{ss,max}$, 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 [redacted] 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 (reported outside CSR)

Exploratory Objectives:	Outcome Measure:
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
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FOT, forced oscillation technique; Gx, genomics; ICS, inhaled corticosteroid

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

This is a phase 2b, randomised, placebo-controlled, parallel arm, 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 subjects with asthma symptomatic on low dose ICS.

The study will be conducted in approximately 100 centres in 8 countries in Europe, US, South Africa, and Japan. It is planned that approximately 714 subjects will be randomised into the study, 102 subjects per arm.

Each subject 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)

In the table, listing and figure outputs, treatment will be presented by delivered dose and the following treatment labels will be used:

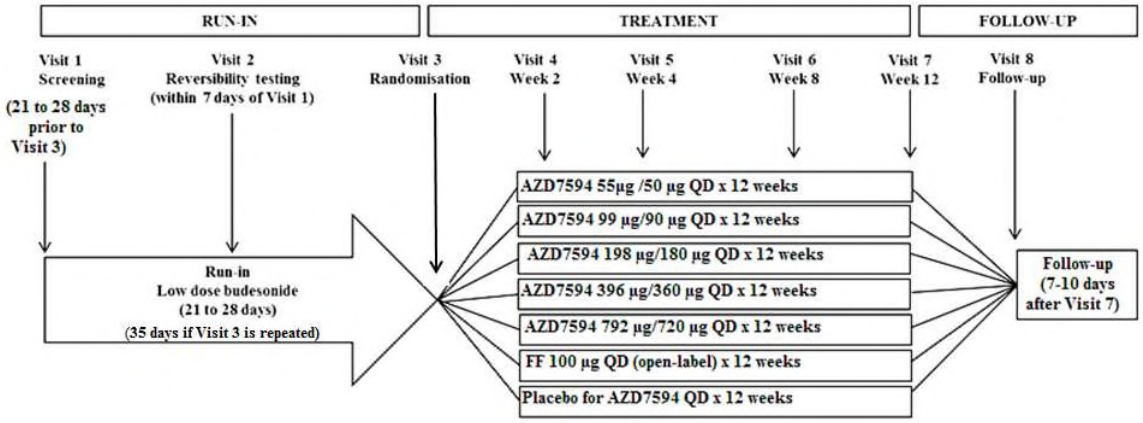
- AZD7594 50 µg
- AZD7594 90 µg
- AZD7594 180 µg
- AZD7594 360 µg
- AZD7594 720 µg
- Placebo
- FF (open-label)

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

The primary objective is to determine the efficacy of AZD7594 as assessed by change from baseline in trough FEV_1 at Week 12, when compared to placebo as defined in Section 4.9.2.

The study will consist of a Run-in Period (Visits 1 to 3), a 12-week Treatment Period (Visits 4 to 7) and a Follow-up Contact (Visit 8), see Figure 1. All subjects will be provided with budesonide for the Run-in Period, and a short-acting beta agonist (SABA) (salbutamol/albuterol) as rescue medication for use throughout the Run-in and Treatment Periods.

Figure 1 Study Flow Chart



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

The assessments to be performed at each study visit are detailed in Table 1.

Table 1 Study Plan

	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			

	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**
Blood sample for Gx (optional)			X[h]						
[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	

	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**
Collect eDiary							X	X	
Pregnancy test for females[q]	X		X		X	X	X	X	
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 subjects 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 subject is taking a LABA, fixed dose combination ICS/LABA treatment or a LAMA, in which case the subject 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 subjects 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 subjects 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 subject 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 subjects who have signed the informed consent form for the Gx sub-study.

[i] [redacted]

[j] Safety laboratory assessments require subjects 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 subjects 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 subject 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 subjects (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 subjects as PK sampling and a selected subset of FF treated subjects. 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 (subjects 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). Subjects 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; [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.

3.2 Efficacy and Safety Variables

3.2.1 Pulmonary function variables

3.2.1.1 Spirometry

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)

FEV_1 and FVC are measured at Visits 2, 3, 4, 5, 6, 7 and Early Termination Visit (ETV). SABA rescue medication (salbutamol/albuterol) should be withheld at least 6 hours before any pulmonary function tests.

Two 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.

3.2.1.2 Fractional exhaled nitric oxide

To investigate the effect of AZD7594 on airway inflammation, the measurement of F_ENO will be performed in accordance with American Thoracic Society/ European Respiratory Society (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.

F_ENO will be performed at Visits 1, 2, 3, 4, 5, 6, 7 and ETV.

3.2.2 eDiary variables

ACQ-5 (Asthma Control Questionnaire -5), morning and evening PEF (peak expiratory flow), rescue medication use, night-time awakenings, asthma symptom score and daily symptoms are recorded in an eDiary (Electronic Diary).

At Visit 1, subjects will receive an eDiary (Asthma Monitor 3 [AM3] Diary provided by e-Research Technology [ERT]) to complete during the study. During the Run-in and Treatment Period, subjects 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, subjects 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.

The eDiary variables will be used when deriving the secondary efficacy variables in Section 4.9.3.

3.2.2.1 ACQ-5

The validated ACQ-5 measures both the adequacy of asthma control and changes in asthma control. Subjects are asked to recall how their asthma was during the previous week and to evaluate their symptoms. The questionnaire has five items (see CSP); 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.

Subjects will complete the ACQ-5 within the eDiary while at the study centre at Visits 1, 2, 3, 4, 5, 6, 7 and ETV.

3.2.2.2 Peak expiratory flow

PEF will be measured by the subject at home after completing the morning and evening diary using a peak flow meter during the Run-in and Treatment Period.

The PEF measurement must be done immediately upon waking up, after the subject 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 three attempts should be recorded in the eDiary.

PEF will also be provided as part of Masterscope at clinic visit, as well as being entered into the eDiary on a daily basis. The summaries and analyses of PEF in this SAP will use PEF measurements recorded in the eDiary only.

3.2.2.3 Rescue medication use

Subjects will be provided with a SABA (salbutamol/ albuterol), as rescue medication, to be used as needed, starting from Visit 1. Subjects 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.

3.2.2.4 Asthma symptom score

During the Run-in and Treatment Periods, subjects will record the severity of their asthma symptoms during night-time and day-time each morning and evening, using the eDiary. Asthma symptoms are scored on a scale of 0 to 3, where higher scores represent more severe impairment/symptoms. More details are available in the CSP.

3.2.2.5 Night-time awakening

Subjects 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.

3.2.3 Pharmacokinetic variables

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

Blood samples for PK analysis will be collected from subjects participating in the PK subset at Visits 5 and 7 at the time points detailed in Table 1.

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 8.1 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.

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

Table 2 PK Parameters

$C_{ss,max}$	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
t_{last}	Time of last quantifiable concentration
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
AUC_{0-12}	Area under the plasma concentration-curve from time 0 to 12 hours post-dose

$C_{ss,avg}$	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

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 two 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 will be 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 three consecutive plasma concentrations above the lower limit of quantitation, with at least one of these concentrations following the maximum plasma concentration-time curve (C_{max}).

3.2.4 Pharmacodynamic variables

The PD of AZD7594 will be assessed by measuring cortisol suppression.

As a measure of cortisol suppression, 24-hour plasma cortisol measurements will be performed in the same subset of subjects as PK sampling and a selected subset of FF treated subjects. The targeted sample size for cortisol sampling is approximately 20 subjects 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 (subjects 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).

3.2.5 Safety variables

Safety will be assessed by descriptive analysis of laboratory assessments, physical examination findings, ECG, vital signs and AEs (including SAEs and DAEs).

3.2.5.1 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 Table 1).

The laboratory variables to be measured are presented in Table 3. Additional safety samples may be collected if clinically indicated at the discretion of the Investigator.

The results of tests performed at Visit 3 will be regarded as baseline data.

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 subjects 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 1. 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.

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 subject meets potential Hy's Law (PHL) criteria at any point during the study. Hy's Law (HL) guidance is included in the CSP.

3.2.5.2 Physical examination findings

A complete physical examination will be performed at Screening (Visit 1), at Visit 7, and at the time of an ETV. It 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.

Body weight and height will be measured at Visit 1 (Screening) for calculation of Body Mass Index (BMI). Body weight will be measured again at Visit 7.

3.2.5.3 ECG

ECGs will be performed, after approximately 5 minutes resting in supine position and before any blood sampling and spirometry test, at the times presented in the Study Plan (Table 1). 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

The QTcF interval will be calculated as follows (where RR is in seconds):

$$QTcF = \frac{QT}{\sqrt[3]{RR}}$$

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

3.2.5.4 Vital signs

Vital signs will be collected at the times presented in the Study Plan (Table 1). The vital sign parameters to be assessed (prior to IP administration) are blood pressure and pulse rate measurements.

3.2.5.5 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 ETV).

3.2.6 Exploratory variables

Exploratory outcomes will include the use of FOT as a measure of small airways involvement.

FOT is a non-invasive, lung function test included in this study to evaluate the study treatment effect on small airway physiology. FOT evaluation will be performed in accordance with the schedule provided in Table 1 and prior to spirometry. FOT will be performed in subjects in the US and Europe (excluding Ukraine) only.

The following FOT parameters will be derived by ERT:

- R5 (resistance at 5Hz)
- R20 (resistance at 20Hz)
- R5-R20 (reactance at 5Hz)
- AX (reactance area)

4 STATISTICAL METHODS

4.1 Data Quality Assurance

All tables, figures and data listings to be included in the report will be independently checked for consistency, integrity and in accordance with standard Parexel procedures.

4.2 General Presentation Considerations

'Baseline' is defined as the last value obtained prior to the first dose of study medication unless otherwise stated. 'Study Day' will be calculated relative to the date of randomization i.e.:

if Assessment Date < Randomization Date then;

$$Study\ Day\ =\ Assessment\ Date - Randomization\ Date$$

Else if Assessment Date ≥ Randomization Date then;

$$Study\ Day = Assessment\ Date - Randomization\ Date + 1$$

All results will be presented by treatment with descriptive statistics appropriate to the nature of the variables.

All visit-based summaries will use analysis visits. All post-randomisation scheduled and unscheduled visits (excluding ETV), will be mapped to an appropriate analysis visit as follows:

Table 4 Analysis Visit Mapping

CRF visit	Target day	Protocol Visit Window	Actual assessment day	Analysis visit
Visit 3 (Randomisation)	D1	D1	D1	Randomisation
Visit 4 (Wk 2)	D15	D13 to D17	D2 to D22	Week 2
Visit 5 (Wk 4)	D29	D28 to D30	D23 to D43	Week 4
Visit 6 (Wk 8)	D57	D56 to D58	D44 to D71	Week 8
Visit 7 (Wk 12)	D85	D84 to D86	D72 to D89	Week 12
Visit 8 (TC)	D92	D93 to D103	D90 to D103	Follow-up

Listings will display all values contributing to a time point for a subject. For visit-based summaries, if there is more than one value per subject within a time window, then the closest value will be summarised, or the earliest in the event the values are equidistant from the nominal visit date. The listings will highlight the value for that subject that went into the summary table, wherever feasible.

Continuous data will be summarized in terms of 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 unless otherwise stated. The minimum and maximum will be reported to the same number of decimal places as the raw data recorded in the database. The mean, 95% CI of the mean, SD, SE, median, lower quartile and upper quartile will be reported to one more decimal place than the raw data recorded in the database. For derived continuous data, a maximum of four decimal places will be used for all summary statistics.

Categorical data will be summarized in terms of the number of subjects providing data at the relevant time point (n), frequency counts and percentages.

Percentages will be presented to one decimal place. Percentages will not be presented for zero counts. Percentages will be calculated using n as the denominator unless otherwise stated.

Changes from baseline in categorical data will be summarized using shift tables where appropriate.

P-values greater than or equal to 0.001, in general, will be presented to three decimal places. P-values less than 0.001 will be presented as "<0.001".

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.

4.3 Software

All report outputs will be produced using SAS® version [9.3] or a later version in a secure and validated environment.

4.4 Study Subjects

4.4.1 Disposition of subjects

A clear accounting of the disposition of all subjects who enter the study will be provided, from screening to study completion.

The following summaries will be provided:

- A summary of the number of subjects enrolled into the study, and the number and percentage of subjects entering the Run-in Period, randomised, treated, completing treatment and completing the study, by treatment group and overall. In addition, reasons for not being treated, not completing treatment and not completing the study will be summarised by treatment group and overall (Analysis set: All subjects).
- A summary of the number of subjects randomized per region, country and centre, by treatment group and overall (Analysis population: All subjects)
- A summary of Interactive Voice Recognition System (IVRS) stratification factors ie, region (US, Japan, Rest of World [RoW]) at randomization by treatment group and overall (Analysis population: Full Analysis Set [FAS])

Study disposition will also be presented in a figure.

By-subject listings of disposition details for discontinued subjects and subjects completing the study will be provided. In addition, a by-subject listing of the randomisation scheme and codes will be provided.

4.4.2 Protocol deviations

Important protocol deviations are defined as those deviations from the CSP likely to have an impact on the perceived efficacy and/or safety of study treatments. The impact of important protocol deviations on the efficacy and/or safety results will be investigated by assessing the robustness of the study results and conclusions to the choice of analysis population (see Section 4.5), both including and excluding data potentially affected by important protocol deviations.

Deviations from the CSP will be assessed as "important" by Parexel in conjunction with AstraZeneca. Important deviations from the protocol may lead to the exclusion of subjects from the Per Protocol (PP) set and/or other analysis sets. Important protocol deviations will be identified before database hard lock and unblinding. Important deviations will include the following:

- Violation of inclusion and/or exclusion criteria
- Subjects 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

Important protocol deviations and any action to be taken regarding the exclusion of subjects or affected data from specific analyses are defined in the project-specific Protocol Deviation Specification.

Upon database release, before database hard lock and unblinding, protocol deviation and analysis population outputs will be produced and will be sent to AstraZeneca for review. A Blind Data Review Meeting (BDRM) will be arranged to discuss the outputs and to decide which subjects and/or subject data will be excluded from certain analyses. Decisions made regarding the exclusion of subjects and/or subject data from analyses will be made prior to unblinding and will be documented in the BDRM minutes and approved by AstraZeneca.

The following summaries will be provided:

- A summary of the number and percentage of subjects with an important protocol deviation by treatment group and overall and by type of deviation (Analysis population: FAS)

A by-subject listing of important protocol deviations for all randomised subjects will be provided.

4.5 Analysis Populations

The following summaries will be provided:

- A summary of the number and percentage of subjects in each analysis set by treatment group and overall. Exclusions from each analysis population will also be summarized by reason.

By-subject listings of subjects excluded from each analysis set and the data excluded from FAS and PP set will be provided.

4.5.1 Full analysis set

The (FAS population is defined as all subjects randomised and receiving at least one dose of randomised IP, irrespective of their protocol adherence and continued participation in the study. Subjects will be analysed as randomised, irrespective of whether or not they have prematurely discontinued. Subjects 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.

4.5.2 Safety analysis set

The Safety analysis set consists of all randomised subjects who received at least one dose of IP and for whom any post-dose data are available. Subjects 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.

4.5.3 Pharmacokinetic analysis set

The PK analysis set is defined as all randomised subjects 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 important protocol deviations considered to impact on the analysis of the PK data (eg, disallowed medication, or incorrect study medication received). Subjects will be analysed as treated. All protocol deviations that occur during the study will be considered for their severity/impact and will be taken into consideration when subjects are assigned to the PK analysis set.

The exclusion of any subjects 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 subjects excluded from the PK analysis set will be listed and presented in the individual figures of concentration-time plots only.

4.5.4 Pharmacodynamic analysis set

The PD analysis set is defined as all randomised subjects who took at least one dose of IP and for whom 24-hour cortisol sampling was performed and baseline and post baseline area under the plasma cortisol concentration-time curve from 0 to 24 hours after dosing ($AUEC_{(0\text{-}24)}$) can be calculated, and who have no important protocol deviations considered to impact on the analysis of the PD data. Subjects will be analysed as treated.

4.5.5 Per protocol set

The PP population is defined as a subset of the FAS population constituted by those subjects 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).

4.6 Demographic and Other Baseline Characteristics

Analyses of demographic and baseline characteristics and prior and concomitant medications will be performed on the FAS.

Demographic characteristics to be assessed are age (years), sex, race, ethnic group and country. The following age groups will also be presented for European Union drug Regulating Authorities Clinical Trials (EudraCT) reporting:

- Adults (18-64 years)
- From 65 years
- Elderly (From 65-84 years)
- Elderly 85 years and over

Subject characteristics to be assessed are height (cm), weight (kg) and BMI (kg/m^2). BMI will be calculated as follows:

$$\frac{weight\ (kg)}{height\ (m)^2}$$

Baseline diary data to be assessed include:

- ACQ-5 score at Visit 3
- Average morning PEF (L/min) over the Run-in Period
- Average evening PEF (L/min) over the Run-in Period
- Average daily rescue medication use (number of puffs) over the Run-in Period
- Percentage of night-time awakening days over the Run-in Period

- Average daily asthma symptom score over the Run-in Period
- Percentage of asthma control days over the Run-in Period
- Percentage of rescue-free days over the Run-in Period
- Percentage of symptom-free days over the Run-in Period

For average and/or percentage of days over the Run-in Period, baseline will be defined as the seven days prior to randomisation. The following eDiary sessions will be used to derive the baseline value:

Table 5 eDiary Variables Baseline

Collection Day	Collection Time	Analysis Day
Day -7	Evening	Day -7
Day -6	Morning	
Day -6	Evening	Day -6
Day -5	Morning	
Day -5	Evening	Day -5
Day -4	Morning	
Day -4	Evening	Day -4
Day -3	Morning	
Day -3	Evening	Day -3
Day -2	Morning	
Day -2	Evening	Day -2
Day -1	Morning	
Day -1	Evening	Day -1
Day 1	Morning	

Asthma characteristics to be assessed include:

- Smoking duration (years), calculated as:
$$\frac{(smoking\ end\ date\ -\ smoking\ start\ date) + 1}{365.25}$$
- Smoking consumption (total number of pack-years)
- Smoking status (non-smoker, former smoker)
- Asthma duration (years), calculated as:
$$\frac{(date\ of\ randomisation - date\ of\ diagnosis\ of\ asthma) + 1}{365.25}$$
- Time since last exacerbation (days), calculated as:
$$date\ of\ randomisation - date\ of\ most\ recent\ exacerbation$$
- Prior use of ICS (low/medium/high dose)

The subgroups for prior use of ICS will be identified using the clinical comparability of doses detailed in Table 6.

Table 6 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).

Baseline lung function data to be assessed include:

- Absolute values of the FEV_1 and FVC (pre- and post-SABA test) at Visit 2.
- Percent of predicted values of FEV_1 and FVC (pre-SABA) at Visit 2.
- Percent of predicted values of FEV_1 (pre-SABA) at Visit 3:
  - ≥40 to ≤65%
  - >65 to ≤90%
- Ratio FEV1/FVC at Visit 2 (pre- and post-SABA test)
- Mean bronchodilator reversibility (FEV_1 change in mL from pre-SABA test value) at Visit 2
- Percentage of bronchodilator reversibility (% FEV_1 increase over pre-SABA test value) at Visit 2
- F_ENO (ppb) at Visit 3 (Geometric mean and coefficient of variation [CV] (%) will be presented instead of mean and SD for this variable)
- Asthma severity at screening according to GINA Guidelines 2018 using the pre-SABA value at Visit 2:
  - Group 1: FEV_1 ≥80% predicted
  - Group 2: 60% <FEV_1 <80% predicted
  - Group 3: FEV_1 ≤60% predicted

The following summaries will be provided:

- A summary of demographic characteristics by treatment group and overall
- A summary of subject characteristics by treatment group and overall
- A summary of diary data at baseline by treatment group and overall
- A summary of asthma characteristics by treatment group and overall
- A summary of lung function at baseline by treatment group and overall

By-subject listings of demographic data (including age, sex, race, baseline weight, baseline height and baseline BMI) and the asthma characteristics and baseline lung function data detailed above will be provided.

Screening values for ECGs, laboratory assessments, pregnancy tests and bp 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.

4.6.1 Surgical and medical history

Surgical and medical histories will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 21.0 or later.

The following summaries will be provided:

- A summary of relevant medical history by system organ class (SOC) and preferred term (PT), by treatment group and overall
- A summary of relevant surgical history by SOC and PT, by treatment group and overall

4.7 Prior and concomitant medications

All medications will be classified into anatomical therapeutic chemical (ATC) drug classes using the World Health Organisation (WHO) Drug Dictionary Version March 2018 or later.

Any medications taken by the subject between 15 days prior to signing the ICF and prior to the first dose date of IP will be considered prior medication.

Prior asthma medications will be summarised by therapeutic categories. The therapeutic categories to be considered are:

- SABA
- LABA
- ICS
- ICS/LABA
- SAMA
- LAMA
- SABA/SAMA
- LABA/LAMA
- Leukotriene Receptor Antagonists (LTRAs)
- Xanthines

- Others

Therapeutic categories will be identified during medical review.

Any medication taken by the subject at any time between the date of the first dose (including the date of the first dose) of IP up to the date of last dose of IP in the study overall will be considered concomitant medication. 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 two periods:

1) Prior concomitant medications: medications that the subject started to take prior to the first dose date of IP and continued on or after the first dose date of IP
2) Concomitant medications: medications that the subject started to take on or after the first dose date of IP up to the date of last dose of IP.

Where dates are missing or partially missing, medications will be assumed to be concomitant, unless there is clear evidence (through comparison of partial dates) to suggest that the medication started prior to the first dose of IP or after the last dose of IP.

The following summaries will be provided:

- A summary of the number and percentage of subjects who used any prior medication by ATC (level 3) and PT, by treatment group and overall
- A summary of the number and percentage of subjects who used any prior asthma medication by therapeutic categories, treatment group and overall
- A summary of disallowed concomitant medications during study treatment by period, ATC (level 3) and PT, treatment group and overall
- A summary of all allowed concomitant medications during study treatment by period, ATC (level 3) and PT, treatment group and overall

The identification of disallowed concomitant medications will be conducted as part of the medical review.

Multiple records for a subject in the same ATC level 3 category and PT will be counted only once in each summary.

4.8 Treatment Compliance

Subjects will be provided with an eDiary to record their intake of the IP on a daily basis whilst not in clinic. When subjects attended a visit in clinic, intake of IP will be documented in the ERT Masterscope.

Compliance as measured by the eDiary should be ≥80% in the Run-in Period and is expected to be ≥80% during the Treatment Period. Compliance should be ≥80% at each

study visit during the relevant period for that period to be considered compliant. The compliance value associated to each study visit shows the compliance for the period since the previous visit. A scheduled session (morning/ evening) is considered to be compliant if a complete set of answers and 3 PEF measurements are available. eDiary compliance is derived by ERT.

Compliance with IP will be calculated using the following equation:

$$IP\ Compliance\ (\%) = \frac{Number\ of\ doses\ taken}{Number\ of\ intended\ doses}\ x\ 100$$

The number of intended doses is equal to one dose per day throughout the duration of the study for each subject, eg, would be 84 doses if a subject completes the study.

Subjects who are treatment compliant will be defined as having IP compliance between 80% to 120% inclusive.

The following summaries will be provided:

- A summary of the IP compliance by treatment group and overall, including the number and percentage of compliant subjects per definition above (Analysis population: FAS).
- A summary of eDiary compliance by treatment group and visit, including the number and percentage of compliant subjects per definition above (Analysis population: FAS).

By-subject listings of IP administration and treatment compliance data and subjects receiving the various batches of IP will be provided.

4.9 Efficacy Evaluation

4.9.1 Analysis and data conventions

4.9.1.1 Multi-centre studies

Region is a stratification factor for randomisation, and all statistical analyses will adjust for region by including it as a main effect term in any modelling procedures. A subgroup analysis for the primary efficacy endpoint by region will also be made. No per centre (where the term 'centre' defines each investigator site) summaries or analyses will be made.

4.9.1.2 Adjustments for covariates

The primary efficacy analysis will be adjusted for the following baseline covariates:

1. Region (stratification variable) (US, Japan, RoW)
2. Baseline FEV_1 (L)

4.9.1.3 Handling of dropouts or missing data

Summary statistics will be based on non-missing values. For hypothesis tests, estimates and CIs, missing values for continuous efficacy endpoints analysed via likelihood methods (eg, mixed models for repeated measures [MMRM]) will not be directly imputed as they are handled within the analysis itself, under the assumption that the model specification is correct and that the data is missing at random.

4.9.1.4 Multiple comparisons/multiplicity

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.

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

An overview of the key results, with application of the step-down closed testing procedure for the primary endpoint, will be provided.

4.9.1.5 Interim analyses

Not applicable.

4.9.1.6 Examination of subgroups

The uniformity of the treatment effect for the primary efficacy endpoint will be examined for the following subgroups:

1. % Predicted FEV_1 (≥40 to ≤65% or >65 to ≤90%) at Visit 3 (randomisation)
2. Prior use of ICS (low/medium/high dose)
3. Smoking status (non-smoker, former smoker)

4. Region (US, Japan, RoW)

The change from baseline in trough FEV_1 will be summarised by visit and treatment group for each subgroup.

Subgroup analyses will be performed using the same MMRM model as for the primary efficacy endpoint, with the addition of a subgroup term, a subgroup-by-treatment interaction term and a subgroup-by-treatment-by visit interaction term. The treatment effect least squares (LS) mean differences for each treatment comparison at Week 12 along with their CIs will be obtained for each level of the subgroup from this single model. All subjects with a non-missing subgroup category will be included in the analysis, but results of the analysis will only be presented if the number of subjects in the subgroup category is at least 5 in all treatment groups. The results of all subgroup analyses will be displayed in tabular form and will also be displayed in a forest plot.

4.9.2 Primary efficacy variable – change from baseline in trough FEV_1 at Week 12

All primary efficacy summaries and analyses will be based upon the FAS as defined in Section 4.5. The analysis will be repeated using the PP set as a sensitivity analysis.

For FEV_1 and FVC , baseline will be defined as the mean of the two measured values before first IP administration (30 minutes apart, at −45 minutes and −15 minutes, before IP administration) on Day 1 (Visit 3). If one of those two measurements is missing, the remaining one will be used instead. If both are missing, the screening value (pre-SABA test at Visit 2) will be used.

For FEV_1 and FVC, the trough will be defined as the mean of the two measurements 30 minutes apart (23 hours after last dose) pre-dose for every visit throughout the Treatment Period (Visit 4/Week 2 to Visit 7/Week 12). If one of these two measurements is missing, the remaining one will be used as trough FEV_1/FVC instead.

Change from baseline in trough FEV_1 at each visit will be summarised by treatment group. A plot showing the LS mean change (+/- SE) from baseline in trough FEV_1 over time within each treatment group will be provided.

The effect of treatment in terms of the change from Baseline to Week 12 in trough FEV_1 will be analysed using a MMRM. All post-baseline visit trough FEV_1 data throughout the Treatment Period (Visit 4/ Week 2 to Visit 7/ Week 12) will be used in the model. The MMRM 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.

The within-subject 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. The restricted maximum likelihood (REML) method will be applied.

Each treatment effect and treatment differences comparing all active treatments to placebo at each visit (Week 2, Week 4, Week 8, Week 12) will be estimated by the 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 active comparator (FF) will be compared to placebo only. The comparison will be used for bench marking.

In addition, the overall treatment effect and treatment difference over the 12-week 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.

Diagnostic plots will be presented in statistical appendices to assess the suitability of the model.

The homogeneity of the treatment effect for a number of important subgroups will be investigated as described in 4.9.1.6.

By-subject listings of the individual efficacy response data and efficacy assessments will be provided.

4.9.3 Secondary efficacy variables

All secondary efficacy summaries and analyses will be based upon the FAS as defined in Section 4.5. No multiplicity adjustments will be applied for the secondary variables.

By-subject listings of the secondary efficacy assessments will be provided.

4.9.3.1 Change from baseline in trough FEV_1 at Weeks 2, 4, 8, and average over the Treatment Period

The analysis of change from baseline in trough FEV_1 at Weeks 2, 4 and 8 and the average over the Treatment Period will be conducted as part of the analysis for the primary endpoint described in Section 4.9.2.

4.9.3.2 Change from baseline in F_ENO at Weeks 2, 4, 8, 12, and average over the Treatment Period

Change from baseline in F_ENO at each visit and average over the Treatment Period will be summarised by treatment group and the following summary statistics will be presented: n, geometric mean, CV (%), median, minimum and maximum. A plot showing the geometric LS mean change (+/- SE) from baseline in F_ENO over time within each treatment group will be provided.

The analysis of change from baseline in log-transformed F_ENO will be performed as described for the primary endpoint in Section 4.9.2. No subgroup analyses will be performed.

These analyses will be done on the natural log-scale and the results will be back-transformed to linear scale. Hence treatment effects will be presented in terms of geometric LS means and treatment differences and associated CIs will be presented in terms of geometric LS mean ratios. Due to the log-transformation, the geometric LS means represent a relative change from baseline rather than an absolute change from baseline.

4.9.3.3 Change from baseline in trough FVC at Week 12 and average over the Treatment Period

The summary and analysis of change from baseline in trough FVC will be performed as described for the primary endpoint in Section 4.9.2. All scheduled visits will be included in the analysis although Week 12 is of primary interest. No subgroup analyses will be performed.

4.9.3.4 Change from baseline in ACQ-5 score at Week 12 and average over the Treatment Period

The summary and analysis of change from baseline in ACQ-5 score will be performed as described for the primary endpoint in Section 4.9.2. All scheduled visits will be included in the analysis although Week 12 is of primary interest. ACQ-5 score at visit 3 will be considered as baseline. No subgroup analyses will be performed.

4.9.3.5 Change from baseline in average morning PEF over the Treatment Period

Average morning PEF will be derived as follows:

$$\frac{Sum\ of\ morning\ PEF\ values\ in\ period}{Number\ of\ morning\ sessions\ eDiary\ was\ completed\ in\ period}$$

Where period is either Run-in Period (visit 1 to 3) or Treatment Period (visit 4 to 7, including ETV).

Baseline will be defined as average morning PEF over the seven days prior to randomisation (see Table 5). At least five sessions with non-missing data within the seven days must be available in order to derive a baseline average.

The change from baseline in average morning PEF over the Treatment Period will be summarised by treatment group and week. The following eDiary sessions will be used to derive the analysis weeks. At least five sessions with non-missing data within an analysis week must be available in order to derive an average for that week:

Table 7 eDiary Variables Weeks

Analysis Week	First Session Included	Last Session Included
Baseline	-D7 Evening	D1 Morning
Week 1	D1 Evening	D8 Morning
Week 2	D8 Evening	D15 Morning
Week 3	D15 Evening	D22 Morning
Week 4	D22 Evening	D29 Morning
Week 5	D29 Evening	D36 Morning
Week 6	D36 Evening	D43 Morning
Week 7	D43 Evening	D50 Morning
Week 8	D50 Evening	D57 Morning
Week 9	D57 Evening	D64 Morning
Week 10	D64 Evening	D71 Morning
Week 11	D71 Evening	D78 Morning
Week 12	D78 Evening	D85 Morning
12 Week Treatment Period	D1 Evening	D85 Morning

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 change from baseline in average morning PEF over the Treatment Period. At least 60 sessions with non-missing data within the treatment period must be available in order to derive an average value.

Each treatment effect and treatment differences comparing all active treatments, to placebo will be estimated by the LS means, along with their SE and 95% CI, and the p-value corresponding to the between-treatment group difference. The active comparator (FF) will be compared to placebo only. The comparison will be used for bench marking.

Diagnostic plots will be presented in statistical appendices to assess the suitability of the model.

4.9.3.6 Change from baseline in average evening PEF over the Treatment Period

Average evening PEF will be derived as follows:

$$\frac{Sum\ of\ evening\ PEF\ values\ in\ period}{Number\ of\ evening\ sessions\ eDiary\ was\ completed\ in\ period}$$

Where period is either Run-in Period (visit 1 to 3) or Treatment Period (visit 4 to 7, including ETV).

Baseline will be defined as average evening PEF over the seven days prior to randomisation (see Table 5). At least five sessions with non-missing data within the seven days must be available in order to derive a baseline average.

The summary and analysis of change from baseline in average evening PEF over the Treatment Period will be performed as described in Section 4.9.3.5. At least five days with non-missing data within an analysis week must be available in order to derive an average for that week. At least 60 days with non-missing data within the treatment period must be available in order to derive an average value.

4.9.3.7 Change from baseline in average daily use of rescue medication over the Treatment Period

Daily use of rescue medication will be the average of the use of rescue medication recorded in the evening for the current study day and the use of rescue medication recorded in the morning of the next study day. Eg, the daily use of rescue medication (number of puffs) for day n will be derived as follows:

$$\frac{(Use\ of\ rescue\ medication\ recorded\ in\ evening\ of\ day\ n) + (Use\ of\ rescue\ medication\ recorded\ in\ morning\ of\ day\ n+1)}{2}$$

Both the values of evening use of rescue medication for day n and morning use of rescue medication for day n+1 must be non-missing, otherwise the daily use of rescue medication for day n will be set to missing.

Average daily use of rescue medication will be derived as follows:

$$\frac{Sum\ of\ daily\ use\ of\ rescue\ medication\ in\ period}{Number\ of\ days\ with\ non-missing\ daily\ use\ of\ rescue\ medication\ in\ period}$$

Where period is either Run-in Period (visit 1 to 3) or Treatment Period (visit 4 to 7, including ETV).

Baseline will be defined as average daily use of rescue medication (number of puffs) over the seven days prior to randomisation (see Table 5). At least five days with non-missing data within the seven days must be available in order to derive a baseline average.

The summary and analysis of change from baseline in average daily use of rescue medication over the Treatment Period will be performed as described in Section 4.9.3.5. At least five days with non-missing data within an analysis week must be available in order to derive an average for that week. At least 60 days with non-missing data within the treatment period must be available in order to derive an average value.

4.9.3.8 Change from baseline in percent night-time awakening days over the Treatment Period

Percentage of night-time awakening days will be derived as follows:

$$\frac{Number\ of\ days\ in\ period\ where\ patient\ recorded\ a\ night-time\ awakening}{Number\ of\ days\ eDiary\ was\ completed\ in\ period}\ x\ 100$$

Where period is either Run-in Period (visit 1 to 3) or Treatment Period (visit 4 to 7, including ETV).

Baseline will be defined as the percentage of night-time awakening days over the seven days prior to randomisation (see Table 5). At least five days with non-missing data within the seven days must be available in order to derive a baseline average.

The summary and analysis of change from baseline in percent night-time awakening days over the Treatment Period will be performed as described in Section 4.9.3.5. At least five days with non-missing data within an analysis week must be available in order to derive an average for that week. At least 60 days with non-missing data within the treatment period must be available in order to derive an average value.

4.9.3.9 Change from baseline in average daily asthma symptom score over the Treatment Period

Daily asthma symptom score will be the average of the evening score recorded for the current study day and the morning score of the next study day. Eg, the daily asthma score for day n will be derived as follows:

$$\frac{(Evening\ asthma\ symptom\ score\ for\ day\ n) + (Morning\ asthma\ score\ for\ day\ n+1)}{2}$$

Both the values of evening asthma symptom score for day n and morning asthma symptom score for day n+1 must be non-missing, otherwise the daily asthma symptom score for day n will be set to missing.

Average daily asthma symptom score will be derived as follows:

$$\frac{Sum\ of\ daily\ asthma\ symptom\ scores\ in\ period}{Number\ of\ days\ with\ non-missing\ daily\ asthma\ symptom\ score\ in\ period}$$

Where period is either Run-in Period (visit 1 to 3) or Treatment Period (visit 4 to 7, including ETV).

Baseline will be defined as average daily asthma symptom score over the seven days prior to randomisation (see Table 5). At least five days with non-missing data within the seven days must be available in order to derive a baseline average.

The summary and analysis of change from baseline in average daily asthma symptom score over the Treatment Period will be performed as described in Section 4.9.3.5. At least five days with non-missing data within an analysis week must be available in order to derive an average for that week. At least 60 days with non-missing data within the treatment period must be available in order to derive an average value.

4.9.3.10 Change from baseline in percent asthma control days over the Treatment Period

An asthma control day is defined as a day that fulfils all of the below criteria:

- A day with no asthma symptoms (ie, asthma symptom score = 0, for both the evening and the following morning assessment)
- A night with no awakenings due to asthma symptoms (the answer to the question "Did your asthma cause you to wake up last night" should be 'No' assessed the following morning)
- A day with no use of rescue medication (ie, both evening and following morning e-Diary entries indicate no rescue medication was taken)

All of the above criteria need to be non-missing in order to determine an asthma control day otherwise it will be set to missing.

This means for defining asthma control for day n, the evening assessment for day n and morning assessment for day n+1 will be used.

Percentage of asthma control days will be derived as follows:

$$\frac{Number\ of\ asthma\ control\ days\ in\ period}{Number\ of\ days\ eDiary\ was\ completed\ in\ period}\ x\ 100$$

Where period is either Run-in Period (visit 1 to 3) or Treatment Period (visit 4 to 7, including ETV).

Baseline will be defined as the percentage of asthma control days over the seven days prior to randomisation (see Table 5). At least five days with non-missing data within the seven days must be available in order to derive a baseline average.

The summary and analysis of change from baseline in percent asthma control days over the Treatment Period will be performed as described in Section 4.9.3.5. At least five days with non-missing data within an analysis week must be available in order to derive an average for that week. At least 60 days with non-missing data within the treatment period must be available in order to derive an average value.

4.9.3.11 Change from baseline in percent rescue-free days over the Treatment Period

A rescue-free day is defined as a day with no use of rescue medication (ie, both evening and following morning e-Diary entries indicate no rescue medication was taken). If use of rescue medication data is missing, rescue-free day will also be set to missing.
This means for defining rescue-free for day n, the evening assessment for day n and morning assessment for day n+1 will be used.

Percentage of rescue-free days will be derived as follows:

$$\frac{Number\ of\ rescue-free\ days\ in\ period}{Number\ of\ days\ eDiary\ was\ completed\ in\ period}\ x\ 100$$

Where period is either Run-in Period (visit 1 to 3) or Treatment Period (visit 4 to 7, including ETV).

Baseline will be defined as the percentage of rescue-free days over the seven days prior to randomisation (see Table 5). At least five days with non-missing data within the seven days must be available in order to derive a baseline average.

The summary and analysis of change from baseline in percent rescue-free days over the Treatment Period will be performed as described in Section 4.9.3.5. At least five days with non-missing data within an analysis week must be available in order to derive an average for that week. At least 60 days with non-missing data within the treatment period must be available in order to derive an average value.

4.9.3.12 Change from baseline in percent symptom-free days over the Treatment Period

A symptom-free day is defined as a day that fulfils all of the below criteria:

- A day with no asthma symptoms (ie, asthma symptom score = 0, for both the evening and the following morning assessment)
- A night with no awakenings due to asthma symptoms (the answer to the question "Did your asthma cause you to wake up last night" should be 'No' assessed the following morning)

All of the above criteria need to be non-missing in order to determine a symptom-free day otherwise it will be set to missing.

This means for defining symptom-free for day n, the evening assessment for day n and morning assessment for day n+1 will be used.

Percentage of symptom-free days will be derived as follows:

$$\frac{Number\ of\ symptom-free\ days\ in\ period}{Number\ of\ days\ eDiary\ was\ completed\ in\ period}\ x\ 100$$

Where period is either Run-in Period (visit 1 to 3) or Treatment Period (visit 4 to 7, including ETV).

Baseline will be defined as the percentage of symptom free days over the seven days prior to randomisation (see Table 5). At least five days with non-missing data within the seven days must be available in order to derive a baseline average.

The summary and analysis of change from baseline in percent symptom-free days over the Treatment Period will be performed as described in Section 4.9.3.5. At least five days with non-missing data within an analysis week must be available in order to derive an average for that week. At least 60 days with non-missing data within the treatment period must be available in order to derive an average value.

4.9.3.13 Time to first CompEx event, time to recurrent CompEx event, and CompEx event rate

CompEx is a composite surrogate endpoint for severe exacerbations of asthma, recently developed by AstraZeneca (**Fuhlbrigge et al, 2017**).

Asthma exacerbations will be evaluated by the investigator at each visit and will be recorded on the EXACA eCRF page. Severe exacerbations are defined as those episodes that lead to hospitalisation, emergency room visit and/or treatment with oral corticosteroids.

Severe exacerbation rate will be summarised by treatment group including number of subjects with at least one exacerbation and number of exacerbations. Rate summaries of exacerbations that lead to hospitalisation, emergency room visit and/or treatment with oral corticosteroids will also be presented.

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

A subject will be considered to have a CompEx event during the planned Treatment Period if the subject has one or both of the following:

1. A severe asthma exacerbation,
2. An objective deterioration, which is defined as either the threshold criterion or the slope criterion (or both), as defined below, being met for ≥2 consecutive days.

For this purpose, "2 consecutive days" means strictly the same 2 consecutive days when assessing multiple requirements within those days. For the eDiary data (which is captured twice during the day), one day will be defined by the morning/evening pairing for consistency with published precedent for the CompEx endpoint. (Note: other eDiary endpoints in this trial will use an evening/morning pairing to define one day.) The morning eDiary recordings captured on the first day of treatment will not be included in the calculation of the CompEx endpoint.

Threshold criterion:

a. ≥15% decrease from baseline in either morning or evening home-based PEF, *and* at least one of the following:
b. ≥1.5 doses increase from baseline in rescue medication in either the morning (for preceding night) or evening (for preceding day)
c. ≥1 score increase from baseline, or the absolute maximal symptom score, in either the morning or evening.

For (b), the number of doses of rescue medication is defined as the number of puffs of inhaler recorded in the morning and evening, respectively.

For (c), the asthma symptom score (scored 0-3) as described in Section 3.2.2.4 will be used, recorded in the morning and evening, respectively. The maximal symptom score is therefore 3.

Assessment of the threshold criterion in any rolling 2-day consecutive period will be based on the available data during that period. The threshold criterion can be met with non-missing values for fewer than the six variables specified above, provided those non-missing values meet the criterion.

Slope criterion:
One of (a), (b) or (c) above is met for ≥2 consecutive days *and* the regression slope requirement over the preceding 5 days is also met.

The regression slope requirement in the preceding 5 days is that all of the following are met:

- Morning PEF slope ≤ -3%/day
- Evening PEF slope ≤ -3%/day
- Morning (preceding night) rescue medication slope ≥ 0.3 doses/day
- Evening (preceding day) rescue medication slope ≥ 0.3 doses/day
- Morning asthma symptom score slope ≥ 0.2 score/day
- Evening asthma symptom score slope ≥ 0.2 score/day

In all of the above cases, the regression slope is the point estimate of the slope obtained from a linear regression of the absolute values of each of the six variables separately against day number, with no other variables included in the regression model.

For morning and evening PEF, the regression slope thus obtained will first also be divided by the baseline PEF value before applying the above criterion. The following table shows how the timing for the 5-day requirement for the regression slopes fits with the 2-consecutive day requirement, where "Day 0" here refers to the first of the 2 consecutive days (shaded) to be used each time the rolling 2 consecutive day assessment is made:

Table 8 Timing for assessment of CompEx slope criterion

	Day -4	Day -3	Day -2	Day -1	Day 0	Day 1
Threshold (a), (b), (c)					x	x
Slope	x	x	x	x	x	

A regression slope will be calculated provided there are at least two non-missing values in the required 5 days. If one or more of the six variables above does not have at least two

non-missing values in the required 5 days, then the slope requirement therefore cannot be met.

The start date of a CompEx event is defined as the earliest of the exacerbation or objective deterioration start dates which meets the definition. Objective deterioration start date is defined as the earliest Day 0 (in notation from Table 8) from any series of rolling 2 consecutive days which first qualifies using either the threshold or slope criterion.

The end date of a CompEx event is defined as the latest of the exacerbation or objective deterioration end dates which meets the definition. Objective deterioration end date is defined as the latest Day 1 (in notation from Table 8 from any series of rolling 2 consecutive days which last qualifies using either the threshold or slope criterion.

If the end date of the first CompEx event and the start date of the second CompEx event are less than 7 days apart for any subject, then these will be counted as one CompEx event.

For CompEx analyses, only on-treatment events will be considered.

Time-to-first-event will be defined as:

$$[Start\ date\ of\ first\ event\ or\ censoring - date\ of\ randomisation] + 1$$

Date of first event will be the first start date of a CompEx event as defined above. For subjects who do not experience an on-treatment CompEx event, date of censoring will be the maximum of date of last dose or last day of eDiary recording.

For recurrent events, there must be a gap of 7 days between events ie, at least 7 days between end date of first CompEx event and start date of second CompEx event. Events that occur closer in time will be collapsed into one event.

The time during the event and the 7 days after each event will not be considered when defining time at risk for the CompEx event rate. Time at risk will be defined as:

$$[Date\ of\ last\ treatment - date\ of\ randomisation] + 1 - recovery\ time$$

Where recovery time is defined as:

$$\sum_{i=1}^{k} [min(i^{th}\ event\ end\ date + 7, date\ of\ last\ treatment) - i^{th} event\ start\ date + 1]$$

CompEx will be analysed as follows:

- Cox proportional hazards model for time to first event

Time to first CompEx event will be analysed using a Kaplan-Meier plot and a Cox proportional hazards model to estimate the hazard ratios for the AZD7594/FF treatment groups vs placebo and corresponding 95% CIs and p-values. Region and treatment will be included as covariates in the model.

Diagnostic plots will be presented in statistical appendices to assess the suitability of the model.

- Marginal means/rates model for time to recurrent event

Time to recurrent CompEx event will be analysed using a marginal means and rates model to estimate the rate ratios for the AZD7594/FF treatment groups vs placebo and corresponding 95% CIs and p-values. Region and treatment will be included as covariates in the model.

Diagnostic plots will be presented in statistical appendices to assess the suitability of the model.

- Negative binomial model for event rate

CompEx event rate will be analysed using a negative binomial model, to estimate the rate ratios for the AZD7594/FF treatment groups vs placebo and corresponding 95% CIs and p-values. The analysis will be performed using the GENMOD procedure with CompEx event count as the dependent variable, using a log link and the negative binomial distribution to account for overdispersion, and with log-transformed time at risk (days) as an offset variable. The model will include treatment and region (US, Japan, and Row) as covariates.

Diagnostic plots will be presented in statistical appendices to assess the suitability of the model.

4.10 Safety Evaluation

All safety summaries and analyses will be based upon the Safety analysis set as defined in Section 4.5.

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.

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.

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.

4.10.1 Extent of exposure

The extent of exposure (days) will be derived as follows:

$$Duration\ of\ exposure\ (days) = Date\ of\ last\ dose - Date\ of\ first\ dose + 1$$

The following extent of exposure summaries will be provided:

- A summary of the duration of exposure to treatment (days) and cumulative exposure over time (≥1 day, ≥28 days), by treatment group.

4.10.2 Adverse events

AEs will be coded by SOC and PT using MedDRA Version 21.0 or later.

Treatment-emergent AEs (TEAEs) are defined as AEs which develop after the date of first dose of IP and not more than 7 days after the date of the last dose of IP during the study.

TEAEs will be included in the summary tables. Any AE occurring before the first dose of IP, or more than 7 days after the last dose of IP, will be included in the data listings but will not be included in the summary tables of AEs.

Where dates are missing or partially missing, AEs will be assumed to be treatment-emergent, unless there is clear evidence (through comparison of partial dates) to suggest that the AE started prior to the first dose of study treatment or more than 7 days after the last dose of study treatment.

The following AE summaries will be provided:

- A summary of the number and percentage of subjects reporting a TEAE in any category by treatment group
- A summary of the number of TEAEs reported in any category by treatment group
- A summary of the number and percentage of subjects reporting a TEAE with a frequency of ≥2% by treatment group and PT
- A summary of the number and percentage of subjects reporting a non-serious adverse event occurring in greater than 5% of subjects by treatment group, SOC and PT
- A summary of the number of TEAEs reported by treatment group, SOC and PT
- A summary of the number and percentage of subjects reporting a TEAE by treatment group, SOC and PT

- A summary of the number and percentage of subjects reporting a TEAE by treatment group, causality and PT
- A summary of the number and percentage of subjects reporting a TEAE by treatment group, intensity and PT

TEAE summaries will be ordered in terms of international order for SOC, and alphabetically for PT within SOC.

For the summary of TEAE with a frequency of ≥2%, TEAEs will be ordered by decreasing frequency in the highest AZD7594 treatment group.

For each subject and each AE, the worst intensity recorded will be attributed and used in the by-intensity summaries. Similarly, the worst causality will be attributed and used in the by-causality summaries. Multiple occurrences of a TEAE in the same subject will only be counted once overall.

A by-subject listing of all AEs (including non-treatment-emergent events) will be provided. This listing will be presented by treatment group and will include: subject identifier, treatment, age, sex, race, AE (PT, and verbatim term), study day of onset, duration, intensity, seriousness, action taken, causality, outcome and concomitant medication (CM) given (including CM number).

4.10.3 Deaths, serious adverse events, and other significant adverse events

TEAEs will be included in the summary tables below.

The following AE summaries will be provided:

- A summary of the number and percentage of subjects reporting a TEAE with outcome of death by treatment group, SOC and PT
- A summary of key subject information for subjects reporting TEAE with outcome of death
- A summary of the number of SAEs reported by treatment group, SOC and PT
- A summary of the number and percentage of subjects reporting a SAE by treatment group, SOC and PT
- A summary of key subject information for subjects reporting a SAE
- A summary of the number and percentage of subjects reporting a DAE by treatment group, SOC and PT
- A summary of key subject information for subjects reporting a DAE

4.10.4 Clinical laboratory evaluation

The following summaries will be provided:

- A summary of the observed absolute values and change from baseline in each haematology and clinical chemistry laboratory parameter by treatment group and time point.
- A summary of baseline versus last observation on treatment in each laboratory parameter by treatment group (shift table)
- A summary of baseline versus maximum observation on treatment in each laboratory parameter by treatment group (shift table)
- A summary of baseline versus minimum observation on treatment in each laboratory parameter by treatment group (shift table)
- A summary of key subject information for subjects reporting changes outside reference ranges in each laboratory parameter
- A summary of the number and percentage of subjects reporting changes outside reference ranges in each laboratory parameter
- A plot of ALT (Alanine aminotransferase) versus total bilirubin, expressed as multiples of upper limit of normal (ULN)
- A plot of AST (Aspartate aminotransferase) versus total bilirubin, expressed as multiples of ULN
- A summary of the number and percentage of subjects reporting maximum on-treatment ALT and AST by maximum total bilirubin for assessing HL criteria
- A summary of individual subject data for subjects with PHL ie, subjects with combined ALT or AST, and bilirubin elevations

By-subject listings of all laboratory data will be provided including subject identifier, treatment, age, sex, race, visit, category, lab test name, result and standard units. Laboratory reference ranges will also be listed and out of range values will be flagged.

4.10.5 Vital signs, ECG, physical findings and other observations related to safety

Potentially clinically significant (PCS) ECG values will be identified. The predefined criteria (based on severity) for PCS ECG values are displayed in Table 9

Table 9 PCS ECG predefined criteria

Variable	Unit	Outside lower limit if	Outside upper limit if	AZ extended reference range - low	AZ extended reference range - high	Treatment emergent increase if	Extended treatment emergent increase if
Heart rate	bpm	<50	>100	<45	>120	NA	NA
				<30	>150		
RR interval	ms	<600	>1200	<500	>1333	NA	NA
				<400	>2000		

PR interval	ms	<110	>220	<100	>240	>40	>60
QRS	ms	<75	>115	<70	>120	>15	>30
QT	ms	<320	>450	<300	>480	>30	>60
					>500		
QTcF	ms	<320	>450*	<300	>480*	>30*	>60*
					>500*		

- * Cut-off values for categorical analyses as recommended by ICH E14 (Note, more than one category for high range increases in QT/QTc values)
- ms = milliseconds, bpm = beats per minute: NA= not applicable. Note, no standard criteria are established for treatment emergent increases or decreases in RR intervals or heart rates, or for treatment emergent decreases in PR, QRS or QT/QTc intervals
- Note, lower and upper RR interval limits and low and high RR interval reference ranges (all in ms), represent respectively the upper and lower heart rate limits and high and low heart rate reference ranges (all in bpm)

Notable changes from pre-dose at each post-dose time point for vital sign parameters will be identified. The predefined criteria for notable changes in vital signs values are displayed in Table 10.

Table 10 Vital sign notable change predefined criteria

Vital sign		Observed value	Notable change from baseline
Systolic BP (mmHg)	High	⩾ 140	Increase of ⩾ 20
	Low	< 90	Decrease of ⩾ 20
Diastolic BP (mmHg)	High	⩾ 90	Increase of ⩾ 10
	Low	< 60	Decrease of ⩾ 10
Pulse Rate (bpm)	High	≥ 110	Increase of ≥ 20
	Low	< 50	Decrease of ≥ 20

BP = Blood pressure.

For by-visit summaries, the last non-missing assessment (including repeat assessments) recorded at each applicable scheduled visit will be summarized.

The following summaries will be provided:

- A summary of the observed absolute values and change from baseline in each vital sign parameter by treatment group and time point.
- A summary of key subject information for subjects reporting notable changes outside predefined criteria in each vital sign parameter
- A summary of the number and percentage of subjects experiencing notable changes from baseline outside predefined criteria, by vital sign parameter and treatment group
- A summary of the observed absolute values and change from baseline in each ECG parameter by treatment group and time point. Both pre- and post-IP measurements will be presented at each time point.

- A summary of the number and percentage of subjects with QTcF intervals exceeding predefined upper limits (as stated in Table 9)
- A summary of ECG assessment (normal/abnormal (clinically significant, not clinically significant)), baseline versus last observation on treatment. Post-IP measurement at last observation on treatment will be used.
- A summary of key subject information for subjects reporting PCS ECG values outside predefined criteria by treatment group and visit
- A summary of the number and percentage of subjects reporting PCS ECG values outside predefined criteria, by ECG parameter and treatment group

By-subject listings of vital sign parameters, ECG results, ECG abnormalities and weight, height and BMI will also be provided.

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

4.10.6 Safety monitoring (Independent Data Monitoring Committee [IDMC], Data Monitoring Committee [DMC], Data and Safety Monitoring Board [DSMB])

Not applicable.

4.11 Other Analyses

4.11.1 Pharmacokinetics

All PK summaries and analyses will be based upon the PK analysis set as defined in Section 4.5.

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 (CV), arithmetic mean, arithmetic SD, median, minimum and maximum based on the PK analysis set. Plasma concentrations that are BLQ will be reported as 'BLQ' with the lower limit of quantification (LLOQ) defined in the tables, figures, and listings. The number of BLQ values (n below LLOQ) will be reported for each time point. For calculation of descriptive statistics, concentrations that are BLQ will be handled as described below:

- At a time point where 50% or less of the plasma concentrations are BLQ, then all BLQ values will be set to the LLOQ, and all descriptive statistics will be calculated.

- At a time point where more than 50%, but not all, of the concentrations are BLQ, the geometric mean, geometric CV, arithmetic mean, and arithmetic SD will be reported as 'NC' (not calculable). The maximum value will be reported from the individual data, and the minimum and median will be set as 'BLQ'.

- At a time point where all concentrations are BLQ, no descriptive statistics will be calculated. 'NA' (not applicable) will be presented for geometric CV, and arithmetic SD, and 'BLQ' will be presented for geometric mean, arithmetic mean, median, minimum, and maximum.

If an embedded BLQ value is considered anomalous within the concentration-time profile, this value will be excluded from descriptive statistics.
Any PK samples with actual collection time deviating by > 10% from the protocol scheduled collection time will be excluded from the summary tables and related figures, but the data will still be used in the PK analysis to determine the PK parameters.

For PK concentration and parameter data, if there are less than 3 values available in a data series, then only the maximum, minimum, and n will be reported; the remaining descriptive statistics will be reported as 'NC'. Concentrations that are BLQ are considered a value.

For PK concentration data, the listings will be presented to the same precision as the data received from the bioanalytical laboratory. For PK parameters, the listings will be presented according to the following conventions:

- $C_{ss,max}$, $C_{ss,min}$, and $C_{ss,avg}$ will be presented to the same precision as the data received from the bioanalytical laboratory.
- $t_{ss,max}$ and t_{last} will be presented as received in the data, usually to 2 decimal places
- AUC_{last}, AUC_{τ}, AUC_{0-12}, $C_{ss,max}/D$, AUC_{τ}/D, and %Fluctuation will be presented to 3 significant figures.

For PK concentration data, all descriptive statistics will be presented to 4 significant figures, with the exception of minimum and maximum, which will be presented to 3 significant figures. For PK parameter data, the descriptive statistics will be presented according to the following conventions:

- $C_{ss,max}$, $C_{ss,min}$, $C_{ss,avg}$, AUC_{last}, AUC_{τ}, $C_{ss,max}/D$, AUC_{τ}/D, and %Fluctuation: descriptive statistics will be presented to 4 significant figures, with the exception of minimum and maximum, which will be presented to 3 significant figures.
- $t_{ss,max}$ and t_{last}: all descriptive statistics will be presented as received in the data, usually to 2 decimal places

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. For combined individual figures, concentrations that are BLQ will be regarded as missing, with the exception of BLQ values that occur prior to the first quantifiable value.

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. The descriptive statistics presented in the summary concentration table will be used to create these plots.

All plasma PK parameters defined in Section 3.2.3 will be listed for each subject and all plasma PK parameters, except for $AUC_{0-12,}$ will be summarised by treatment using similar descriptive statistics. For t_{max} and t_{last} only n, median, minimum and maximum will be reported.

Data from subjects 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 primary PK parameters 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. Delivered dose will be used for assessing dose proportionality.

4.11.2 Pharmacodynamics

All PD summaries and analyses will be based upon the PD analysis set as defined in Section 4.5.

Cortisol suppression will imply the measurement of the area under the plasma cortisol concentration-time curve from zero to 12 hours after dosing ($AUEC_{(0-12)}$), and from zero to 24 hours after dosing ($AUEC_{(0-24)}$) as compared to placebo. AUEC is defined as the area under the curve and is calculated using the linear trapezoidal rule.

Non-missing cortisol values at the following time points are required in order to calculate the $AUEC_{0-12}$: pre-dose; at least one value between 2 hours and 12 hours post-dose (inclusive). Otherwise the $AUEC_{0-12}$ will be missing.

Where d_i is the cortisol value obtained at time t_i; t_i is the time (in hours before IP administration) for which d_i is measured: On Day -1; $t_1 = -12$, $t_2 = -8$ $t_3 = -4$ and $t_4 = -2$. On Day 1; $t_5 = 0$ (pre-dose).

Where d_i is the cortisol value obtained at time t_i; t_i is the time (in hours after IP administration) for which d_i is measured: $t_1 = 0$ (pre-dose), $t_2 = 2$, $t_3 = 4$, $t_4 = 6$, $t_5 = 8$, $t_6 = 10$ and $t_7 = 12$.

Non-missing cortisol values at the following time points are required in order to calculate the $AUEC_{0-24}$: pre-dose; at least one value between 2 hours and 24 hours post-dose (inclusive). Otherwise the $AUEC_{0-24}$ will be missing.

CCI

Where d_i is the cortisol value obtained at time t_i; t_i is the time (in hours before IP administration) for which d_i is measured: On Day -1;$t_1 = -24$, $t_2 = -22$, $t_3 = -20$, $t_4 = -18$, $t_5 = -16$, $t_6 = -14$, $t_7 = -12$, $t_8 = -8$ $t_9 = -4$ and $t_{10} = -2$. On Day 1; $t_{11} = 0$ (pre-dose).

CCI

Where d_i is the cortisol value obtained at time t_i; t_i is the time (in hours after IP administration) for which d_i is measured: $t_1 = 0$ (pre-dose), $t_2 = 2$, $t_3 = 4$, $t_4 = 6$, $t_5 = 8$, $t_6 = 10$, $t_7 = 12$, $t_8 = 16$, $t_9 = 20$, $t_{10} = 22$ and $t_{11} = 24$.

The log AUEC will be used (rather than the raw), since the distribution of cortisol AUEC data is not expected to approximate to a normal distribution.

The $AUEC_{(0-12)}$ and $AUEC_{(0-24)}$ will be listed by subject and time point and $AUEC_{(0-24)}$ will also be summarised (n, geometric mean, geometric CV, median, arithmetic mean, arithmetic SD, minimum and maximum) by treatment.

The change from baseline in log-transformed $AUEC_{(0-24)}$ at Day 84 will be analysed by ANCOVA approach with treatment as a fixed effect, and log-transformed baseline (Day -1) $AUEC_{(0-24)}$ as a covariate. These analyses will be done on the natural log-scale and the results will be back-transformed to linear scale. Hence treatment effects will be presented in terms of geometric LS means and treatment differences and associated CIs will be presented in terms of geometric LS mean ratios. Due to the log-transformation, the geometric LS means represent a relative change from baseline rather than an absolute change from baseline.

The estimated ratio for each AZD7594 arm versus placebo and FF versus placebo, and their associated 95% CIs and p-values will be presented.

4.11.3 Exploratory Analyses

All exploratory analyses will be performed on the FAS.

4.11.3.1 ACQ-5 responder 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 subject 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 (PROC GLIMMIX) approach. The GLIMMIX model will include treatment, visit, region (US, Japan, and RoW) and visit by treatment interaction as covariates. The number and percentage of responders at each visit as well as the estimated odds ratio for each AZD7594 arm versus placebo and FF versus placebo, and their associated 95% CI and p-value will be presented.

4.11.3.2 Change from baseline in measures of resistance and reactance via FOT

The summary and analysis of change from baseline (pre-dose, Visit 3) in measures of resistance (R5-R20) and reactance (AX) via FOT will be performed as described for the primary endpoint in Section 4.9.2. All scheduled visits will be included in the analysis although Week 12 is of primary interest. No subgroup analyses will be performed.

R5 and R20 will be listed only.

4.12 Determination of Sample Size

Approximately 102 subjects will be randomised to each arm (overall randomisation ratio 1:1:1:1:1:1:1 in order to ensure at least 86 evaluable subjects per arm. This sample size was derived to 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-subject 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 subjects to be randomised is approximately 714 subjects. Additional subjects will be screened to account for any ineligibility rate prior to randomisation. From previous studies, the screening failure rate was estimated to be approximately 50%, therefore approximately 1400-1500 screened subjects will be required to achieve the goal of approximately 714 randomised subjects.

4.13 Changes in the Conduct of the Study or Planned Analysis

According to AZ Authoring Guidance for referencing participants in studies the term "subject" is to be used for document headings, appendix titles, and within tables, figures, and listings.

The CSP uses "patient" when referencing participants in the study. To ensure consistency with Tables, Listings & Figures (TLF) shells, it was agreed with AZ that the SAP will use the word "subject" and therefore text may differ compared to corresponding sections in the CSP.

Due to upcoming studies with AZD7594 in younger subjects having a shorter sampling period it was requested to add one additional PK and one additional PD parameter to be included in the SAP:

- AUC (0-12): area under the concentration-time curve from time 0 to 12 hours post-dose
- AUEC (0-12): area under the plasma cortisol concentration-time curve from 0 to 12 hours after dosing

These parameters will not be analysed or plotted, just listed per subject and timepoint.

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