Division	:	Worldwide Development
Information Type	:	Reporting and Analysis Plan (RAP)

Title	:	Reporting and Analysis Plan 207040 for an open label, randomised, parallel group clinical study to evaluate the effect of the Connected Inhaler System (CIS) on adherence to Relvar/Breo ELLIPTA therapy, in asthmatic subjects with poor control.
Compound Number	:	GW685698+GW642444 (GSK2285997)
Effective Date	:	21-FEB-2019

Description:

- The purpose of this RAP is to describe the planned analyses and output to be included in the Clinical Study Report (CSR) for Protocol 207040.
- This RAP is intended to describe the study population, efficacy and safety analyses required for the study.
- This RAP will be provided to the study team members to convey the content of the final Statistical Analysis Complete (SAC) deliverable.

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1. INTRODUCTION

The purpose of this reporting and analysis plan (RAP) is to describe the analyses to be included in the Clinical Study Report (CSR) for Protocol 207040 [GlaxoSmithKline Document Number: 2016N307903_01 (Dated: 10SEP2018)].

Revision Chronology:		
2016N307903_00	22-JUN-2017	Original
2016N307903_01	10-SEP-2018	Amendment 1

All data displays (Tables, Figures & Listings) will use the term "Subject" which reflects CDISC and GSK Data Display Standards terminology.

2. SUMMARY OF KEY PROTOCOL INFORMATION

2.1. Changes to the Protocol Defined Statistical Analysis Plan

Changes from the planned statistical analysis specified in protocol amendment 1 are outlined in Table 1.

Table 1 Changes to Protocol Defined Analysis Plan

Protocol	**Reporting & Analysis Plan**	
Statistical Analysis Plan	**Statistical Analysis Plan**	**Rationale for Changes**
Duration of run-in included in analysis models as a continuous covariate, measured in days.	Duration of run-in included in analysis models as a categorical covariate of number of visits.	Participants can complete the run-in period in 1, 2 or 3 visits, use of a categorical covariate is more flexible than the assumption of a linear relationship.
Missing data due to a medical device incident will be assumed to be missing at random within the last 3 months treatment period.	Missing data due to a medical device incident will be assumed to be missing at random within each month of the treatment period.	Monthly adherence rates are used within the imputation model to allow for variation in adherence over time.
Participants who prematurely discontinue from study will have their post-withdrawal daily adherence data imputed using data from the control arm	Participants who prematurely discontinue from use of the ELLIPTA maintenance sensor will have subsequent adherence data imputed using data from the control arm	The ELLIPTA maintenance sensor may be discontinued without withdrawal from the study
Protocol Section 11.3 Populations for Analyses	RAP Section 4 Analysis Populations	The analysis populations have been updated to follow the study populations standard definitions and statistical displays

Protocol	Reporting & Analysis Plan	
Statistical Analysis Plan	**Statistical Analysis Plan**	**Rationale for Changes**
	Mean change from baseline (Randomisation) in ASUI and SGRQ total score at Month 6 included in the RAP as an additional endpoint	To support the exploratory summaries and analyses for ASUI and SGRQ continuous endpoint
Composite endpoint - Percentage of patients who have either an ACT total score of ≥ 20 or an increase from baseline of ≥ 3 in ACT total score at Month 6 (Visit 10).	Composite endpoint - Percentage of patients who have either an ACT total score of ≥ 20 and/or an increase from baseline of ≥ 3 in ACT total score at Month 6 (Visit 10).	The condition 'and/or' will be applied to the composite ACT endpoint to replace 'or' to clarify that participants who achieve both an ACT total score of ≥ 20 and an increase from baseline of ≥ 3 in ACT total score at Month 6, in addition to those who only achieve one, will be considered a responder.
	Change from baseline (Visit 2, 3 or 4) in FeNO measured at Month 1 (Visit 5) and Month 6 (Visit 10)	To support the exploratory summary of impact of adherence on the biomarker Fractionated Exhaled Nitric Oxide (FeNO)

2.2. Study Objectives and Endpoints

Objectives	Endpoints
Primary Objectives	**Primary Endpoints**
To compare the effect of 6 months use of the CIS on adherence to ELLIPTA maintenance therapy when both the participant and the HCP are supplied with data from the maintenance sensor versus no data supplied to the participant and HCP (Arm 1 vs Arm 5)	Percentage of ELLIPTA doses taken (daily adherence[1.]) between the beginning of month 4 and the end of month 6 as determined by the maintenance sensor
Secondary Objectives	**Secondary Endpoints**
To compare the effect of 6 months use of the CIS on adherence to ELLIPTA maintenance therapy for the following aspects of the CIS: • Maintenance data only supplied to participants versus no data supplied to the participant (Arm 2 vs Arm 5) • Rescue and Maintenance data supplied to participant and HCP versus no data supplied to the participant and HCP (Arm 3 vs Arm 5) • Rescue and Maintenance data only supplied to participant versus no data supplied to the participant (Arm 4 vs	• Percentage of ELLIPTA doses taken (daily adherence[1.]) between the beginning of month 4 and the end of month 6 as determined by the maintenance sensor

Objectives	Endpoints
Arm 5)	
To compare the effect of the CIS on adherence to ELLIPTA maintenance therapy of the individual CIS treatment arms versus no data supplied to the participant and HCP.	• Percentage of ELLIPTA doses taken (daily adherence[1].) between the beginning of month 1 and the end of month 3 • Percentage of ELLIPTA doses taken (daily adherence) between the beginning of month 1 and the end of month 6
To evaluate the effect of 6 months use of the CIS on a participant's rescue medicine usage	• Percentage of rescue free days measured between the beginning of month 4 and the end of month 6 as determined by the rescue sensor records of date, time, and number of inhaler actuations. • Total rescue use measured between the beginning of month 4 and the end of month 6 as determined by the rescue sensor records of date, time, and number of inhaler actuations.
To evaluate the effect of 6 months use with the CIS on a participant's asthma control	• Change from baseline (Randomisation) in ACT total score at Month 6, measured at baseline (Visit 2, 3 or 4) and Month 6 (Visit 10) • Percentage of patients becoming controlled as defined as an Asthma Control Test score ≥20 at Month 6 (Visit 10) • Percentage of patients with an increase from baseline ≥ 3 in ACT total score at Month 6 (Visit 10) • Composite endpoint - Percentage of patients who have either an ACT total score of ≥ 20 and/or an increase from baseline of ≥ 3 in ACT total score at Month 6 (Visit 10).
Exploratory and Other Objectives	**Exploratory Endpoints**
To evaluate the effect of 6 months use of the CIS on adherence to ELLIPTA maintenance therapy on the following aspects of the CIS: • HCP having access to sensor data • Rescue Medication data being available	• Percentage of ELLIPTA doses taken (daily adherence) between the beginning of month 4 and the end of month 6 as determined by the maintenance sensor

• To evaluate the effect of 6 months use with CIS on health care utilisation	• Health care utilisation endpoints will include the following and will be collected from a participant's medical records.
	  • Number of outpatient visits relating to asthma
	  • Number of primary care visits relating to study HCP dashboard review (for relevant study arms)
	  • Number of and duration of hospitalisations, and ER visits due to asthma
	  • Annualised rate of severe exacerbations
	  • Number of unscheduled visits to primary care related to Asthma

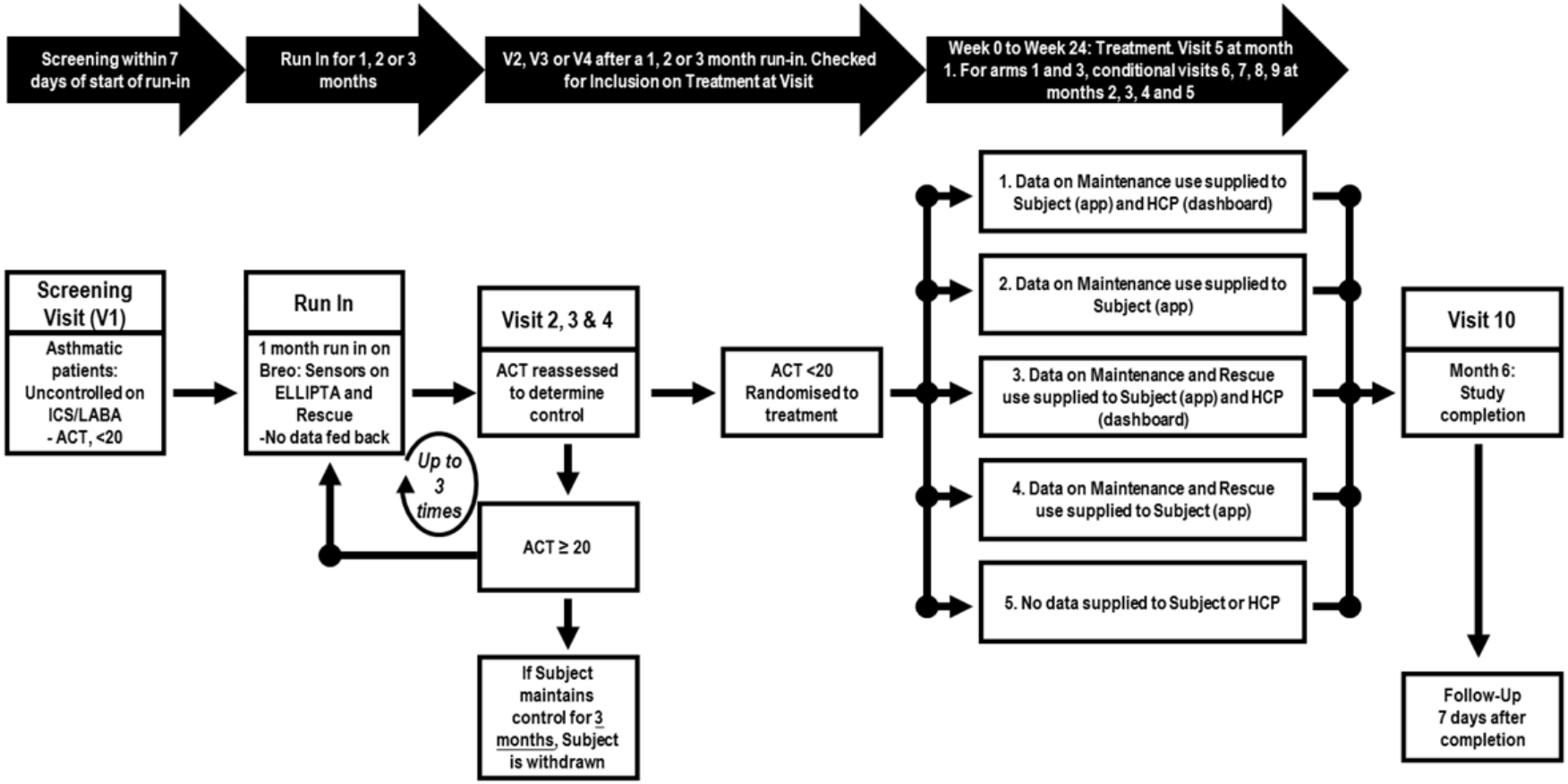
To evaluate the effect of 6 months use with CIS on the following patient reported	• Percentage of patients meeting a responder threshold of ≥ 0.09 points improvement from baseline

Objectives	Endpoints
outcomes (PROs): • Asthma Symptom Utility Index (ASUI) • St Georges Respiratory Questionnaire (SGRQ) • Patient Activation Measure (PAM) • Medication Adherence Report Scale for Asthma (MARS-A) • Beliefs in Medicine Questionnaire (BMQ).	(Randomisation) for the ASUI total score at Month 6 • Mean change from baseline (Randomisation) in ASUI total score at Month 6 • Percentage of patients meeting a responder threshold of ≥ 4 points improvement from baseline (Randomisation) for the SGRQ total score at Month 6 • Mean change from baseline (Randomisation) in SGRQ total score at Month 6 • Mean change from baseline (Screening) in PAM total score at Month 6 • Mean change from baseline (Screening) in MARS-A total score at Month 6 • Mean change from baseline (Screening) at Month 6 in BMQ: o General Benefit score o General Harm score o General Overuse score o Specific Necessity score o Specific Concern score
• To assess the reliability and usability of the CIS	• Incidence of Medical Device Incidents between the beginning of Month 1 and the end of Month 6.
• To explore impact of adherence on the biomarker Fractionated Exhaled Nitric Oxide (FeNO)	• FeNO at Screening (Visit 1), Randomisation (Visit 2,3 or 4), Month 1 (Visit 5) and Month 6 (Visit 10). • Change from baseline (Visit 2, 3 or 4) in FeNO measured at Month 1 (Visit 5) and Month 6 (Visit 10)
• To explore impact of adherence on the physiological marker Peak Expiratory Flow (PEF)	• PEF at Screening (Visit 1), Randomisation (Visit 2,3 or 4), Month 1 (Visit 5) and Month 6 (Visit 10). • Change from baseline (Visit 2, 3 or 4) in PEF measured at Month 1 (Visit 5) and Month 6 (Visit 10)
• To characterize patient experience of the CIS for participants	• Exit Questionnaires at Month 6 (Visit 10) • Exit Interviews for a sub set of participants at Month 6 (Visit 10)
Safety Objectives	**Safety Endpoints**
To evaluate the incidence of SAEs, Non-Serious Adverse Events that lead to withdrawal from study and Non-Serious Adverse Drug Reactions in asthmatic participants using the CIS	• SAEs, Non-Serious Adverse Events that lead to withdrawal and Non-Serious Adverse Drug Reactions

1. Daily adherence is defined as the participant taking one dose of Relvar/Breo ELLIPTA, within a 24-hour period, starting at 12.00am each day

2.3. Study Design

Overview of Study Design and Key Features



Design Features	This is an open-label, randomised, multi-centre, parallel group study consisting of 5 treatment arms, in asthmatic patients currently on a fixed dose Inhaled Corticosteroids (ICS)/ Long-Acting Beta2-Agonist (LABA) maintenance therapy. Further details of the study design can be found in Section 5 (Study Design) of the 207040 protocol

Overview of Study Design and Key Features	
	[GlaxoSmithKline Document Number 2016N307903_01].
Time & Events	Refer to Appendix 1: Schedule of Activities
Treatment Assignment	All randomised participants will receive Relvar/Breo ELLIPTA, at the dose allocated at the run in. Salbutamol Metered Dose Inhaler (MDI) rescue medication will be prescribed to participants to use as needed throughout the study for relief of asthma symptoms as per usual practice All participants will have sensors attached to both their Relvar/Breo ELLIPTA and salbutamol MDI. It is the type of data provided by the CIS (either Relvar/Breo ELLIPTA alone or Relvar/Breo ELLIPTA and salbutamol MDI), as well as who sees that data, (participant alone or participant and HCP), that defines the treatment arms. Participants will be randomized 1:1:1:1:1 to one of the five treatments arms for the duration of the treatment period: • Arm 1: Data on Maintenance use supplied to Participant (app) and HCP (dashboard) • Arm 2: Data on Maintenance use supplied to Participant (app) • Arm 3: Data on Maintenance and Rescue use supplied to Participant (app) and HCP (dashboard) • Arm 4: Data on Maintenance and Rescue use supplied to Participant (app) • Arm 5: No data supplied to Participant or HCP The treatment period for the study is 6 months. However, due to the flexible run in period a participant could be on the study for approximately 7, 8 or 9 months in total. GSK RandAll NG will be used to generate the randomisation schedule. Centralized randomisation will be used. GSK RAMOS NG will be used for treatment allocation.

2.4. Statistical Hypothesis

The main purpose of the study is to compare the effect of 6 months use with the Connected Inhaler System (CIS) on adherence to Relvar/Breo ELLIPTA maintenance therapy with adherence to Relvar/Breo ELLIPTA maintenance therapy without CIS use (sensor alone), in participants with poorly controlled asthma.

All participants receive Relvar/Breo ELLIPTA, either at the dose they are already prescribed or at the equivalent dose to their current ICS/LABA maintenance therapy if switched onto Relvar/Breo ELLIPTA at enrolment. All participants will have sensors attached to both their Relvar/Breo ELLIPTA and Salbutamol MDI. It is the type of data provided by the CIS (either Relvar/Breo ELLIPTA alone or Relvar/Breo ELLIPTA and salbutamol MDI), as well as who sees that data (participant alone or participant and HCP) that defines the treatment arms.

This study aims to demonstrate the superiority of the CIS on adherence to Relvar/Breo ELLIPTA with an app compared to Relvar/Breo ELLIPTA (with sensor alone).

The primary endpoint is mean percentage of ELLIPTA doses taken (daily adherence) between Months 4 and 6 as determined by the maintenance sensor daily adherence over the last three months of the study period (between months 4 to 6).

The test for the primary treatment comparison will be a test between Arm 1 versus Arm 5. This will be based on a two-sided hypothesis testing approach: the null hypothesis is the difference between Arm 1 and Arm 5 is equal to zero. The alternative hypothesis is that the difference is not equal to zero. The hypotheses associated with the statistical test of the primary endpoint are written below:

H0: $Ti - Tj = 0$

(where i = Arm 1 and j = Arm 5) The null hypothesis: that the difference in response between Arm 1 and Arm 5 is zero.

Ha: $Ti - Tj \neq 0$

The alternative hypothesis: that the difference is not zero.

Other comparisons of interest for the primary endpoint are the individual comparisons of Arms 2, 3 and 4 with Arm 5 in order to obtain estimated mean treatment differences, 95% confidence intervals (CIs) and p-values. This will be a descriptive comparison to inform on the relative benefits of the individual aspects of the CIS and no formal inference is planned.

The effect on adherence to maintenance therapy between arms with HCP and no HCP interaction i.e. Arm 1 v Arm 2 and Arm 3 v Arm 4, and arms with rescue medication use feedback versus none i.e. Arm 1 v Arm 3 and Arm 2 v Arm 4, will be also assessed.

The comparisons of interest for the other secondary and safety endpoints are as stated above for the primary endpoint. Arms 1, 2, 3 and 4 will be individually compared to Arm

5, as relevant to the endpoint, to obtain estimated mean treatment differences, 95% confidence intervals and p-values. This will be a descriptive comparison and no formal inference is planned.

3. PLANNED ANALYSES

To minimize the risk of breaking the study blind during the pre-programming of analysis datasets and displays for the final analyses, an unblinded team of programmers will scramble the data in a secure area according to a pre-defined blinding strategy, before releasing to Clinical Statistics and Programming (S&P).

3.1. Interim Analyses

An interim analysis was originally planned to be conducted when 50% of subjects complete 6 months of study treatment in order to conduct a sample size re-estimation. However the requirement for the interim analysis and sample size-re-estimation was decided no longer necessary and removed from the study protocol.

3.2. Final Analyses

The final planned analyses will be performed after the completion of the following sequential steps:

1. All participants have completed the study or have been withdrawn as defined in the protocol.
2. All required database cleaning activities have been completed and final database release (DBR) and database freeze (DBF) has been declared by Data Management (DM).
3. System Independent (SI) data to Study Data Tabulation Model (SDTM) data conversion has completed by Conversion Service Provider at Source Data Lock (SDL).
4. All criteria for unblinding the randomisation codes have been met.
5. Randomisation codes have been distributed according to RandAll NG procedures. Release of randomisation code, unblinding of study treatment and participant level treatment of SDTM data, and related quality control activities have been completed by S&P.
6. DBF on SDTM datasets has been declared by DM upon receipt of the final, treatment unblinded SDTM data from S&P.

4. ANALYSIS POPULATIONS

Population	Definition / Criteria	Analyses Evaluated
All participants	• All participants who signed the ICF	Study Population
Screened	• All participants who were screened for eligibility.	Study Population
Enrolled	• All participants who passed screening and entered the study. Included are: Run-in Failures; Randomized Participants Note screening failures are excluded from the Enrolled population as they did not enter the study.	Study Population Safety
Randomized	• All participants who were randomly assigned to a treatment arm in the study. • This population will be based on the treatment arm the participant was randomised to.	Study Population
Intent-To-Treat (ITT)	• The ITT population comprises all randomised participants, excluding those who were randomised in error. A participant who is recorded as a screen or run-in failure but is randomised, and does not receive a dose of study treatment, is considered to have been randomised in error. Any other participant who received a randomisation number will be considered to have been randomised. • This population will be based on the treatment arm the participant was randomised to.	Study Population Efficacy (ELLIPTA Adherence, Rescue Medications Use, PRO, PEF and FeNO) Safety

Refer to Section 10.8 Appendix 8: List of Data Displays which will detail the population used for each display.

4.1. Protocol Deviations

This dataset will be the basis for the summaries and listings of protocol deviations. A separate summary and listing of all inclusion/exclusion criteria deviations will also be provided. This summary will be based on data as recorded on the inclusion/exclusion page of the eCRF.

5. CONSIDERATIONS FOR DATA ANALYSES AND DATA HANDLING CONVENTIONS

5.1. Study Treatment & Sub-group Display Descriptors

Treatment Group Descriptions									
	Relvar/Breo ELLIPTA Sensor Data Available to		Salbutamol/Rescue MDI Sensor Data Available to		RandAll NG Randomisation System		Data Displays for Reporting		
Arm	Participant	HCP	Participant	HCP	Code	Description	Full Description	Short Description	Order in Table, List, Figure (TLF)
1	X	X			1	Data on Maintenance use supplied to Participant (app) and HCP (dashboard)	Arm 1: Maintenance use data supplied to Participant and HCP	Arm 1	1
2	X				2	Data on Maintenance use supplied to Participant (app)	Arm 2: Maintenance use data supplied to Participant	Arm 2	2
3	X	X	X	X	3	Data on Maintenance and Rescue use supplied to Participant (app) and HCP (dashboard)	Arm 3: Maintenance and Rescue use data supplied to Participant and HCP	Arm 3	3
4	X		X		4	Data on Maintenance and Rescue use supplied to Participant (app)	Arm 4: Maintenance and Rescue use data supplied to Participant	Arm 4	4
5					5	No data supplied to Participant or HCP	Arm 5: No data supplied to Participant or HCP	Arm 5	5

Arm 1: Maintenance use data supplied to Participant and HCP, Arm 2: Maintenance use data supplied to Participant, Arm 3: Maintenance and Rescue use data supplied to Participant and HCP, Arm 4: Maintenance and Rescue use data supplied to Participant, Arm 5: No data supplied to Participant or HCP.

All participants will have sensors attached to both their Relvar/Breo ELLIPTA and Salbutamol (albuterol) MDI. It is the type of data provided by the CIS (either Relvar/Breo ELLIPTA alone or Relvar/Breo ELLIPTA and salbutamol MDI), as well as who sees that data (participant alone or participant and HCP) that defines the treatment arms. See Section 5.1 Study Treatment & Sub-group Display Descriptors for a description of what data is fed back to whom for each treatment arm, and the treatment group descriptors.

Where possible the full description will be used in data displays. If it is necessary to use the short description, for example in figure legends, the footnote shown under the table in Section 5.1 Study Treatment & Sub-group Display Descriptors will be included. Where treatment comparisons are included in a data display and the full treatment descriptions do not also appear within the display, the same footnote will be included.

5.2. Baseline Definitions

Baseline adherence will be the percentage of ELLIPTA doses taken (daily adherence) during the last 28 days of the run-in period prior to randomisation. This will be determined using the randomisation date. A minimum of 14 run-in days prior to randomisation will be required to determine baseline adherence otherwise it will be set to missing. Any missing intermittent daily adherence data will be imputed as non-adherent i.e. the participant will be assumed to have not taken their treatment within the 24-hour time period/window, where there is no evidence of a medical device incident having occurred. Missing data due to a medical device incident such as,

- device failure
- technical failure of the ELLIPTA maintenance sensor
- data transmission failure,

will be assumed to be missing at random (MAR). For each participant the baseline percentage adherence measure will be calculated as the number of days a participant is adherent divided by the number of days without medical device incident within the baseline assessment period * 100. See Section 10.2.2 Definitions of Assessment Windows for Adherence and Rescue Medication Use Analyses, for the definition of the baseline assessment period.

Baseline rescue free days will be the percentage rescue free days (RFDs) during the last 28 days of the run-in period prior to randomisation. This baseline will be determined in the same manner as the adherence baseline.

Where baseline assessments are determined from the randomisation visit, no unscheduled assessments will be considered as the baseline value.

Where baseline assessments are determined from the screening visit, Visit 1 will be used and no unscheduled screening visits will be considered as the baseline value.

If time is not collected, Day 1 assessments are assumed to be taken prior to first dose and used as baseline.

Parameter	Study Assessments Considered as Baseline			Baseline Used in Data Display
	Visit 1 Screening	Study Days -28 to -1	Randomisation Visit, Study Day 1 (Pre-Dose)	
Efficacy				
ELLIPTA Adherence Endpoints (%)		x		% adherence from Day -28 to Day -1
Rescue Free Days (RFDs) (%)		x		% RFDs from Day -28 to Day -1
Total Rescue Use (TRU) (puffs)		x		Total use from Day -28 to Day -1
ACT Total score			x	Randomisation
SGRQ Total score			x	Randomisation
ASUI Total score			x	Randomisation
PAM-13 Total score	x			Screening
BMQ Total score	x			Screening
MARS-A Total score	x			Screening
PEF (litres/minute)			x	Randomisation - use maximum value at visit
FeNO (parts per billion)			x	Randomisation - use maximum value at visit

Notes:

- Day 1 is referenced as Day 0 (Randomisation visit at either Visit 2 or 3 or 4) in Section 2.3 and Section 10.1 Appendix 1: Schedule of Activities but will be reported as Day 1 per Clinical Data Interchange Standards Consortium (CDISC) reporting guidelines.
- Unless otherwise stated, if the baseline for an endpoint is missing it will not be imputed using a different timepoint or derivation but will remain missing.

5.3. Multicentre Studies

It is likely that many centres will enrol very small number of participants. Consequently, all centres within the same country will be pooled. In addition, if there are any countries enrolling very small numbers in total (<12 in the Intent to Treat population), these countries will be pooled with another country within a similar geographical region. All amalgamations will be finalised and documented prior to unblinding the treatment arm codes. These amalgamations will be used wherever region is incorporated into an analysis or summary.

In this multicentre global study, enrolment will be presented by centre, country and region (if required).

5.4. Examination of Covariates, Other Strata and Subgroups

5.4.1. Covariates and Other Strata

Unless otherwise stated, all models used for adherence and rescue free days will allow for fixed effects due to randomised treatment arm, baseline (of the analysis variable), duration of run-in (visits), country, gender, and age (years - determined from screening date). Randomised treatment arm, duration of run-in, country, and gender will be included as categorical covariates; baseline and age will be included as continuous covariates.

The covariates to be considered in the patient reported outcomes (PRO) analyses include randomised treatment arm, age (years - determined from screening date), gender, country and baseline (of the analysis variable), if relevant.

The covariate region will replace country should amalgamation of countries, as described in Section 5.3 Multicentre Studies, be required.

The list of covariates and other strata may be used in descriptive summaries and statistical analyses, some of which may also be used for subgroup analyses.

5.4.2. Examination of Subgroups

The following outcomes will be summarized by randomised treatment arm within subgroups defined by country.

- Enrollment
- Demographic characteristics
- Ellipta adherence

For these summaries, subgroups will be defined as in Table 2.

Table 2

Category	Subgroups
Country	• US, Canada, Germany, Italy, Netherlands, Spain, UK
Baseline ACT total score	• <=15, 16 - 19
Age (years – as determine from screening date)	• 18-35, 36-48, 49-58, >58 years

Notes: Details of the planned summaries are presented in Section 10.8 Appendix 8: List of Data Displays

5.5. Multiple Comparisons and Multiplicity

No adjustments for multiplicity will be applied.

5.6. Other Considerations for Data Analyses and Data Handling Conventions

Other considerations for data analyses and data handling conventions are outlined in the appendices:

Section	Component
10.1	Appendix 1: Schedule of Activities
10.2	Appendix 2: Assessment Windows
10.3	Appendix 3: Study Phases and Treatment Emergent Adverse Events
10.4	Appendix 4: Data Display Standards & Handling Conventions
10.5	Appendix 5: Derived and Transformed Data
10.6	Appendix 6: Reporting Standards for Missing Data
10.7	Appendix 7: Abbreviations & Trade Marks
10.8	Appendix 8: List of Data Displays

6. STUDY POPULATION ANALYSES

6.1. Overview of Planned Study Population Analyses

Study population summaries will be based on the ITT population, unless otherwise specified.

Study population displays including summaries and lists of study populations, screening and run-in status, participant study and study drug disposition, participant enrolment, inclusion and exclusion and important protocol deviations, demographic, age, race and baseline characteristics (including height, weight and BMI), medical conditions, family and smoking history and prior and concomitant medications will be based on GSK Core Data Standards. Details of the planned displays are presented in Section 10.8 Appendix 8: List of Data Displays.

Concomitant medications will be coded using the GSK Drug coding dictionary. Summaries of the number and percentage of participants taking concomitant medications will be displayed by ingredient without regard to Anatomical Therapeutical Chemical (ATC) classifications. These summaries will include single-ingredient medications and will present multi-ingredient medications according to the combination of the component ingredients. Summaries will be split into asthma and non-asthma concomitant medications, as well as into those taken pre-screening, during run-in, whilst on-treatment and post-treatment (as described in Section 10.3.1 Study Phases).

Asthma maintenance concomitant medications taken by participants in the 12 months prior to screening (pre-screening) will also be summarised as well as those used to treat severe exacerbations experienced whilst on study.

6.2. Supplementary Information for Study Population Displays

6.2.1. Disease and Baseline Characteristics

Summary of attendance at each scheduled clinic visit will be presented.

Summaries and lists of the Relvar/Breo ELLIPTA and Salbutamol MDI sensor statuses as well as the App status during the study will be presented.

Asthma exacerbation history (12-month history) at screening will be summarised with frequency distributions of the number of exacerbations treated with oral/systemic corticosteroids not involving hospitalization; the number of exacerbations treated without oral/systemic corticosteroids not involving hospitalization; the number of exacerbations requiring hospitalization; and the total number of exacerbations (i.e., those not involving hospitalization and those involving hospitalization).

Asthma duration will also be summarised.

The screening and baseline lung function test and exhaled nitric oxide summaries will include screening (Visit 1) pre-bronchodilator and pre-ICS/LABA, PEF (in litres per minute (L/min)) and FeNO (millilitres per second (mL/sec)). Baseline PEF (L/min) and

FeNO (mL/sec) measured at Randomisation (Visit 2/3/4) will also be summarised. Additionally, screening and baseline PEF will be summarised by country.

Prescription details (12-month history) at screening will be summarised with frequency distributions of the number of asthma maintenance therapy prescriptions requested or prescribed; the number of asthma maintenance therapy requested or prescribed that would need to be 100% compliant. Compliance in the previous 12 months will be calculated as 100 * (Actual number of prescriptions) / (Number of prescriptions needed to be 100% compliant) and summarised. These data will also be listed.

6.2.2. Preferred Time of Dosing

Summary statistics to summarise percentage of total ELLIPTA doses taken at preferred time of dosing for each participant will be presented. A participant is considered as having taken their dose at their preferred time if the actual time of the ELLIPTA dose is recorded ±1 hour of their preferred time as captured on the eCRF at screening. A histogram of individual dose deviations (in minutes) from preferred time will also be presented per treatment group. These data will also be listed.

6.2.3. Study Medication Exposure and Compliance

Duration (days) of exposure to study medication will be calculated based on randomisation date and latest (stop) of all dates recorded for the participant. Duration will be summarised categorically and with descriptive statistics. Total years exposed to Relvar/Breo after randomisation will also be presented. Further details are presented in Section 10.5 Appendix 5: Derived and Transformed Data

Calculation of Relvar/Breo study medication compliance after randomisation, will be based on the ELLIPTA device dose counter (which displays the number of doses remaining) as described in Section 10.5 Appendix 5: Derived and Transformed Data. Treatment compliance (calculated as a percentage) will be summarised categorically and with descriptive statistics.

All exposure and compliance data will be listed.

A summary of the number of puffs per day as recorded by the ELLIPTA Relvar/Breo and MDI sensors will be summarised and graphically presented.

6.2.4. HCP dashboard review

The actions taken by the HCP post the dashboard data review will be summarized and listed by visit for Arms 1 and 3.

7. EFFICACY ANALYSES

7.1. Primary Efficacy Analysis

The primary analysis will estimate the treatment arm effect of 6 months use of the Relvar/Breo ELLIPTA maintenance therapy with CIS when both the participant and the HCP are supplied with data from the ELLITPA sensor versus no data supplied to the participant and HCP (Arm 1 vs Arm 5).

7.1.1. Endpoint

The primary endpoint is the percentage of ELLIPTA doses taken (daily adherence) between the beginning of Month 4 and the end of Month 6 as determined by the maintenance sensor. Daily adherence is defined as the participant taking one dose of Relvar/Breo ELLIPTA, within a 24-hour period, starting at 12.00am each day of the run-in and treatment period.

7.1.2. Summary Measure

The mean difference in daily adherence between Arm 1 and Arm 5 will be estimated from an Analysis of Covariance (ANCOVA) model allowing for effects due to randomised treatment arm, baseline adherence, duration of run-in (visits), country, gender, and age (years).

7.1.3. Population of Interest

The primary efficacy analysis will be based on the Intent-To-Treat population.

7.1.4. Strategy for Intercurrent (Post-Randomisation) Events

The following steps in Table 3 will be applied sequentially when deriving the primary endpoint. See Section 10.5.3.1 ELLIPTA Device Sensor Assessments for full details of the missing data imputations process.

Table 3

Intercurrent Event Estimation Rules (to be applied sequentially)	Intercurrent Event (IE)	Strategy with Rationale	Estimation Method following IE
1	**None (completed as randomised)** **Without discontinuation of CIS feedback or ELLIPTA maintenance sensor** • Premature discontinuation from rescue/salbutamol MDI sensor • Change of dose of ELLIPTA **Discontinuation of CIS feedback, but not ELLIPTA maintenance sensor** • Premature discontinuation from App and/or HCP interaction	**Treatment policy:** Directly assessed using observed adherence data while ELLIPTA maintenance sensor is in use, regardless of whether the CIS feedback is discontinued.	Data are available; no imputation required
2	**Discontinuation of ELLIPTA maintenance sensor only**	**Treatment policy:** Without the ELLIPTA maintenance sensor, no CIS feedback is possible, assume • participants continue to take ELLIPTA as	Jump to Reference (J2R) Imputation

Intercurrent Event Estimation Rules (to be applied sequentially)	Intercurrent Event (IE)	Strategy with Rationale	Estimation Method following IE
		they would have without the CIS intervention • adherence will be like that in the control (no CIS feedback) group	
3	**Discontinuation of ELLIPTA**	**<u>Whilst on treatment:</u>** ELLIPTA adherence is only a relevant measure while ELLIPTA treatment is appropriate. It is assumed that ELLIPTA treatment is no longer appropriate if the participant discontinues ELLIPTA but remains in the study or withdraws for a reason related to ELLIPTA.	Follow-up after ELLIPTA discontinuation is excluded, i.e. no data; adherence is weighted by proportion of months 4 to 6 for which data is included*
4	**Premature withdrawal from the study, not related to ELLIPTA discontinuation or CIS, and concurrent with discontinuation of the ELLIPTA maintenance sensor**	**<u>Hypothetical:</u>** When study withdrawal is unrelated to ELLIPTA or the CIS then reasonable to assume that participant would have continued with ELLIPTA and their CIS intervention, had the unrelated event not occurred	Missing at Random (MAR) Imputation

* Discontinuation of ELLIPTA prior to the start of month 4 will lead to a participant being excluded from the primary analysis

7.1.4.1. Events prior to premature discontinuation of the ELLIPTA maintenance sensor

The treatment policy estimand is directly assessed using the observed adherence data while the ELLIPTA maintenance sensor is in use, regardless of whether the CIS feedback is discontinued.

Any missing intermittent adherence data will be imputed as non-adherent i.e. the participant will be assumed to have not taken their treatment within the 24-hour time period/window, where there is no evidence of device or technical/transmission failure.

Missing intermittent adherence data due to a medical device incident such as device failure, technical failure of the sensor, or data transmission failure will be assumed to be missing at random (MAR). For each participant, the percentage adherence measure will be calculated from the proportion of the number of days a participant is adherent divided by the number of days data provided in that month.

7.1.4.2. Events following premature discontinuation of the ELLIPTA maintenance sensor

It is assumed that participants would continue to take ELLIPTA as they would have without the CIS intervention (J2R imputation) following discontinuation of the ELLIPTA maintenance sensor.

It is assumed that ELLIPTA treatment is no longer appropriate if the participant discontinues ELLIPTA but remains in the study or withdraws for a reason related to ELLIPTA. The ELLIPTA adherence endpoint is no longer considered relevant and subsequent follow-up is excluded from the analysis, with participants weighted in the analysis by the proportion of months 4 to 6 for which data is included.

It is assumed that participants would continue to take ELLIPTA as they would have with their allocated CIS intervention (MAR imputation) following concurrent discontinuation of the ELLIPTA maintenance sensor and withdrawal unrelated to ELLIPTA or CIS.

See Section 10.5.3.1 ELLIPTA Device Sensor Assessments for further derivation details.

7.1.5. Statistical Analyses / Methods

Details of the planned displays will be provided in Section 10.8, Appendix 8: List of Data Displays and will be based on GSK data standards and statistical principles.

Unless otherwise specified, endpoints /variables defined in Section 7.1.1, Endpoint will be summarised using descriptive statistics, graphically presented (where appropriate) and listed.

7.1.5.1. Statistical Methodology Specification

Endpoint / Variables
The primary endpoint is the percentage of ELLIPTA doses taken (daily adherence) between the beginning of Month 4 and the end of Month 6 as determined by the maintenance sensor. Daily adherence is defined as the participant taking one dose of Relvar/Breo ELLIPTA within a 24 hour period, starting at 12.00am each day of treatment period.
Multiple Imputation Specification

Imputation will be carried out using monthly adherence rates for months 1 to 6. 1000 draws will be used. For each draw, four intermediate imputation datasets will be created to allow for the handling of fully unobserved months (using set A imputations) and partially unobserved months (using set B imputations).
 	
• Set A where the partially observed month is directly estimated under the MAR assumption as the proportion of the number of days a participant is adherent divided by the number of days data provided in that month.
 	
  • J2R imputations
 	
  • MAR imputations
 	
• Set B where the partially observed month is set to missing.
 	
  • J2R imputations
 	
  • MAR imputations
 	
The timing of the intercurrent events of discontinuation of the ELLIPTA maintenance sensor, discontinuation of ELLIPTA and withdrawal from study will be used to identify the proportion of each month to be assigned as observed data, J2R imputed data, MAR imputed data, or no data. The strategy for handling intercurrent events is described in Section 7.1.4 Strategy for Intercurrent (Post-Randomisation) Events.
 	
Within each imputation draw, for each month, the observed and any imputed data will be combined to provide a percentage adherence value. The values for months 4 to 6 will be combined to create the value for the primary analysis and the weight to be assigned to each participant.
 	
Multiple imputation using Rubin's rules will be used to estimate the treatment effect and associated standard error, by performing the ANCOVA analysis described below on the primary endpoint within each dataset.
 	
The multiple imputation will be implemented using the methods described in Carpenter, 2013, using the macros available from https://missingdata.lshtm.ac.uk/2017/04/06/gsk-five-macros/..

Model Specification
The analysis will be performed on the percentage adherence between Months 4 and 6 using an Analysis of Covariance (ANCOVA) model allowing for effects due to randomised treatment arm, baseline adherence, duration of run-in (visits), country, gender, and age (years). Baseline adherence will be the percentage ELLIPTA doses taken (daily adherence) during the last 28 days of the run-in period prior to randomisation. Randomised treatment arm, duration of run-in (visits), country, and gender will be included as categorical covariates; baseline adherence and age (years) will be included as continuous covariates.

Each participant will be weighted by the proportion of months 4 to 6 for which data is included in the percentage adherence endpoint (both observed and imputed data are accounted for in the weighting).

Data from all 5 treatment arms will be included in the model and used to estimate the difference between Arm 1 and Arm 5 for the primary objective.

Model Checking & Diagnostics

Normality assumptions underlying the ANCOVA model used for analysis will be examined in a limited number of imputed datasets by obtaining a normal probability plot of the residuals and a plot of the residuals versus the fitted values (i.e. checking the normality assumption and constant variance assumption of the model respectively) to gain confidence that the model assumptions are reasonable.

If there are any departures from the distributional assumptions, alternative models may be explored using appropriately transformed data.

Interactions with treatment will be explored for other model covariates and tests for interactions will be at the 2-sided 10% significance level. Any significant interactions that are found will be thoroughly investigated and where necessary, extra outputs will be produced.

Model Results Presentation

Summary statistics (n, mean, standard deviation, median, minimum, maximum) of the primary endpoint will be provided, based on the observed percentages.

The adjusted means for each treatment and the estimated treatment difference for the primary treatment comparison of Arm 1 versus Arm 5 will be presented together with a 95% confidence interval for the difference and corresponding Wald test statistic and p-value from the multiple imputation procedure.

Subgroup Analyses

For the analysis by baseline total ACT score (<=15, 16-19), the model will additionally include the baseline ACT total score category and randomised treatment arm-by-baseline ACT total score category interaction as covariates.

For the analysis by age group (18-35, 36-48, 49-58, >58 years), the model will additionally include age group and randomised treatment arm-by-age group interaction as covariates.

The adjusted means for each treatment and the estimated treatment difference for the treatment comparisons of Arm 2 versus Arm 5, Arm 3 versus Arm 5 and Arm 4 versus Arm 5 will be presented together with the 95% confidence interval for the differences and corresponding p-values from the multiple imputation procedure.

Sensitivity Analysis

- A sensitivity analysis will be performed estimating the treatment effect by utilizing a generalized linear model (GLM) and not running the multiple imputation process. The model will follow a binomial distribution with the logit link function. The covariates included in the GLM will be the same as those included in the primary analysis. Model assumptions will be checked using standardised residual plots, and model results presentation will be the same as described for the primary analysis. Missing data will be assumed to be MAR.

7.2. Secondary Efficacy Analyses

The secondary analysis of daily adherence during month 4 to 6 will estimate the treatment effect of 6 months use of the ELLIPTA maintenance therapy with CIS for the following aspects of the CIS:

- Maintenance data only supplied to participants versus no data supplied to the participant (Arm 2 vs Arm 5)
- Rescue and Maintenance data supplied to participant and HCP versus no data supplied to the participant and HCP (Arm 3 vs Arm 5)
- Rescue and Maintenance data only supplied to participant versus no data supplied to the participant (Arm 4 vs Arm 5)

In addition, secondary analyses of daily adherence during month 1 to 6 and month 1 to 3 will estimate the treatment effect of 6 months use of the ELLIPTA maintenance therapy with CIS when the participant and the HCP are supplied with data from maintenance and rescue sensors versus no data supplied to participant and HCP (Arm 1, 2, 3, 4 vs Arm 5).

Secondary analysis to evaluate the effect of 6 months use of the CIS on a participant's rescue medication usage will be conducted, as well as an evaluation of the effect of 6 months use with the CIS on participant's asthma control.

7.2.1. ELLIPTA Adherence Measure Endpoints

The adherence secondary endpoints are:

- The percentage of ELLIPTA doses taken (daily adherence) between the beginning of Month 4 and the end of Month 6 as determined by the maintenance sensor. Daily adherence is defined as the participant taking one dose of Relvar/Breo ELLIPTA, within a 24-hour period, starting at 12.00am each day of the run-in and treatment period.
- The percentage of ELLIPTA doses taken (daily adherence) between the beginning of Month 1 and the end of Month 6 as determined by the maintenance sensor. Daily adherence is defined as the participant taking one dose of Relvar/Breo ELLIPTA, within a 24-hour period, starting at 12.00am each day of the run-in and treatment period.
- The percentage of ELLIPTA doses taken (daily adherence) between the beginning of Month 1 and the end of Month 3 as determined by the maintenance sensor. Daily adherence is defined as the participant taking one dose of Relvar/Breo ELLIPTA, within a 24-hour period, starting at 12.00am each day of the run-in and treatment period.

7.2.1.1. Summary Measure

The mean difference in daily adherence between the comparisons of interest will be estimated from an Analysis of Covariance (ANCOVA) model allowing for effects due to randomised treatment, baseline adherence, duration of run-in (visits), country, gender, and age (years).

7.2.1.2. Population of Interest

The secondary efficacy analyses will be based on the Intent-To-Treat population.

7.2.1.3. Strategy for Intercurrent (Post-Randomisation) Events

The steps detailed in Section 7.1.4 Strategy for Intercurrent (Post-Randomisation) Events will be applied sequentially when deriving the secondary adherence endpoints.

7.2.1.3.1. *Events prior to premature discontinuation of the ELLIPTA maintenance sensor*

The treatment policy estimand is directly assessed using the observed adherence data while the ELLIPTA maintenance sensor is in use, regardless of whether the CIS feedback is discontinued.

Any missing intermittent adherence data will be imputed as non-adherent i.e. the participant will be assumed to have not taken their treatment within the 24-hour time period/window, where there is no evidence of device or technical/transmission failure.

Missing intermittent adherence data due to a medical device incident such as device failure, technical failure of the sensor, or data transmission failure will be assumed to be missing at random (MAR). For each participant, the percentage adherence measure will be calculated from the proportion of the number of days a participant is adherent divided by the number of days data provided in that month.

7.2.1.3.2. *Events following premature discontinuation of the ELLIPTA maintenance sensor*

It is assumed that participants would continue to take ELLIPTA as they would have without the CIS intervention (J2R imputation) following discontinuation of the ELLIPTA maintenance sensor.

It is assumed that ELLIPTA treatment is no longer appropriate if the participant discontinues ELLIPTA but remains in the study or withdraws for a reason related to ELLIPTA. The ELLIPTA adherence endpoint is no longer considered relevant and subsequent follow-up is excluded from the analysis, with participants weighted in the analysis by the proportion of months 4 to 6 for which data is included.

It is assumed that participants would continue to take ELLIPTA as they would have with their allocated CIS intervention (MAR imputation) following concurrent discontinuation of the ELLIPTA maintenance sensor and withdrawal unrelated to ELLIPTA or CIS.

See Section 10.5.3.1 ELLIPTA Device Sensor Assessments further derivation details.

7.2.1.4. Statistical Analyses / Methods

Details of the planned displays will be provided in Section 10.8, Appendix 8: List of Data Displays and will be based on GSK data standards and statistical principles.

Unless otherwise specified, endpoints /variables defined in Section 7.1.1, Endpoint will be summarised using descriptive statistics, graphically presented (where appropriate) and listed.

7.2.1.5. Statistical Analyses / Methodology Specification

7.2.1.5.1. *The percentage of ELLIPTA doses taken (daily adherence) between the beginning of Month 4 and the end of Month 6*

Endpoint / Variables
Percentage of ELLIPTA doses taken (daily adherence) between the beginning of Month 4 and the end of Month 6 as determined by the maintenance sensor for the following treatment arm comparisons: • Arm 2 vs Arm 5 • Arm 3 vs Arm 5 • Arm 4 vs Arm 5 Daily adherence is defined as the participant taking one dose of Relvar/Breo ELLIPTA within a 24-hour period, starting at 12.00am each day of treatment period.
Multiple Imputation Specification

Imputation will be carried out using monthly adherence rates for months 1 to 6. 1000 draws will be used. For each draw, four intermediate imputation datasets will be created to allow for the handling of fully unobserved months (using set A imputations) and partially unobserved months (using set B imputations).
• Set A where the partially observed month is directly estimated under the MAR assumption as the proportion of the number of days a participant is adherent divided by the number of days data provided in that month.
  • J2R imputations
  • MAR imputations
• Set B where the partially observed month is set to missing.
  • J2R imputations
  • MAR imputations
The timing of the intercurrent events of discontinuation of the ELLIPTA maintenance sensor, discontinuation of ELLIPTA and withdrawal from study will be used to identify the proportion of each month to be assigned as observed data, J2R imputed data, MAR imputed data, or no data. The strategy for handling intercurrent events is described in Section 7.1.4 Strategy for Intercurrent (Post-Randomisation) Events.
Within each imputation draw, for each month, the observed and any imputed data will be combined to provide a percentage adherence value. The values for months 4 to 6 will be combined to create the value for the secondary analysis and the weight to be assigned to each participant.
Multiple imputation using Rubin's rules will be used to estimate the treatment effect and associated standard error, by performing the ANCOVA analysis described below on the secondary endpoint within each dataset.
The multiple imputation will be implemented using the methods described in Carpenter, 2013, using the macros available from https://missingdata.lshtm.ac.uk/2017/04/06/gsk-five-macros/..

Model Specification

The analysis will be performed on the percentage adherence between Months 4 and 6 using an Analysis of Covariance (ANCOVA) model allowing for effects due to randomised treatment arm, baseline adherence, duration of run-in (visits), country, gender, and age (years).

Baseline adherence will be the percentage ELLIPTA doses taken (daily adherence) during the last 28 days of the run-in period prior to randomisation. Randomised treatment, duration of run-in (visits), country, and gender will be included as categorical covariates; baseline adherence and age (years) will be included as continuous covariates.

Each participant will be weighted by the proportion of months 4 to 6 for which data is included in the percentage adherence endpoint (both observed and imputed data are accounted for in the weighting).

Data from all 5 treatment arms will be included in the model, and used to estimate the difference between:

- Arm 2 and Arm 5
- Arm 3 and Arm 5
- Arm 4 and Arm 5

Model Checking & Diagnostics

Normality assumptions underlying the ANCOVA model used for analysis will be examined in a limited number of imputed datasets by obtaining a normal probability plot of the residuals and a plot of the residuals versus the fitted values (i.e. checking the normality assumption and constant variance assumption of the model respectively) to gain confidence that the model assumptions are reasonable.

If there are any departures from the distributional assumptions, alternative models may be explored using appropriately transformed data.

Interactions with treatment will be explored for other model covariates and tests for interactions will be at the 2-sided 10% significance level. Any significant interactions that are found will be thoroughly investigated and where necessary, extra outputs will be produced.

Model Results Presentation

Summary statistics (mean, standard deviation, median, minimum, maximum) of the primary endpoint will be provided, based on the observed percentages.

The adjusted means for each treatment and the estimated treatment difference for the treatment comparisons of Arm 2 versus Arm 5, Arm 3 versus Arm 5 and Arm 4 versus Arm 5 will be presented together with the 95% confidence interval for the differences and corresponding p-values from the multiple imputation procedure.

Subgroup Analyses

For the analysis by baseline total ACT score (<=15, 16-19), the model will additionally include the baseline ACT total score category and randomised treatment arm-by-baseline ACT total score category interaction as covariates.

For the analysis by age group (18-35, 36-48, 49-58, >58 years), the model will additionally include age group and randomised treatment arm-by-age group interaction as covariates.

The adjusted means for each treatment and the estimated treatment difference for the treatment comparisons of Arm 2 versus Arm 5, Arm 3 versus Arm 5 and Arm 4 versus Arm 5 will be presented together with the 95% confidence interval for the differences and corresponding p-values from the multiple imputation procedure.

Sensitivity Analysis

- A sensitivity analysis will be performed estimating the treatment effect by utilizing a generalized linear model (GLM) and not running the multiple imputation process. The model will follow a binomial distribution with the logit link function. The covariates included in the GLM will be the same as those included in the primary analysis. Model assumptions will be checked using standardised residual plots, and model results presentation will be the same as described for the primary analysis. Missing data will be assumed to be MAR.

7.2.1.5.2. *The percentage of ELLIPTA doses taken (daily adherence) between the beginning of Month 1 and the end of Month 6*

Endpoint / Variables

Percentage of ELLIPTA doses taken (daily adherence) between the beginning of Month 1 and the end of Month 6 as determined by the maintenance sensor for the following treatment arm comparisons:

- Arm 1 vs Arm 5
- Arm 2 vs Arm 5
- Arm 3 vs Arm 5
- Arm 4 vs Arm 5

Daily adherence is defined as the participant taking one dose of Relvar/Breo ELLIPTA within a 24-hour period, starting at 12.00am each day of treatment period.

Multiple Imputation Specification

Imputation will be carried out using monthly adherence rates for months 1 to 6. 1000 draws will be used. For each draw, four intermediate imputation datasets will be created to allow for the handling of fully unobserved months (using set A imputations) and partially unobserved months (using set B imputations).

- Set A where the partially observed month is directly estimated under the MAR assumption as the proportion of the number of days a participant is adherent divided by the number of days data provided in that month.
    - J2R imputations
    - MAR imputations
- Set B where the partially observed month is set to missing.
    - J2R imputations
    - MAR imputations

The timing of the intercurrent events of discontinuation of the ELLIPTA maintenance sensor, discontinuation of ELLIPTA and withdrawal from study will be used to identify the proportion of each month to be assigned as observed data, J2R imputed data, MAR imputed data, or no data. The strategy for handling intercurrent

events is described in Section 7.1.4 Strategy for Intercurrent (Post-Randomisation) Events.

Within each imputation draw, for each month, the observed and any imputed data will be combined to provide a percentage adherence value. The values for months 4 to 6 will be combined to create the value for the primary analysis and the weight to be assigned to each participant.

Multiple imputation using Rubin's rules will be used to estimate the treatment effect and associated standard error, by performing the ANCOVA analysis described below on the primary endpoint within each dataset.

The multiple imputation will be implemented using the methods described in Carpenter, 2013, using the macros available from https://missingdata.lshtm.ac.uk/2017/04/06/gsk-five-macros/.

Model Specification

The analysis will be performed on the percentage adherence between Months 1 and 6 using an Analysis of Covariance (ANCOVA) model allowing for effects due to randomised treatment arm, baseline adherence, duration of run-in (visits), country, gender, and age (years).

Baseline adherence will be the percentage ELLIPTA doses taken (daily adherence) during the last 28 days of the run-in period prior to randomisation. Randomised treatment, duration of run-in (visits), country, and gender will be included as categorical covariates; baseline adherence and age (years) will be included as continuous covariates.

Each participant will be weighted by the proportion of months 1 to 6 for which data is included in the percentage adherence endpoint (both observed and imputed data are accounted for in the weighting).

Data from all 5 treatment arms will be included in the model, and used to estimate the difference between:

- Arm 1 and Arm 5
- Arm 2 and Arm 5
- Arm 3 and Arm 5
- Arm 4 and Arm 5

Model Checking & Diagnostics

Normality assumptions underlying the ANCOVA model used for analysis will be examined in a limited number of imputed datasets by obtaining a normal probability plot of the residuals and a plot of the residuals versus the fitted values (i.e. checking the normality assumption and constant variance assumption of the model respectively) to gain confidence that the model assumptions are reasonable.

If there are any departures from the distributional assumptions, alternative models may be explored using appropriately transformed data.

Interactions with treatment will be explored for other model covariates and tests for interactions will be at the 2-sided 10% significance level. Any significant interactions that are found will be thoroughly investigated and where necessary, extra outputs will be produced.

Model Results Presentation

Summary statistics (n, mean, standard deviation, median, minimum, maximum) of the primary endpoint will be provided, based on the observed percentages.

The adjusted means for each treatment arm and the estimated treatment arm difference for the treatment comparisons of Arm 1 versus Arm 5, Arm 2 versus Arm 5, Arm 3 versus Arm 5 and Arm 4 versus Arm 5 will be presented together with the 95% confidence interval for the differences and corresponding p-values from the multiple imputation procedure.

Sensitivity Analysis

- A sensitivity analysis will be performed estimating the treatment effect by utilizing a generalized linear model (GLM) and not running the multiple imputation process. The model will follow a binomial distribution with the logit link function. The covariates included in the GLM will be the same as those included in the primary analysis. Model assumptions will be checked by using standardised residual plots, and the model results presentation will be the same as described for the primary analysis. Missing data will be assumed to be MAR.

7.2.1.5.3. *The percentage of ELLIPTA doses taken (daily adherence) between the beginning of Month 1 and the end of Month 3*

Endpoint / Variables

Percentage of ELLIPTA doses taken (daily adherence) between the beginning of Month 1 and the end of Month 3 as determined by the maintenance sensor for the following treatment arm comparisons:

- Arm 1 vs Arm 5
- Arm 2 vs Arm 5
- Arm 3 vs Arm 5
- Arm 4 vs Arm 5

Daily adherence is defined as the participant taking one dose of Relvar/Breo ELLIPTA within a 24-hour period, starting at 12.00am each day of treatment period.

Multiple Imputation Specification

Imputation will be carried out using monthly adherence rates for months 1 to 6. 1000 draws will be used. For each draw, four intermediate imputation datasets will be created to allow for the handling of fully unobserved months (using set A imputations) and partially unobserved months (using set B imputations).

- Set A where the partially observed month is directly estimated under the MAR assumption as the proportion of the number of days a participant is adherent divided by the number of days data provided in that month.
    - J2R imputations
    - MAR imputations
- Set B where the partially observed month is set to missing.
    - J2R imputations
    - MAR imputations

The timing of the intercurrent events of discontinuation of the ELLIPTA maintenance sensor, discontinuation of ELLIPTA and withdrawal from study will be used to identify the proportion of each month to be assigned as observed data, J2R imputed data, MAR imputed data, or no data. The strategy for handling intercurrent

events is described in Section 7.1.4 Strategy for Intercurrent (Post-Randomisation) Events.

Within each imputation draw, for each month, the observed and any imputed data will be combined to provide a percentage adherence value. The values for months 4 to 6 will be combined to create the value for the primary analysis and the weight to be assigned to each participant.

Multiple imputation using Rubin's rules will be used to estimate the treatment effect and associated standard error, by performing the ANCOVA analysis described below on the primary endpoint within each dataset.

The multiple imputation will be implemented using the methods described in Carpenter, 2013, using the macros available from https://missingdata.lshtm.ac.uk/2017/04/06/gsk-five-macros/.

Model Specification

The analysis will be performed on the percentage adherence between Months 1 and 3 using an Analysis of Covariance (ANCOVA) model allowing for effects due to randomised treatment arm, baseline adherence, duration of run-in (visits), country, gender, and age (years).

Baseline adherence will be the percentage ELLIPTA doses taken (daily adherence) during the last 28 days of the run-in period prior to randomisation. Randomised treatment arm, duration of run-in (visits), country, and gender will be included as categorical covariates; baseline adherence and age (years) will be included as continuous covariates.

Each participant will be weighted by the proportion of months 1 to 3 for which data is included in the percentage adherence endpoint (both observed and imputed data are accounted for in the weighting).

Data from all 5 treatment arms will be included in the model, and used to estimate the difference between:

- Arm 1 and Arm 5
- Arm 2 and Arm 5
- Arm 3 and Arm 5
- Arm 4 and Arm 5

Model Checking & Diagnostics

Normality assumptions underlying the ANCOVA model used for analysis will be examined in a limited number of imputed datasets by obtaining a normal probability plot of the residuals and a plot of the residuals versus the fitted values (i.e. checking the normality assumption and constant variance assumption of the model respectively) to gain confidence that the model assumptions are reasonable.

If there are any departures from the distributional assumptions, alternative models may be explored using appropriately transformed data.

Interactions with treatment will be explored for other model covariates and tests for interactions will be at the 2-sided 10% significance level. Any significant interactions that are found will be thoroughly investigated and where necessary, extra outputs will be produced.

Model Results Presentation

Summary statistics (n, mean, standard deviation, median, minimum, maximum) of the primary endpoint will be provided, based on the observed percentages.

The adjusted means for each treatment and the estimated treatment difference for the treatment comparisons of Arm 1 versus Arm 5, Arm 2 versus Arm 5, Arm 3 versus Arm 5 and Arm 4 versus Arm 5 will be presented together with the 95% confidence interval for the differences and corresponding p-values from the multiple imputation procedure.
Sensitivity Analysis
• A sensitivity analysis will be performed estimating the treatment effect by utilizing a generalized linear model (GLM) and not running the multiple imputation process. The model will follow a binomial distribution with the logit link function. The covariates included in the GLM will be the same as those included in the primary analysis. Model assumptions will be checked by using standardised residual plots, and the model results presentation will be the same as described for the primary analysis. Missing data will be assumed to be MAR.

7.2.2. MDI Rescue Medication Use Endpoints

- Percentage of rescue free days measured between the beginning of month 4 and the end of month 6 as determined by the MDI rescue sensor records of date, time, and number of inhaler actuations.
- Total rescue use measured between the beginning of month 4 and the end of month 6 as determined by the MDI rescue sensor records of date, time, and number of inhaler actuations.

7.2.2.1. Summary Measure

The rescue medicine summary measures are:

- The mean difference in percentage of rescue free days between the treatment arms will be estimated from an Analysis of Covariance (ANCOVA) model allowing for effects due to randomised treatment, baseline rescue-free, duration of run-in (visits), country, gender, and age (years).
- The mean total rescue use for the treatment arms will be summarised using summary statistics (n, mean, SD, median, min, max) for each treatment arm for each Month separately, and totalled Month 4 – 6.

7.2.2.2. Population of Interest

These secondary efficacy analyses will be based on the Intent-To-Treat population.

7.2.2.3. Strategy for Intercurrent (Post-Randomisation) Events

It is assumed that salbutamol MDI rescue medication use does not permanently discontinue for asthmatic participants, regardless of whether they are used in addition to maintenance therapy or not.

The following steps in Table 4 will be applied sequentially when deriving the rescue free days endpoint. See Section 10.5.3.2 MDI Device Sensor Assessments for full details of the missing data imputations process.

Table 4

Intercurrent Event Estimation Rules (to be applied sequentially)	Intercurrent Event (IE)	Strategy with Rationale	Estimation Method following IE
1	**None (completed as randomised)** **Without discontinuation of CIS feedback or MDI eSensor** • Premature discontinuation from ELLIPTA eSensor • Premature discontinuation from ELLIPTA • Change of dose of ELLIPTA **Discontinuation of CIS feedback, but not MDI eSensor** • Premature discontinuation from App and/or HCP interaction	**Treatment policy:** Directly assessed using observed rescue data while MDI sensor is in use, regardless of whether the CIS feedback is discontinued.	Data are available; no imputation required

Intercurrent Event Estimation Rules (to be applied sequentially)	Intercurrent Event (IE)	Strategy with Rationale	Estimation Method following IE
2	**Discontinuation from MDI eSensor but not the study**	**Hypothetical:** Without the sensor, no CIS feedback is possible and so it is assumed that rescue use will be like that in the control group for those randomised to Arm 3 and 4. Since Arms 1 and 2 never have CIS feedback, without the sensor it is assumed that rescue use will continue as before.	MAR imputation (Arms 1&2) J2R imputation (Arms 3&4)
3	**Premature withdrawal from the study**	**Hypothetical:** Without the sensor, no CIS feedback is possible and so it is assumed that rescue use will be like that in the control group for those randomised to Arm 3 and 4. Since Arms 1 and 2 never have CIS feedback, without the sensor it is assumed that rescue use will continue as before.	MAR imputation (Arms 1&2) J2R imputation (Arms 3&4)
4	**Premature withdrawal from the study not related to CIS, and concurrent with discontinuation of the MDI sensor**	**Hypothetical:** When study withdrawal is unrelated to the CIS then it is reasonable to assume that the participant would have continued with MDI and the Sensor, had the unrelated event not occurred.	Missing at Random (MAR) Imputation

7.2.2.3.1. *Events following premature discontinuation of the MDI sensor*

It is assumed that participants would continue to take MDI as they would have without the CIS intervention (jump to reference imputation) following discontinuation of the MDI sensor if receiving treatment Arms 3 and 4, otherwise continue to take MDI as they would have with their allocated CIS interventions (MAR).

It is assumed that participants would continue to take MDI as they would have with their allocated CIS interventions (MAR) following concurrent discontinuation of MDI sensor and withdrawal from study if unrelated to CIS.

7.2.2.4. Statistical Analyses / Methods

Details of the planned displays will be provided in Section 10.8, Appendix 8: List of Data Displays and will be based on GSK data standards and statistical principles.

Unless otherwise specified, endpoints /variables defined in Section 7.2.2 MDI Rescue Medication Use Endpoints, Section 7.1.1 Endpoint will be summarised using descriptive statistics, graphically presented (where appropriate) and listed.

7.2.2.5. Statistical Analyses / Methodology Specification

Endpoint / Variables
The percentage of rescue free days measured between the beginning of month 4 and the end of month 6 as determined by the MDI rescue sensor for the following treatment arm comparisons
Multiple Imputation Specification

Imputation will be carried out using monthly rescue free rates for months 1 to 6. 1000 draws will be used. For each draw, four intermediate imputation datasets will be created to allow for the handling of fully unobserved months (using set A imputations) and partially unobserved months (using set B imputations).
• Set A where the partially observed month is directly estimated under the MAR assumption as the proportion of the number of days a participant is adherent divided by the number of days data provided in that month.
  • J2R imputations
  • MAR imputations
• Set B where the partially observed month is set to missing.
  • J2R imputations
  • MAR imputations
The timing of the intercurrent events of discontinuation of the MDI sensor and withdrawal from study will be used to identify the proportion of each month to be assigned as observed data, J2R imputed data or MAR imputed data. The strategy for handling intercurrent events is described in Section 7.2.2.3 Strategy for Intercurrent (Post-Randomisation) Events.

Within each imputation draw, for each month, the observed and any imputed data will be combined to provide a percentage rescue free day value. The values for months 4 to 6 will be combined to create the value for the secondary analysis and the weight to be assigned to each participant.

Multiple imputation using Rubin's rules will be used to estimate the treatment effect and associated standard error, by performing the ANCOVA analysis described below on the secondary endpoint within each dataset.

The multiple imputation will be implemented using the methods described in Carpenter, 2013, using the macros available from https://missingdata.lshtm.ac.uk/2017/04/06/gsk-five-macros/.

Model Specification

The analysis will be performed on the percentage of rescue free days between Months 4 and 6 using an Analysis of Covariance (ANCOVA) model allowing for effects due to randomised treatment arm, baseline rescue free days percentage, duration of run-in (visits), country, gender, and age (years).

Baseline rescue free days will be the percentage rescue free days during the last 28 days of the run-in period prior to randomisation. Randomised treatment, duration of run-in (visits), country, and gender will be included as categorical covariates; baseline rescue free days percentage and age (years) will be included as continuous covariates.

Each participant will be weighted by the proportion of months 4 to 6 for which data is included in the percentage rescue free days endpoint (both observed and imputed data are accounted for in the weighting).

Data from all 5 treatment arms will be included in the model, and used to estimate the difference between:

- Arm 1 and Arm 5
- Arm 2 and Arm 5
- Arm 3 and Arm 5
- Arm 4 and Arm 5

Model Checking & Diagnostics

Normality assumptions underlying the ANCOVA model used for analysis will be examined in a limited number of imputed datasets by obtaining a normal probability plot of the residuals and a plot of the residuals versus the fitted values (i.e. checking the normality assumption and constant variance assumption of the model respectively) to gain confidence that the model assumptions are reasonable.

If there are any departures from the distributional assumptions, alternative models may be explored using appropriately transformed data.

Interactions with treatment will be explored for other model covariates and tests for interactions will be at the 2-sided 10% significance level. Any significant interactions that are found will be thoroughly investigated and where necessary, extra outputs will be produced.

Model Results Presentation

Summary statistics (mean, standard deviation, median, minimum, maximum) of the primary endpoint will be provided, based on the observed percentages.

The adjusted means for each treatment and the estimated treatment difference for the treatment comparisons of Arm 1 versus Arm 5, Arm 2 versus Arm 5, Arm 3 versus Arm 5 and Arm 4 versus Arm 5 will be presented together with the 95% confidence interval for the differences and corresponding p-values from

the multiple imputation procedure.

Endpoint / Variables
Total rescue use measured between the beginning of month 4 and the end of month 6 as determined by the MDI rescue sensor
Summary
The endpoint will be summarised using descriptive statistics (n, mean, SD, median, min, max) for each treatment arm. To explore the effect of 6 months use of the CIS on a participant's rescue medicine usage, the following displays will be presented, • Summary statistics (n, mean, SD, median, min, max) of Total rescue use measured between the beginning of month 4 and the end of month 6 as determined by the MDI rescue sensor • Total rescue use will be summarized by each individual month (Month 1 – Month 6) and then displayed as a total between month 4 – 6.

7.2.3. Asthma Control Endpoints

The asthma control secondary endpoints are:

- Change from baseline (Randomisation) in ACT total score at Month 6 (Visit 10), measured at baseline (Visit 2, 3 or 4) and Month 6 (Visit 10)
- Percentage of patients becoming controlled as defined as an Asthma Control Test score ≥20 at Month 6 (Visit 10)
- Percentage of patients with an increase from baseline ≥ 3 in ACT total score at Month 6 (Visit 10)
- Percentage of patients who have either an ACT total score of ≥ 20 and/or an increase from baseline of ≥ 3 in ACT total score at Month 6 (Visit 10)

7.2.3.1. Summary Measure

The asthma control summary measures are:

- The difference in LS means of the change from baseline in ACT total score at month 6, along with a 95% confidence interval and p-value for the difference, analysed using an MMRM model.
- An adjusted odds ratio on percentage of patients becoming controlled as defined as an ACT total score ≥ 20 at Month 6, along with a 95% confidence interval and p-value for the percentage, analysed using a logistic regression model.
- An adjusted odds ratio on percentage of patients with an increase from baseline ≥ 3 in ACT total score at Month 6, along with a 95% confidence interval and p-value for the percentage, analysed using a logistic regression model.
- An adjusted odds ratio on percentage of patients who have either an ACT total score of ≥ 20 and/or an increase from baseline of ≥ 3 in ACT total score at Month 6, along with a 95% confidence interval and p-value for the percentage, analysed using a logistic regression model.

7.2.3.2. Population of Interest

The asthma control analyses will be based on the Intent-to-Treat population.

7.2.3.3. Strategy for Intercurrent (Post-Randomisation) Events

Intercurrent events for the asthma control outcomes were identified as:

- Early discontinuation of ELLIPTA
- Early discontinuation of the APP
- Early discontinuation of ELLIPTA sensor
- Early discontinuation of MDI sensor
- Early withdrawal from study
- Use of MDI rescue medication
- Use of prohibited medications
- Change of dose of ELLIPTA

The "Treatment policy" strategy will be applied to handle the "Early discontinuation of ELLIPTA sensor", "Early discontinuation of the APP", "Early discontinuation of MDI sensor", "Use of MDI rescue medication", "Use of prohibited medications" and "change of dose of ELLIPTA" for all asthma control exploratory endpoints. The strategy implies direct use of ACT data irrespective of the occurrence of these intercurrent events.

7.2.3.3.1. Change from baseline (Randomisation) in ACT total score at Month 6 (Visit 10)

The "treatment policy" strategy will be applied to all handle all the intercurrent events listed in Section 7.2.3.3 Strategy for Intercurrent (Post-Randomisation) Events. In other words, all observed data before early discontinuation of the study respective of treatment arm status (on-treatment) or CIS discontinuation status will be included in the analysis. No missing data will be imputed, missing data will be considered MAR. Therefore, the primary treatment arm effect to be estimated will be the mean change from baseline in ACT total score at month 6 and remaining on study.

7.2.3.3.2. Percentage of patients becoming controlled as defined as an Asthma Control Test score ≥20 at Month 6 (Visit 10)

The "Composite" strategy will be used for the "Early discontinuation of ELLIPTA" and 'Early discontinuation of study" intercurrent events. In the occurrence of these intercurrent events, the effect to be estimated will be the effect on the outcome of achieving an ACT total score of ≥ 20 at month 6 and remaining on ELLIPTA (off-ELLIPTA treatment data is not collected). Participants who do not meet the improvement threshold, have missing values for their ACT total score at month 6, or prematurely discontinue using ELLIPTA or the study will be classified as non-responders in all planned analyses for this endpoint.

The "Treatment policy" strategy will be used to handle discontinuation of the APP/sensor. This means direct assessment of ACT total score at month 6 against the responder criteria, irrespective of CIS discontinuation status.

7.2.3.3.3. Percentage of patients with an increase from baseline ≥ 3 in ACT total score at Month 6 (Visit 10)

The "Composite" strategy will be used for the "Early discontinuation of ELLIPTA" and 'Early discontinuation of study" intercurrent events. In the occurrence of these intercurrent events, the effect to be estimated will be the effect on the outcome of achieving an increase from baseline of ≥ 3 in ACT total score at month 6 and remaining on ELLIPTA (off-ELLIPTA treatment data is not collected). Participants who do not meet the improvement threshold, have missing values for their ACT total score at month 6, or discontinue using ELLIPTA or the study will be classified as non-responders in all planned analyses for this endpoint.

The "Treatment policy" strategy will be used to handle discontinuation of the APP/sensor. This means direct assessment of ACT total score at month 6 against the responder criteria, irrespective of CIS discontinuation status.

7.2.3.3.4. Percentage of patients who have either an ACT total score of ≥ 20 and/or an increase from baseline of ≥ 3 in ACT total score at Month 6 (Visit 10)

The "Composite" strategy will be used for the "Early discontinuation of ELLIPTA" and 'Early discontinuation of study" intercurrent events. In the occurrence of these intercurrent events, the effect to be estimated will be the effect on the composite outcome of achieving an ACT total score of ≥ 20 and/or an increase from baseline of ≥ 3 in ACT total score at month 6 and remaining on ELLIPTA (off-ELLIPTA treatment data is not collected). Participants who do not meet the improvement threshold, have missing values for their ACT total score at month 6, or discontinue using ELLIPTA during or the study will be classified as non-responders in all planned analyses for this endpoint.

The "Treatment policy" strategy will be used to handle discontinuation of the APP/sensor. This means direct assessment of ACT total score at month 6 against the responder criteria, irrespective of CIS discontinuation status.

7.2.3.4. Statistical Analyses / Methodology Specification

Details of the planned displays will be provided in 10.8 Appendix 8: List of Data Displays and will be based on GSK data standards and statistical principles.

Unless otherwise specified, endpoints/variables defined in Section 7.2.3.1 Summary Measure will be summarised using descriptive statistics, graphically presented (where appropriate) and listed.

7.2.3.4.1. Change from baseline in ACT total score at month 6

Endpoint / Variables
Change from baseline in ACT total score Month 6 (visit 10)
Model Specification
This endpoint will be analysed using a mixed model repeated measures (MMRM) model utilising the REML estimation approach and the default unstructured covariance matrix structure. Whilst missing data are not implicitly imputed in this analysis, there is an underlying assumption that the data are MAR. All non-missing data for a participant will be used within the analysis and, via modelling of the within-participant correlation structure, the derived treatment differences will be adjusted to take into account missing data. Terms fitted in the model will include: • Dependent Variable: change from baseline in ACT total score • Covariates: o Fixed categorical: randomised treatment arm, visit (month 1 and 6), gender and country. o Fixed continuous: baseline ACT total score and age o Interaction terms: randomised treatment arm-by-visit, baseline ACT total score-by-visit o Random effect: participant
Model Checking & Diagnostics
• If this model fails to converge, alternative correlation structures may be considered • Appropriate graphs will be reviewed as part of the model checking process to ensure that distributional assumptions hold. These will include a normal probability plot of the residuals and a plot of the residuals versus the fitted values (checking the normality assumption and constant variance assumption of the model, respectively). • Interactions with treatment will be explored for other model covariates and tests for interactions will be at the 2-sided 10% significance level. Any significant interactions that are found will be thoroughly investigated and where necessary, extra outputs will be produced.
Model Results Presentation
Adjusted mean change from baseline values for each treatment arm will be presented with their associated standard errors. The estimated treatment difference along with corresponding standard error, 95% confidence interval (CI) and p-value will be presented for the treatment comparisons at month 6 (Visit 10).

7.2.3.4.2. ACT total score ≥20 at month 6

Endpoint / Variables
Percentage of patients becoming controlled as defined as an Asthma Control Test score ≥20 at Month 6 (Visit 10)
Model Specification
This endpoint will be analysed using a logistic regression model. Only the month 6 (visit 10) data will be included in the model. Month 1 (visit 5) data will not be implemented since by this timepoint participants may not have reverted to steady medicating behaviour. Will not be included since participants may not have reverted to normally medicating practise within one month's use of the CIS/ Terms in the model: • Dependent variable: ACT total score ≥20 responder/non-responder at month 6 (binary score)

- Covariates:
  - Categorical: randomised treatment arm, gender and country
  - Continuous: baseline ACT total score and age.

Patients who have a missing ACT total score at month 6 (visit 10) (i.e. no ACT data on-treatment) will be classified as non-responders at that visit.

Computation of confidence intervals for the odds ratios is based in the individual Wald tests.

Model Checking & Diagnostics

If the likelihood maximisation algorithm fails to converge due to complete or quasi-complete separation of the data then Firth's penalized likelihood (Firth, 1993) will be implemented by use of the FIRTH option on the MODEL statement in PROC LOGISTIC.

The fit of the logistic regression model will be assessed by examining the ROC curve and other diagnostic plots

Model Results Presentation

The number and percentage of participants with a response within each randomised treatment arm will be presented by visit, together with the adjusted odds ratio comparing CIS Arms 1, 2, 3, 4 with Arm 5, associated 95% CIs and p-values.

7.2.3.4.3. Increase from Baseline of ≥ 3 in ACT total score at month 6

Endpoint

Percentage of patients with an increase from baseline ≥ 3 in ACT total score at Month 6 (Visit 10)

Model Specification

This endpoint will be analysed using a logistic regression model. Only the month 6 (visit 10) data will be included in the model. Month 1 (visit 5) data will not be implemented since by this timepoint participants may not have reverted to steady medicating behaviour.

Terms in the model:

- Dependent variable: Increase from baseline of ≥ 3 in ACT total score at month 6 responder/non-responder (binary score)
- Covariates:
  - Categorical: randomised treatment arm, gender and country
  - Continuous: baseline ACT total score and age.

Patients who have a missing ACT total score at month 6 (visit 10) (i.e. no ACT data on-treatment) will be classified as non-responders at that visit.

Computation of confidence intervals for the odds rations is based in the individual Wald tests.

Model Checking & Diagnostics

If the likelihood maximisation algorithm fails to converge due to complete or quasi-complete separation of the data then Firth's penalized likelihood (Firth, 1993) will be implemented by use of the FIRTH option on the MODEL statement in PROC LOGISTIC.

The fit of the logistic regression model will be assessed by examining the ROC curve and other diagnostic plots

Model Results Presentation
The number and percentage of participants with a response within each randomised treatment arm will be presented by visit, together with the adjusted odds ratio comparing CIS Arms 1, 2, 3, 4 with Arm 5, associated 95% CIs and p-values.

7.2.3.4.4. ACT total score of ≥ 20 and/or an increase from baseline of ≥ 3 in ACT total score at Month 6 (Visit 10).

Endpoint
Percentage of patients who have either an ACT total score of ≥ 20 and/or an increase from baseline of ≥ 3 in ACT total score at Month 6 (Visit 10).
Model Specification

This endpoint will be analysed using a logistic regression model. Only the month 6 (visit 10) data will be included in the model. Month 1 (visit 5) data will not be implemented since by this timepoint participants may not have reverted to steady medicating behaviour.
 	
Terms in the model:
• Dependent variable: Composite ACT total score ≥ 20 and/or increase from baseline of ≥ 3 in ACT total score at month 6 responder/non-responder (binary score)
• Covariates:
  ○ Categorical: randomised treatment arm, gender and country
  ○ Continuous: baseline ACT total score and age.
 	
Patients who have a missing ACT total score at month 6 (visit 10) (i.e. no ACT data on-treatment) will be classified as non-responders at that visit.
 	
Computation of confidence intervals for the odds rations is based in the individual Wald tests.

Model Checking & Diagnostics
If the likelihood maximisation algorithm fails to converge due to complete or quasi-complete separation of the data then Firth's penalized likelihood (Firth, 1993) will be implemented by use of the FIRTH option on the MODEL statement in PROC LOGISTIC. The fit of the logistic regression model will be assessed by examining the ROC curve and other diagnostic plots.
Model Results Presentation
The number and percentage of participants with a response within each randomised treatment arm will be presented by visit, together with the adjusted odds ratio comparing CIS Arms 1, 2, 3, 4 with Arm 5, associated 95% CIs and p-values.

7.3. Exploratory and Other Analyses

The impact of the HCP having access to sensor data on percentage of ELLIPTA doses taken (daily adherence) between the beginning of month 4 and the end of month 6 as determined by the maintenance sensor will be assessed by the following comparisons:

- Arm 1 vs Arm 2

- Arm 3 vs Arm 4

The impact of having Rescue Medication data being available on the percentage of ELLIPTA doses taken (daily adherence) between the beginning of month 4 and the end of month 6 as determined by the maintenance sensor will be assessed by the following comparisons:

- Arm 1 vs Arm 3
- Arm 2 vs Arm 4

These estimates will be generated from the multiple imputation analysis used to assess the primary endpoint.

The effect of 6 months use with CIS on health care utilisation will be explored as well as its effect on the following patient reported outcomes (PROs); asthma system utility index (ASUI). St. Georges Respiratory Questionnaire (SGRQ), Patient Activation Measure (PAM), Medication Adherence Report Scale for Asthma (MARS-A), Beliefs in Medicine Questionnaire (BMQ).

The reliability and usability of the CIS, as well as the impact of the adherence on Fractional exhaled nitric oxide (FeNO) and Peak Expiratory Flow (PEF) will be assessed.

7.3.1. Exploratory ELLIPTA Adherence Measure Analyses

7.3.1.1. Endpoint

The percentage of ELLIPTA doses taken (daily adherence) between the beginning of Month 4 and the end of Month 6 as determined by the maintenance sensor. Daily adherence is defined as the participant taking one dose of Relvar/Breo ELLIPTA, within a 24-hour period, starting at 12.00am each day of the run-in and treatment period

7.3.1.2. Summary Measure

The mean difference in daily adherence between the comparisons of interest will be estimated from an Analysis of Covariance (ANCOVA) model allowing for effects due to randomised treatment, baseline adherence, duration of run-in (visits), country, gender, and age (years).

7.3.1.3. Population of Interest

The exploratory adherence analyses will be based on the Intent-To-Treat population.

7.3.1.4. Strategy for Intercurrent (Post-Randomisation) Events

The steps detailed in Section 7.1.4 Strategy for Intercurrent (Post-Randomisation) Events will be applied sequentially when deriving the secondary adherence endpoints. See Section 10.5.3.1 ELLIPTA Device Sensor Assessments for further derivation details.

7.3.1.4.1. Events prior to premature discontinuation of the ELLIPTA maintenance sensor

The treatment policy estimand is directly assessed using the observed adherence data while the ELLIPTA maintenance sensor is in use, regardless of whether the CIS feedback is discontinued.

Any missing intermittent adherence data will be imputed as non-adherent i.e. the participant will be assumed to have not taken their treatment within the 24-hour time period/window, where there is no evidence of device or technical/transmission failure.

Missing intermittent adherence data due to a medical device incident such as device failure, technical failure of the sensor, or data transmission failure will be assumed to be missing at random (MAR). For each participant, the percentage adherence measure will be calculated from the proportion of the number of days a participant is adherent divided by the number of days data provided in that month.

7.3.1.4.2. Events following premature discontinuation of the ELLIPTA maintenance sensor

It is assumed that participants would continue to take ELLIPTA as they would have without the CIS intervention (J2R imputation) following discontinuation of the ELLIPTA maintenance sensor.

It is assumed that ELLIPTA treatment is no longer appropriate if the participant discontinues ELLIPTA but remains in the study or withdraws for a reason related to ELLIPTA. The ELLIPTA adherence endpoint is no longer considered relevant and subsequent follow-up is excluded from the analysis, with participants weighted in the analysis by the proportion of months 4 to 6 for which data is included.

It is assumed that participants would continue to take ELLIPTA as they would have with their allocated CIS intervention (MAR imputation) following concurrent discontinuation of the ELLIPTA maintenance sensor and withdrawal unrelated to ELLIPTA or CIS.

7.3.1.5. Statistical Analyses / Methods

Details of the planned displays will be provided in Section 10.8, Appendix 8: List of Data Displays and will be based on GSK data standards and statistical principles.

Unless otherwise specified, endpoints /variables defined in Section 7.3.1.1 Endpoint will be summarised using descriptive statistics, graphically presented (where appropriate) and listed.

7.3.1.6. Statistical Analyses / Methodology Specification

7.3.1.6.1. *The percentage of ELLIPTA doses taken (daily adherence) between the beginning of Month 4 and the end of Month 6*

Endpoint / Variables

The percentage of ELLIPTA doses taken (daily adherence) between the beginning of Month 4 and the end of Month 6 as determined by the maintenance sensor for the following treatment arm comparisons:
 	
• HCP having access to sensor data
  • Arm 1 vs Arm 2
  • Arm 3 vs Arm 4
• Rescue medication data being available
  • Arm 1 vs Arm 3
  • Arm 2 vs Arm 4
 	
Daily adherence is defined as the participant taking one dose of Relvar/Breo ELLIPTA within a 24-hour period, starting at 12.00am each day of treatment period.

Multiple Imputation Specification

Imputation will be carried out using monthly adherence rates for months 1 to 6. 1000 draws will be used. For each draw, four intermediate imputation datasets will be created to allow for the handling of fully unobserved months (using set A imputations) and partially unobserved months (using set B imputations).
 	
• Set A where the partially observed month is directly estimated under the MAR assumption as the proportion of the number of days a participant is adherent divided by the number of days data provided in that month.
  • J2R imputations
  • MAR imputations
• Set B where the partially observed month is set to missing.
  • J2R imputations
  • MAR imputations
 	
The timing of the intercurrent events of discontinuation of the ELLIPTA maintenance sensor, discontinuation of ELLIPTA and withdrawal from study will be used to identify the proportion of each month to be assigned as observed data, J2R imputed data, MAR imputed data, or no data. The strategy for handling intercurrent events is described in Section 7.1.4 Strategy for Intercurrent (Post-Randomisation) Events.
 	
Within each imputation draw, for each month, the observed and any imputed data will be combined to provide a percentage adherence value. The values for months 1 to 6 will be combined to create the value

for the secondary analysis and the weight to be assigned to each participant.

Multiple imputation using Rubin's rules will be used to estimate the treatment effect and associated standard error, by performing the ANCOVA analysis described below on the secondary endpoint within each dataset.

The multiple imputation will be implemented using the methods described in Carpenter, 2013, using the macros available from https://missingdata.lshtm.ac.uk/2017/04/06/gsk-five-macros/.

Model Specification

The analysis will be performed on the percentage adherence between Months 4 and 6 using an Analysis of Covariance (ANCOVA) model allowing for effects due to randomised treatment arm, baseline adherence, duration of run-in (visits), country, gender, and age (years).

Baseline adherence will be the percentage ELLIPTA doses taken (daily adherence) during the last 28 days of the run-in period prior to randomisation. Randomised treatment, duration of run-in (visits), country, and gender will be included as categorical covariates; baseline adherence and age (years) will be included as continuous covariates.

Each participant will be weighted by the proportion of months 4 to 6 for which data is included in the percentage adherence endpoint (both observed and imputed data are accounted for in the weighting).

Data from five individual CIS treatment arms will be included in the model, and used to estimate the difference between:

- Arm 1 and Arm 2
- Arm 3 and Arm 4
- Arm 1 and Arm 3
- Arm 2 and Arm 4

Model Checking & Diagnostics

Normality assumptions underlying the ANCOVA model used for analysis will be examined in a limited number of imputed datasets by obtaining a normal probability plot of the residuals and a plot of the residuals versus the fitted values (i.e. checking the normality assumption and constant variance assumption of the model respectively) to gain confidence that the model assumptions are reasonable.

If there are any departures from the distributional assumptions, alternative models may be explored using appropriately transformed data.

Interactions with treatment will be explored for other model covariates and tests for interactions will be at the 2-sided 10% significance level. Any significant interactions that are found will be thoroughly investigated and where necessary, extra outputs will be produced.

Model Results Presentation

Summary statistics (mean, standard deviation, median, minimum, maximum) of the primary endpoint will be provided, based on the observed percentages.

The adjusted means for each treatment arm and the estimated treatment arm difference for the treatment arm comparisons of interest will be presented together with the 95% confidence interval for the differences

and corresponding p-values from the multiple imputation procedure.

7.3.2. Exploratory Health Care Utilization Analyses

7.3.2.1. Endpoints

- Number of outpatient visits relating to asthma
- Number of primary care visits relating to study HCP dashboard review (for relevant study arms)
- Number of and duration of hospitalisations, and ER visits due to asthma
- Annualised rate of severe exacerbations
- Number of unscheduled visits to primary care related to Asthma

7.3.2.2. Population of Interest

The exploratory analyses will be based on the Intent-To-Treat population.

Endpoint
Healthcare Utilisation - • Number of outpatient visits relating to asthma • Number of and duration of hospitalisations, and ER visits due to asthma • Number of unscheduled visits to primary care related to Asthma
Summary

• The number and percentage of participants by frequency of unscheduled healthcare resource contacts (0, 1, 2, 3, 4, >4) will be summarized by contact type and treatment arm to characterize the level of healthcare associated with an asthma exacerbation. The frequency counts for each participant will be the total sum of contacts (or days in hospital) by type.
• The following types of healthcare contact for an exacerbation are recorded in the eCRF:
  • Number of telephone calls
  • Number of home/day visits
  • Number of home/night visits
  • Number of physician office/practice visits
  • Number of urgent care/outpatient visits
  • Number of emergency room visits
  • Number of inpatient hospitalisation days
  • Number of contacts due to an exacerbation

Endpoint
Healthcare Utilisation - • Number of primary care visits relating to study HCP dashboard review (for relevant study arms)
Summary
• The number and percentage of participants by frequency of unscheduled healthcare resource contacts (0, 1, 2, 3, 4, >4) will be summarized by contact type and treatment arm to characterize the level of healthcare associated with an asthma exacerbation. The frequency counts for each participant will be the total sum of contacts (or days in hospital) by type.

Endpoint
Healthcare Utilisation - • Annual rate of severe asthma exacerbations
Summary
• The number and percentage of participants reporting an asthma exacerbation (on-treatment and post-treatment) will be summarised by treatment arm. • The number and percentage of participants with each number of exacerbations (0, 1, 2, 3, 4, >4) and the total number of exacerbations per treatment arm will also be summarised. • For the purposes of summarizing these data, the annualized rate of severe asthma exacerbations for the ITT population will be calculated for each participant as o the number of exacerbations / time on Relvar/Breo (in years) from randomisation. • The summaries will include on-treatment exacerbations, from randomisation date to min(stop date of exposure + 1 day, date of study discontinuation). • The number and percentage of participants with an exacerbation that led to withdrawal of study, hospitalization, systemic/oral corticosteroids/antibiotics/medication being taken, or emergency room visit will be summarised by treatment arm. • A listing of severe exacerbations will be provided.

7.3.3. Exploratory Patient Reported Outcomes (PROs) Analyses

7.3.3.1. Endpoints

- Percentage of patients meeting a responder threshold of ≥ 0.09 points improvement from baseline (randomisation) for the ASUI total score at month 6
- Change from baseline (randomisation) in ASUI total score at month 6
- Percentage of patients meeting a responder threshold of ≥ 4 points improvement (decrease) from baseline (randomisation) for the SGRQ total score at month 6
- Change from baseline (randomisation) in SRGQ total score at month 6
- Change from baseline (screening) in PAM total score at month 6
- Change from baseline (screening) in MARS-A total score at month 6
- Change from baseline (screening) in BMQ – General Benefit score at month 6
- Change from baseline (screening) in BMQ – General Harm score at month 6
- Change from baseline (screening) in BMQ – General Overuse score at month 6
- Change from baseline (screening) in BMQ – Specific Necessity score at month 6
- Change from baseline (screening) in BMQ – Specific Concern score at month 6

7.3.3.2. Summary Measure

The PRO summary measures to determine treatment arm effect are:

- An adjusted odds ratio on percentage of patients meeting a responder threshold of ≥ 0.09 points improvement from baseline for the ASUI total score at Month 6, along with a 95% confidence interval and p-value for the percentage, analysed using a logistic regression model.
- The difference in LS means of the change from baseline in ASUI total score at month 6, along with a 95% confidence interval and p-value for the difference, analysed using an MMRM model.
- An adjusted odds ratio on percentage of patients meeting a responder threshold of ≥ 4 points improvement (decrease) from baseline for the SGRQ total score at Month 6, along with a 95% confidence interval and p-value for the percentage, analysed using a logistic regression model.
- The difference in LS means of the change from baseline in SGRQ total score at month 6, along with a 95% confidence interval and p-value for the difference, analysed using an MMRM model.
- Mean change from baseline (screening) in PAM-13 total score at month 6.
- Mean change from baseline (screening) in MARS-A total score at month 6
- Mean change from baseline (screening) in BMQ – General Benefit score at month 6
- Mean change from baseline (screening) in BMQ – General Harm score at month 6
- Mean change from baseline (screening) in BMQ – General Overuse score at month 6
- Mean change from baseline (screening) in BMQ – Specific Necessity score at month 6
- Mean change from baseline (screening) in BMQ – Specific Concern score at month 6

7.3.3.3. Population of Interest

The PRO exploratory summaries and analysis will be based on the "Intent-to-Treat" population.

7.3.3.4. Strategy for Intercurrent (Post-Randomisation) Events

Intercurrent events for the ASUI and SGRQ outcomes were identified as:

- Early discontinuation of ELLIPTA
- Early discontinuation of the APP
- Early discontinuation of ELLIPTA sensor
- Early discontinuation of MDI sensor
- Early withdrawal from study
- Use of MDI rescue medication
- Use of prohibited medications
- Change of dose of ELLIPTA

The "Treatment policy" strategy will be applied to handle the "Early discontinuation of ELLIPTA sensor", "Early discontinuation of the APP", "Early discontinuation of MDI sensor", "Use of MDI rescue medication", "Use of prohibited medications" and "change of dose of ELLIPTA" for all PRO exploratory endpoints. The strategy implies direct use of PRO data irrespective of the occurrence of these intercurrent events.

7.3.3.4.1. *Percentage of patients meeting a responder threshold of ≥ 0.09 points improvement from baseline (randomisation) for the ASUI total score at Month 6 (Visit 10)*

The "Composite" strategy will be used for the "Early discontinuation of ELLIPTA" and 'Early discontinuation of study" intercurrent events. In the occurrence of these intercurrent events, the effect to be estimated will be the effect on the outcome of achieving an improvement from baseline of ≥ 0.09 in ASUI total score at month 6 and remaining on ELLIPTA (off-ELLIPTA treatment data is not collected). Participants who do not meet the improvement threshold, have missing values for their ASUI total score at month 6, or discontinue using ELLIPTA or the study will be classified as non-responders in all planned analyses for this endpoint.

The "Treatment policy" strategy will be used to handle discontinuation of the APP/sensor. This means direct assessment of ASUI total score at month 6 against the responder criteria, irrespective of CIS discontinuation status.

7.3.3.4.2. *Change from baseline (randomisation) in ASUI total score at month 6 (Visit 10)*

The "treatment policy" strategy will be applied to all handle all the intercurrent events listed in 7.4.3.4. In other words, all observed data before early discontinuation of the study respective of treatment status (on-treatment) or CIS discontinuation status will be included in the analysis. No missing data will be imputed, missing data will be considered MAR. Therefore, the primary treatment effect to be estimated will be the mean change from baseline in ASUI total score at month 6 and remaining on the study.

7.3.3.4.3. *Percentage of patients meeting a responder threshold of ≥ 4 points improvement (decrease) from baseline (randomisation) for the SGRQ total score at month 6 (Visit 10)*

The "Composite" strategy will be used for the "Early discontinuation of ELLIPTA" and 'Early discontinuation of study" intercurrent events. In the occurrence of these intercurrent events, the effect to be estimated will be the effect on the outcome of achieving an improvement from baseline of ≥ 4 in SGRQ total score at month 6 and remaining on ELLIPTA (off-ELLIPTA treatment data is not collected). Participants who do not meet the improvement threshold, have missing values for their SGRQ total score at month 6, or discontinue using ELLIPTA or the study will be classified as non-responders in all planned analyses for this endpoint.

The "Treatment policy" strategy will be used to handle discontinuation of the APP/sensor. This means direct assessment of SGRQ total score at month 6 against the responder criteria, irrespective of CIS discontinuation status.

7.3.3.4.4. *Change from baseline (Randomisation) in SGRQ total score at Month 6 (Visit 10)*

The "treatment policy" strategy will be applied to all handle all the intercurrent events listed in 7.4.3.4. In other words, all observed data before early discontinuation of the study respective of treatment status (on-treatment) or CIS discontinuation status will be included in the analysis. No missing data will be imputed, missing data will be considered MAR. Therefore, the primary treatment effect to be estimated will be the mean change from baseline in SGRQ total score at month 6 and remaining on the study.

7.3.3.4.5. *Change from baseline (Screening) in PAM-13, MARS-A, and BMQ total score at Month 6 (Visit 10)*

The mean change from baseline in PAM-13, MARS-A and all scales for the BMQ questionnaires at month 6 will be summarised using descriptive statistics (n, mean, SD, median, min, max) for each treatment arm. The "treatment policy" strategy will be applied to all handle all the intercurrent events listed in 7.4.3.4. In other words, all observed data before early discontinuation of the study respective of treatment status (on-treatment) or CIS discontinuation status will be included in the analysis. No missing data will be imputed, missing data will be considered MAR. Therefore, the primary treatment arm effect to be estimated will be the mean change from baseline in total score at month 6 and remaining on the study.

No formal statistical analyses will be performed for these endpoints.

7.3.3.5. Statistical Analyses / Methodology Specification

Details of the planned displays will be provided in Section 10.8, Appendix 8: List of Data Displays and will be based on GSK data standards and statistical principles.

Unless otherwise specified, endpoints / variables defined in Section 7.3.3.1, Endpoints, will be summarised using descriptive statistics, graphically presented (where appropriate) and listed.

7.3.3.5.1. Increase from Baseline of ≥ *0.09 in ASUI total score at Month 6 (Visit 10)*

Endpoint / Variables
Percentage of patients meeting a responder threshold of ≥ 0.09 points improvement from baseline for the ASUI total score at Month 6 (Visit 10)
Model Specification

This endpoint will be analysed using a logistic regression model. Only the month 6 (visit 10) data will be included in the model. Month 1 (visit 5) data will not be implemented since by this timepoint participants may not have reverted to steady medicating behaviour
 	
Terms in the model:
• Dependent variable: ASUI responder/non-responder score (binary score)
• Covariates:
  ○ Categorical: randomised treatment arm, gender and country
  ○ Continuous: baseline ASUI total score and age.

Patients who have a missing ASUI total score at month 6 (visit 10) (i.e. no ASUI data on-treatment) will be classified as non-responders at that visit. This rule will apply to all above analyses. Computation of confidence intervals for the odds ratios is based in the individual Wald tests.
Model Checking & Diagnostics
If the likelihood maximisation algorithm fails to converge due to complete or quasi-complete separation of the data then Firth's penalized likelihood (Firth, 1993) will be implemented by use of the FIRTH option on the MODEL statement in PROC LOGISTIC. The fit off the logistic regression model will be assessed by examining the ROC curve and other diagnostic plots.
Model Results Presentation
The number and percentage of participants with a response within each randomised treatment arm will be presented by visit, together with the adjusted odds ratio comparing CIS Arms 1, 2, 3, 4 with Arm 5, associated 95% CIs and p-values.

7.3.3.5.2. Change from baseline (Randomisation) in ASUI total score at Month 6 (Visit 10)

Endpoint / Variables
Mean change from baseline in ASUI total score at Month 6 (Visit 10)
Model Specification

This endpoint will be analysed using a mixed model repeated measures (MMRM) model utilising the REML estimation approach and the default unstructured covariance matrix structure. Whilst missing data are not implicitly imputed in this analysis, there is an underlying assumption that the data are MAR. All non-missing data for a participant will be used within the analysis and, via modelling of the within-participant correlation structure, the derived treatment differences will be adjusted to take into account missing data.
 	
Terms fitted in the model will include:
• Dependent Variable: change from baseline in ASUI total score at month 6
• Covariates:
  ○ Fixed categorical: randomised treatment arm, visit (month 1 and 6), gender and country.
  ○ Fixed continuous: baseline ASUI total score and age
  ○ Interaction terms: randomised treatment arm-by-visit, baseline ASUI total score-by-visit
  ○ Random effect: participant

Model Checking & Diagnostics
• If this model fails to converge, alternative correlation structures may be considered • Appropriate graphs will be reviewed as part of the model checking process to ensure that distributional assumptions hold. These will include a normal probability plot of the residuals and a plot of the residuals versus the fitted values (checking the normality assumption and constant variance assumption of the model, respectively). • Interactions with treatment will be explored for other model covariates and tests for interactions will be at the 2-sided 10% significance level. Any significant interactions that are found will be thoroughly investigated and where necessary, extra outputs will be produced.

Model Results Presentation
Adjusted mean change from baseline values for each treatment arm will be presented with their associated standard errors. The estimated treatment difference along with corresponding standard error, 95% confidence interval (CI) and p-value will be presented for the treatment comparisons at month 6 (Visit 10).

7.3.3.5.3. Increase from Baseline of ≥ *4 in SGRQ total score at Month 6 (Visit 10)*

Endpoint / Variables
Percentage of patients meeting a responder threshold of ≥ 4 points improvement from baseline for the SGRQ total score at month 6
Model Specification

This endpoint will be analysed using a logistic regression model. Only the month 6 (visit 10) data will be included in the model. Month 1 (visit 5) data will not be implemented since by this timepoint participants may not have reverted to steady medicating behaviour
 	
Terms in the model:
• Dependent variable: SGRQ responder/non-responder score (binary score)
• Covariates:
  ○ Categorical: randomised treatment arm, gender and country
  ○ Continuous: baseline SGRQ total score and age.
 	
Patients who have a missing SGRQ total score at month 6 (visit 10) (i.e. no SGRQ data on-treatment) will be classified as non-responders at that visit. This rule will apply to all above analyses.
 	
Computation of confidence intervals for the odds ratios is based in the individual Wald tests.

Model Checking & Diagnostics
If the likelihood maximisation algorithm fails to converge due to complete or quasi-complete separation of the data then Firth's penalized likelihood (Firth, 1993) will be implemented by use of the FIRTH option on the MODEL statement in PROC LOGISTIC. The fit of the logistic regression model will be assessed by examining the ROC curve and other diagnostic plots.
Model Results Presentation
The number and percentage of participants with a response within each randomised treatment arm will be presented by visit, together with the adjusted odds ratio comparing CIS Arms 1, 2, 3, 4 with Arm 5, associated 95% CIs and p-values.

7.3.3.5.4. Change from baseline (Randomisation) in SGRQ total score at Month 6 (Visit 10)

Endpoint / Variables
Mean change from baseline in SGRQ total score at Month 6 (Visit 10)
Model Specification
This endpoint will be analysed using a mixed model repeated measures (MMRM) model utilising the REML estimation approach and the default unstructured covariance matrix structure. Whilst missing data are not implicitly imputed in this analysis, there is an underlying assumption that the data are MAR. All non-missing data for a participant will be used within the analysis and, via modelling of the within-participant correlation

structure, the derived treatment differences will be adjusted to take into account missing data.

Terms fitted in the model will include:

- Dependent Variable: change from baseline in SGRQ total score at month 6
- Covariates:
  - Fixed categorical: randomised treatment arm, visit (month 1 and 6), gender and country.
  - Fixed continuous: baseline SGRQ total score and age
  - Interaction terms: randomised treatment arm-by-visit, baseline SGRQ total score-by-visit
  - Random effect: participant

Model Checking & Diagnostics

- If this model fails to converge, alternative correlation structures may be considered
- Appropriate graphs will be reviewed as part of the model checking process to ensure that distributional assumptions hold. These will include a normal probability plot of the residuals and a plot of the residuals versus the fitted values (checking the normality assumption and constant variance assumption of the model, respectively).
- Interactions with treatment will be explored for other model covariates and tests for interactions will be at the 2-sided 10% significance level. Any significant interactions that are found will be thoroughly investigated and where necessary, extra outputs will be produced.

Model Results Presentation

Adjusted mean change from baseline values for each treatment arm will be presented with their associated standard errors. The estimated treatment difference along with corresponding standard error, 95% confidence interval (CI) and p-value will be presented for the treatment comparisons at month 6 (Visit 10).

7.3.4. Exploratory Fractionated Exhaled Nitric Oxide (FeNO) and Peak Expiratory Flow (PEF) Analyses

7.3.4.1. Endpoints

- FeNO at Screening (Visit 1), Randomisation (Visit 2,3 or 4), Month 1 (Visit 5) and Month 6 (Visit 10).
- Change from baseline (randomisation) in FeNO measured at Month 1 (Visit 5) and Month 6 (Visit 10)
- PEF at Screening (Visit 1), Randomisation (Visit 2,3 or 4), Month 1 (Visit 5) and Month 6 (Visit 10).
- Change from baseline (randomisation) in PEF measured at Month 1 (Visit 5) and Month 6 (Visit 10)

7.3.4.2. Summary Measures

The FeNO and PEF summary measures are:

- Summary statistics (n, mean, SD, median, min, max) for each treatment arm of screening (Visit 1), Randomisation (Visit 2,3 or 4), Month 1 (Visit 5) and Month 6 (Visit 10) and changes from baseline (screening) at month 1 (visit 5) and month 6 (visit 10)

7.3.4.3. Population of Interest

The FeNO and PEF exploratory summaries will be based on the Intent-to-Treat population.

7.3.4.4. Strategy for Intercurrent (Post-Randomisation) Events

Intercurrent events for the FeNO and PEF outcomes were identified as:

- Early discontinuation of ELLIPTA
- Early discontinuation of the APP
- Early discontinuation of ELLIPTA sensor
- Early discontinuation of MDI sensor
- Early withdrawal from study
- Use of MDI rescue medication
- Use of prohibited medications
- Change of dose of ELLIPTA

The "Treatment policy" strategy will be applied to handle all intercurrent event for the FeNO and PEF exploratory endpoints. The strategy implies direct use of FeNO and PEF data irrespective of the occurrence of these intercurrent events.

7.3.4.5. Statistical Analyses / Methodology Specification

Details of the planned displays will be provided in Section 10.8, Appendix 8: List of Data Displays and will be based on GSK data standards and statistical principles.

Unless otherwise specified, endpoints / variables defined in Section 7.3.4.1 Endpoints will be summarised using descriptive statistics, graphically presented (where appropriate) and listed. No formal statistical analyses will be performed for these endpoints.

Endpoint
• FeNO at Screening (Visit 1), Randomisation (Visit 2,3 or 4), Month 1 (Visit 5) and Month 6 (Visit 10) • Change from baseline (randomisation) in FeNO measured at Month 1 (Visit 5) and Month 6 (Visit 10) • PEF at Screening (Visit 1), Randomisation (Visit 2,3 or 4), Month 1 (Visit 5) and Month 6 (Visit 10) • Change from baseline (randomisation) in PEF measured at Month 1 (Visit 5) and Month 6 (Visit 10)
Summary
All endpoints to be summarised using descriptive statistics (n, mean, SD, median, min, max) for each randomised treatment arm. To explore the impact of maintenance adherence levels on FeNO and PEF, the following displays will be presented, • Summary statistics (n, mean, SD, median, min, max) of change from baseline at Month 6 (Visit 10) in FeNO per quartile of the observed primary endpoint measure, percentage of ELLIPTA doses taken (daily adherence) between the beginning of Month 4 and the end of Month 6 as determined by the

maintenance sensor

- Summary statistics (n, mean, SD, median, min, max) of change from baseline at Month 6 (Visit 10) in PEF per quartile of the observed primary endpoint measure, percentage of ELLIPTA doses taken (daily adherence) between the beginning of Month 4 and the end of Month 6 as determined by the maintenance sensor
- Note: the quartiles of a ranked adherence data values are four subsets whose boundaries are the three quartile points (25th, 50th and 75th percentiles)
- A scatter plot of the change from baseline at Month 6 (Visit 10) in FeNO by observed primary endpoint measure will be presented. This will be repeated for change from baseline at Month 6 (Visit 10) in PEF.

7.3.5. Qualitative data from exit interviews

Analysis of the qualitative data from exit interviews will be analyzed following a separate qualitative analysis plan and presented in a separate Clinical Study Report (CSR).

8. SAFETY ANALYSES

Safety analyses will be based on the ITT Population and will include all study data (run-in, on and post-treatment), unless otherwise specified.

Safety endpoints will include:

- Incidence and type of serious adverse events
- Incidence and type of adverse drug reactions (ADR)
- Incidence and type of non-serious adverse events leading to study withdrawal

8.1. Adverse Events Analyses

SAEs, AEs leading to withdrawal and non-serious ADRs will be collected.

The incidence of any given adverse event (SAE, ADR or non-serious AEs leading to withdrawal) for each treatment group is defined as the proportion of participants in that group who have experienced at least one such adverse event during the study period.

Adverse event (SAE or ADR) summaries including the summary of adverse drug reactions (ADRs), Serious (SAEs) and non-serious adverse events leading to withdrawal of study will be based on GSK Core Data Standards. The details of the planned displays are provided in Section 10.8 Appendix 8: List of Data Displays.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary. The version of MedDRA used in reporting will be noted in a footnote of the AE overview table.

For the standard on-treatment and post-treatment AE tables, the number and percentage of participants with all AEs (regardless of causality) will be summarized for each treatment group by system organ class (SOC) and preferred term (PT). The ordering of the SOCs and the PTs within the SOCs will both be in descending order of total incidence. A SOC will not be presented when the overall incidence for any AE within the particular system is zero. If the total incidence for any two or more AEs is equal, the events will be presented in alphabetical order.

8.2. Adverse Events of Special Interest

A comprehensive list of MedDRA terms based on clinical and safety review will be used to identify AEs of special interest to FF and Relvar/Breo. Changes to the MedDRA dictionary may occur between the start of the study and the time of reporting and/or emerging data from on-going studies may highlight additional AEs of special interest; therefore, the list of terms to be used for each event of interest and the specific events of interest will be based on the clinical and safety review agreements documented and in place at time of reporting and prior to unblinding the study. The details of the planned displays are provided in Section 10.8 Appendix 8: List of Data Displays.

The number and percentage of participants with on-treatment AEs of special interest will be summarized for each treatment group by special interest term, subgroup and PT. The ordering of the special interest terms, the subgroups and the PTs within them will all be in descending order of total incidence. If the total incidence for any two or more AEs is equal, the events will be presented in alphabetical order. This summary will be produced for non-serious ADRs, and repeated for serious ADRs, all ADRs and SAEs. The list of MedDRA terms used to identify AEs of special interest will be displayed.

8.3. Pregnancy

Any pregnancies reported during the study will be summarized in CSR case narratives. Any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE or SAE and included in summaries and listings of AEs/SAEs.

8.4. Other Safety Measures

All Relvar/Breo ELLIPTA inhaler device malfunction data for participants reporting at least one inhaler malfunction will be listed.

9. REFERENCES

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10. APPENDICES

10.1. Appendix 1: Schedule of Activities

10.1.1. Protocol Defined Schedule of Events

Procedures	Screen	Run-In			Treatment Period						EW	Follow -up	Notes
Visit/Contact	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**		**V11**	**Conditional Visits**: V3 & V4 are only required if a participant is not included at prior run in visit. V6, V7, V8 & V9 are only required for Treatment arms 1 & 3. Randomisation to treatment arms will occur at Visit 2,3 or 4 when randomisation criteria have been met
Month of Study	**-1**	**0**	**0**	**0**	**1**	**2**	**3**	**4**	**5**	**6**			
Day of Study	**-28**	**0**	**0**	**0**	**28**	**56**	**84**	**112**	**140**	**168**		**175**	
Visit Window (days)		**±2**	**±2**	**±2**	**±2**	**±7**	**±7**	**±7**	**±7**	**±7**		**±2**	
Conditional Visits			**X**	**X**		**X**	**X**	**X**	**X**				
SCREENING ASSESSMENTS													
Written Informed Consent	**X**												Signed by the participant and HCP/ designee prior to any other study assessments. May be completed at a separate visit to screening if required.
Participant Demography	**X**												
Medical History	**X**												
Asthma History	**X**												Including exacerbation history for previous 12 months and those involving hospitalisation
Therapy History	**X**												Maintenance therapy over previous 12 months, including number of prescriptions requested or provided
Physical Exam	**X**												Full physical including height, weight and vital signs
Inclusion/Exclusion Criteria	**X**	**X**	**X**	**X**									ACT assessment for inclusion required at run-in visits
Randomisation		**X**	**X**	**X**									Participant randomised to treatment at only one of V2, V3 or V4 once ACT criteria is met

Procedures	Screen	Run-In			Treatment Period						EW	Follow -up	Notes
Visit/Contact	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**		**V11**	**Conditional Visits**: V3 & V4 are only required if a participant is not included at prior run in visit. V6, V7, V8 & V9 are only required for Treatment arms 1 & 3. Randomisation to treatment arms will occur at Visit 2,3 or 4 when randomisation criteria have been met
Month of Study	**-1**	**0**	**0**	**0**	**1**	**2**	**3**	**4**	**5**	**6**			
Day of Study	**-28**	**0**	**0**	**0**	**28**	**56**	**84**	**112**	**140**	**168**		**175**	
Visit Window (days)		**±2**	**±2**	**±2**	**±2**	**±7**	**±7**	**±7**	**±7**	**±7**		**±2**	
Conditional Visits			**X**	**X**		**X**	**X**	**X**	**X**				
SAFETY ASSESSMENTS													
Concomitant Medication	**X**												
Urine Pregnancy Test	**X**	**X**	**X**	**X**	**X**					**X**	**X**		
SAEs	**X**	**X**											
Non-Serious Adverse Events that leads to withdrawal	**X**	**X**											Non-serious adverse events that leads to dose modification, drug discontinuation, or withdrawal from the trial. Collected from start of run in
Non-serious Adverse Drug Reactions	**X**	**X**											Collected from start of run in
Exacerbations	**X**	**X**											Severe Exacerbation are to be reviewed and recorded. Collected from start of run in
Unscheduled HCP visits		**X**											All secondary care contacts and all primary care contacts related to Asthma
QUESTIONNAIRES & Patient Reported Outcomes (PROs) (Performed in the order given here)													
ACT	**X**	**X**	**X**	**X**	**X**					**X**	**X**		ACT performed at V2, V3 or V4 to confirm inclusion for randomisation
ASUI	**X[1]**	**X[2]**	**X[2]**	**X[2]**	**X**					**X**	**X**		1. PRO's only performed at screening once a participant is included. 2. The PRO's are only performed at the run-in visit (V2, V3 or V4) if a participant is randomised to treatment
SGRQ		**X[2]**	**X[2]**	**X[2]**	**X**					**X**	**X**		
PAM	**X[1]**	**X[2]**	**X[2]**	**X[2]**	**X**					**X**	**X**		
MARS-A	**X[1]**	**X[2]**	**X[2]**	**X[2]**	**X**					**X**	**X**		
BMQ	**X[1]**	**X[2]**	**X[2]**	**X[2]**	**X**					**X**	**X**		
EXIT Questionnaire										**X**	**X**		

Procedures	Screen	Run-In			Treatment Period						EW	Follow -up	Notes
Visit/Contact	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**		**V11**	**Conditional Visits**: V3 & V4 are only required if a participant is not included at prior run in visit. V6, V7, V8 & V9 are only required for Treatment arms 1 & 3. Randomisation to treatment arms will occur at Visit 2,3 or 4 when randomisation criteria have been met
Month of Study	**-1**	**0**	**0**	**0**	**1**	**2**	**3**	**4**	**5**	**6**			
Day of Study	**-28**	**0**	**0**	**0**	**28**	**56**	**84**	**112**	**140**	**168**		**175**	
Visit Window (days)		**±2**	**±2**	**±2**	**±2**	**±7**	**±7**	**±7**	**±7**	**±7**		**±2**	
Conditional Visits			**X**	**X**		**X**	**X**	**X**	**X**				
Exit Interview										**X**	**X**	**X**	Interview is for sub-set of participants who agree to take part and can be performed at V10 or V11 for logistical reason. There is a 14 day window for vendor to schedule and conduct exit interviews.
ASSESSMENTS													
Fractional exhaled Nitric Oxide (FeNO)	**X[1]**	**X[2]**	**X[2]**	**X[2]**	**X**					**X**	**X**		1.PEF & FeNO only performed once a participant is included. 2.PEF and FeNO is only performed at the Run-in visit if a participant is randomised FeNO performed prior to PEF
Peak Expiratory Flow (PEF)	**X[1]**	**X[2]**	**X[2]**	**X[2]**	**X**					**X**	**X**		
HCP dashboard review					**X**	**X**	**X**	**X**	**X**	**X**			Participants in treatment arms 1 and 3 only. HCP will record action and outcome of review.
INVESTIGATIONAL PRODUCT													
Dispense Sensors	**X**												**Sensors must be attached and switched on in clinic.**
Dispense Relvar/Breo ELLIPTA	**X**	**X**											All participants will attend independent dispensing visits to collect their next Relvar/Breo ELLIPTA and/or salbutamol MDI as required. Patients are required to bring the sensor to the dispensing visits. The sensor will be attached to the new device and switched on at the dispensing visit.
Dispense Salbutamol MDI	**X**	**X**											
Training in CIS	**X**	**X**	**X**	**X**	**X**								Participants are trained in fitting the sensors at screening. Following randomisation, participants will be trained in CIS as relevant for their treatment arm. Retraining can be provided at V5.

Procedures	Screen	Run-In			Treatment Period						EW	Follow -up	Notes
Visit/Contact	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**		**V11**	**Conditional Visits**: V3 & V4 are only required if a participant is not included at prior run in visit. V6, V7, V8 & V9 are only required for Treatment arms 1 & 3. Randomisation to treatment arms will occur at Visit 2,3 or 4 when randomisation criteria have been met
Month of Study	**-1**	**0**	**0**	**0**	**1**	**2**	**3**	**4**	**5**	**6**			
Day of Study	**-28**	**0**	**0**	**0**	**28**	**56**	**84**	**112**	**140**	**168**		**175**	
Visit Window (days)		**±2**	**±2**	**±2**	**±2**	**±7**	**±7**	**±7**	**±7**	**±7**		**±2**	
Conditional Visits			**X**	**X**		**X**	**X**	**X**	**X**				
Training in ELLIPTA & MDI correct use	**X**				**X**								Once included a participant should be trained in correct use of ELLIPTA and MDI devices
Correct Use Assessment for ELLIPTA and MDI	**X**				**X**								Inhaler use technique will be assessed for correct use. This need only be recorded in source.
Return Sensors										**X**	**X**		
Return Relvar/Breo ELLIPTA		**X**									**X**		Patients are required to return their devices at the independent dispensing visits. Doses remaining on each returned ELLIPTA inhaler will be recorded.
Return Salbutamol MDI		**X**									**X**		Patients to return used MDI at dispensing visits.

10.2. Appendix 2: Assessment Windows

10.2.1. General

Clinic visits are scheduled to take place as specified in Appendix 1: Schedule of Activities. Individual measurements will be reported based on the visits they are assigned to in the study database without adjustment. Measurements outside visit windows will not be excluded from analyses.

If a circumstance should arise where multiple measurements have been collected and recorded against the same timepoint, then the first valid value will be used for that timepoint.

The maximum value obtained from the multiple PEF and FeNO assessments at a visit will be used in summaries and analyses. Participants who withhold a daily dose of maintenance therapy and rescue medication for 6 hours prior to the assessment will have value included in the summaries.

10.2.2. Definitions of Assessment Windows for Adherence and Rescue Medication Use Analyses

All participants have a sensor on their maintenance and rescue medication to consistently measure their adherence to maintenance and level of rescue medication use in the study. The sensors are attached to participants ELLIPTA Relvar/Breo maintenance treatment and MDI rescue medication from start of Visit 1 until Visit 10. The sensors record the time and date when the Relvar/Breo ELLIPTA cover is opened and closed and the salbutamol MDI rescue medication is actuated.

Study day 1 is defined as the day of randomisation. This could be the day of Visit 2, 3 or 4, dependent on the length of the run-in period. Study day for all other visits, assessments and events are calculated relative to this.

The following information in Table 5 displays which sensor records are summarised for each analysis time period (Analysis Month). Any sensor data recorded post the Month 6 (day 168) time period will not be included in the analysis of ELLIPTA adherence or salbutamol MDI rescue medication use of sensor data.

Table 5 Sensor Data Assessment Windows

Sensor Data Assessment Windows		
Analysis Month	**Analysis Period**	
	Beginning Timepoint	**Ending Timepoint**
Baseline	Latest of either Day -28 or day after Visit 1 (minimum of 14 days must be present to create a baseline)	Day -1 (Day prior to randomisation)
1	Day 1 (Day of randomisation)	Day 28 or discontinuation from adherence/rescue assessment if within month 1
2	Day 29	Day 56 or discontinuation from adherence/rescue assessment if within month 2
3	Day 57	Day 84 or discontinuation from adherence/rescue assessment if within month 3
4	Day 85	Day 112 or discontinuation from adherence/rescue assessment if within month 4
5	Day 113	Day 140 or discontinuation from adherence/rescue assessment if within month 5
6	Day 141	Earliest of either day of visit 10, Day 168 or discontinuation from adherence/rescue assessment if within month 6 if participant is a completer OTHERWISE Day 168 or discontinuation from adherence/rescue assessment if within month 6
Note: 'Discontinuation from adherence/rescue assessment' occurs at the earliest of premature discontinuation from use of the ELLIPTA /MDI sensor, premature discontinuation of ELLIPTA (for adherence measures), or premature withdrawal from the study.		

10.3. Appendix 3: Study Phases and Treatment Emergent Adverse Events

10.3.1. Study Phases

Since participants are on Relvar/Breo study treatment from the time they enter run-in, assessments and events will be classified according to time of occurrence relative to the randomisation date and last stop date of Relvar/Breo treatment. The randomisation and latest exposure treatment stop dates will be used to determine whether an assessment or event was during pre-screening treatment, run-in treatment, on-treatment or post-treatment. If it is not possible to tell whether an assessment or event was on-treatment or not, it will be considered as on-treatment.

10.3.1.1. Study Phases for Concomitant Medication

A medication will be summarised in every study phase (pre-screening, run-in, on- or post-treatment) in which it was taken, so a medication that was started during the run-in period and stopped during the post-randomisation treatment period will appear in both the run-in-treatment and the on-treatment summaries.

On-treatment will be considered to be from the day of randomisation to treatment arm until the last (Relvar/Breo) treatment stop date. Post-treatment will be considered to be from the day after the last treatment stop date and onward. Run-in-treatment will be considered from the screening visit until prior to randomisation to treatment arm date.If a participant's last treatment stop date is missing, this will be assumed to the date of the last recorded on-treatment visit up to Visit 10 (not including the Follow-up visit) or the return of the last Relvar/Breo container, whichever is later.

Study Phase	Definition
Pre-Screening Treatment	Date of Medication < Screening Visit Date
Run-in Treatment	(Date of Medication ≥ Screening Visit date) and (Date of Medication < Randomisation Date)
On-Treatment	(Date of Medication ≥ Randomisation Date) and (Date of Medication ≤ Last Treatment Stop Date)
Post-Treatment	Date of Medication > Last Treatment Stop Date

10.3.1.2. Study Phases for Asthma Exacerbations

Study Phase	Definition
Run-in-Treatment	(Exacerbation Onset Date ≥ Screening Visit date) and (Exacerbation Onset Date < Randomisation Date)
On-Treatment	(Exacerbation Onset Date ≥ Randomisation Date) and (Exacerbation Onset Date ≤ Last Treatment Stop Date)+1
Post-Treatment	Exacerbation Onset Date > Last Treatment Stop Date+1

10.3.1.3. Treatment Emergent Flag for Adverse Events

Study Phase	Definition
Run-in-Treatment*	(AE Start Date ≥ Screening Visit date) and (AE Start Date < Randomisation Date)
On-Treatment	(AE Start Date ≥ Randomisation Date) and (AE Start Date ≤ Last Treatment Stop Date)+1
Post-Treatment	AE Start Date > Treatment Stop Date + 1
Onset Time Since First Dose (days)*	Time Since First Dose will be derived as followed: • If Randomisation Date or AE Onset Date are missing => missing • If Randomisation Date > AE Onset Date then => AE Onset Date – Randomisation Date • If Randomisation Date ≤ AE Onset Date then => AE Onset Date – Randomisation Date + 1

*For participants who enter the run-in treatment phase but do not get randomised, use the last run-in date instead of randomisation date for the "Run-in-Treatment" phase and "Onset Time Since First Dose (days)" as the participants would not have a randomisation date.

10.4. Appendix 4: Data Display Standards & Handling Conventions

10.4.1. Reporting Process

Software	
• The currently supported versions of SAS software will be used.	
Reporting Area	
HARP Server	uksal1x00175
HARP Compound	arenv/arprod/gw685698_gw642444/mid207040/final_01
Analysis Datasets	
• Analysis datasets will be created according to CDISC standards (SDTM IG Version 3.2 & ADaM IG Version 1.0). If the Study Data Standardization Plan (SDSP) exists for a study, ensure the CDISC versions are consistent.	
Generation of RTF Files	
• Rich Text Format (RTF) files will be generated for final reporting effort.	

10.4.2. Reporting Standards

General		
• The current GSK Integrated Data Standards Library (IDSL) will be applied for reporting, unless otherwise stated (IDSL Standards Location: https://spope.gsk.com/sites/IDSLLibrary/SitePages/Home.aspx): • 4.03 to 4.23: General Principles • 5.01 to 5.08: Principles Related to Data Listings • 6.01 to 6.11: Principles Related to Summary Tables • 7.01 to 7.13: Principles Related to Graphics All data displays (Tables, Figures & Listings) will use the term "Subject" which reflects CDISC and GSK Data Display Standards terminology		
Formats		
• GSK IDSL Statistical Principles (5.03 & 6.06.3) for decimal places (DP's) will be adopted for reporting of data based on the raw data collected, unless otherwise stated. • Numeric data will be reported at the precision collected on the eCRF. • The reported precision from non eCRF sources will follow the IDSL statistical principles but may be adjusted to a clinically interpretable number of DP's. • All data will be reported according to the treatment the participant was randomised to unless otherwise stated. • Numeric data will be reported (in listings) at the precision collected in the eCRF or recorded in the raw dataset if from non-eCRF sources.		
Specification of Number of Decimal Places for Descriptive Statistics		
Label	**Description**	**Number of decimal places (dp) more than raw data**
N	Number of participants in the treatment group	Always present to 0 dp
n	Number of participants with non-missing values	Always present to 0 dp
Mean	Arithmetic Mean	1 dp

SD	Standard Deviation	2 dp
Median	Median	1 dp
Min.	Minimum	0 dp
Max.	Maximum	0 dp
Specification of Number of Decimal Places for Statistical Analysis		
Label	**Description**	**Number of decimal places (dp) more than raw data**
LS Mean	Adjusted mean for the treatment group	1 dp
LS Mean Change	Adjusted mean change from baseline for the treatment group	1 dp
Std Err	Standard error	2 dp
Difference	Treatment difference	1 dp
Odds Ratio	Treatment odds ratio	Always present to 2 dp
Relative Risk	Treatment relative risk	Always present to 2 dp
95% CI	95% Confidence interval around difference/ratio/relative risk	Same number of dp as the difference/ratio/relative risk
p-value	p-value	Always present to 3 dp (or <0.001 or >0.999)

Planned and Actual Time

- Reporting for tables, figures and formal statistical analyses:
  - Planned time relative to treatment dosing will be used in figures, summaries, statistical analyses and calculation of any derived parameters, unless otherwise stated.
- Reporting for Data Listings:
  - Planned and actual time relative to study drug dosing will be shown in listings (Refer to IDSL Statistical Principle 5.05.1).
  - Unscheduled or unplanned readings will be presented within the participant's listings.

Unscheduled Visits

- Unscheduled visits will not be included in summary tables and/or figures.
- All unscheduled visits will be included in listings.

Descriptive Summary Statistics

Continuous Data	Refer to IDSL Statistical Principle 6.06.1
Categorical Data	N, n, frequency, %

Graphical Displays

- Refer to IDSL Statistical Principals 7.01 to 7.13.
- The programs for statistical analysis tables will create SAS datasets with the unrounded numbers from the statistical models to be used in any graphs. This will include all LS means, standard errors, treatment differences or ratios and confidence intervals. This will be done for all analysis tables regardless of whether or not a figure is planned as part of statistical analysis complete (SAC).
- The programs for all graphical displays will additionally create a CSV file with the final data that is used in the graph in order to allow the graph to be redrawn for any potential future publication requirement

10.5. Appendix 5: Derived and Transformed Data

10.5.1. General

Study Day

• Calculated as the number of days from first randomisation:
  • Ref Date = Missing → Study Day = Missing
  • Ref Date < Randomisation Date → Study Day = Ref Date – Randomisation Date
  • Ref Date ≥ Randomisation Date → Study Day = Ref Date – (Randomisation Date) + 1

Change from Baseline
• Calculated as the difference between the value of the endpoint at the timepoint of interest and the baseline value as defined in Section 5.2 Baseline Definitions
Time Since First Dose

• Calculated as the number of days from first dose date of post randomisation treatment:
  • Ref Date = Missing → Time Since First Dose = Missing
  • Ref Date < Randomisation Date → Time Since First Dose = Ref Date – Randomisation Date
  • Ref Date ≥ Randomisation Date → Time Since First Dose = Ref Date – (Randomisation Date) +1

Study Treatment Start and Stop Dates
• In this study, participants who permanently discontinue Relvar/Breo study treatment, any sensors or the App may continue in the study attending the remaining visits and completing the scheduled assessments. • Data displays will state if pre-screening, run-in treatment, on-treatment, post-treatment, or both on-treatment and post-treatment data are included in the summary or analysis, when applicable. On-treatment is defined as Relvar/Breo study treatment from the date of randomisation to treatment arm. • Relvar/Breo on-treatment start date will be defined as the randomisation date and Relvar/Breo Treatment Stop Date will be defined as the latest treatment stop date (from the study treatment compliance eCRF log and treatment discontinuation eCRF page). These dates will be used to determine whether a measurement is run-in, on or post-treatment. (See Section 10.3.1 Study Phases).
Multiple Measurements at One Analysis Time Point
• PEF and FeNO assessments are performed multiple times per visit. The maximum value obtained at the visit will be included in summaries of these data.

10.5.2. Study Population

Demographics
Age

• GSK standard IDSL algorithms will be used for calculating age where birth date will be imputed as follows:
  ○ Any participant with a missing day will have this imputed as day '15'.
  ○ Any participant with a missing date and month will have this imputed as PPD

Demographics

- Birth date will be presented in listings as 'YYYY'.
- Completely missing dates of birth will remain as missing, with no imputation applied. Consequently, the age of the participant will not be calculated and will remain missing.
- Age, in whole years, will be calculated with respect to the date of screening (Visit 1).

Body Mass Index

- Calculated as Weight (kg) / [Height (m)]^2

Race

- The five high level Food and Drug Administration (FDA) race categories and designated Asian subcategories are:
  1. African American/African Heritage
  2. American Indian or Alaska Native
  3. Asian
     a. Central/South Asian Heritage
     b. Japanese/East Asian Heritage/South East Asian Heritage
     c. Mixed Asian Heritage (only required if data exists)
  4. Native Hawaiian or other Pacific Islander
  5. White
- These categories and subcategories will be summarized along with all combinations of high level categories which exist in the data. All five of the high level race categories and the two Asian subcategories must appear on the display even if there are no participants in a particular category, but combinations that do not exist in the data do not need to be represented. Combinations will be represented as the concatenation of the high level category terms, e.g., "White & Asian." The designated Asian subcategories will not be summarized as combinations with other categories.
- In addition, the standard race categories collected per IDSL will be summarized along with categories for mixed race. The categories are:
  1. African American/African Heritage
  2. American Indian or Alaska Native
  3. Asian - Central/South Asian Heritage
  4. Asian – East Asian Heritage
  5. Asian – Japanese Heritage
  6. Asian – South East Asian Heritage
  7. Asian – Mixed Race
  8. Native Hawaiian or other Pacific Islander
  9. White – Arabic/North African Heritage
  10. White – White/Caucasian/European Heritage
  11. White – Mixed Race
  12. Mixed Race
- "Asian – Mixed Race" is only used if more than one Asian category is selected, but no non-Asian races. Similarly, "White – Mixed Race" is only used if both of the White categories are selected, and no non-White races. If multiple races of different types are selected, then the overall "Mixed Race" category is used.
- A participant will only be represented in a single category. A participant who selects a combination of races will be counted as "Asian – Mixed Race," "White – Mixed Race," or "Mixed Race," but not in each of the constituent terms. Therefore, the counts will add up to the total number of participants with a response, and the percentages will add to 100%.

Treatment Compliance
• Relvar/Breo treatment compliance, calculated as a percentage, will be based on the total number of inhalations taken from the study drug inhaler(s) and the expected number of inhalations to be taken. • The expected number of inhalations will be derived as the expected number of inhalations per day (1 for OD dosing) multiplied by the number of days on study drug based on treatment start date and treatment stop date. • The total number of inhalations taken will be based on the dose counters of the inhalers, which are re-supplied during the study. If there is no dose counter information at all then the compliance will be missing, however, as long as the information from one dose counter is present, treatment compliance will be calculated. If a dose counter start count is missing then it will be assumed to be 30. All inhalers dispensed will be used, provided the dose counter stop counts are non-missing. • Treatment compliance will be calculated based on the formula: $$Compliance = \left(\frac{Total\_Number\_of\_Inhalations\_Taken}{Expected\_Inhalations \times (Stop\_Date - Start\_Date + 1)} \right) \times 100$$ where *Total_Number_of_Inhalations_Taken* is the total number of doses taken from all inhalers, *Expected_Inhalations* is equal to 1 and *Start_Date* and *Stop_Date* are the earliest treatment start date on or post randomisation and the latest treatment stop date recorded for all the inhalers used in the calculation.
Extent of Exposure and Study Duration

• Relvar/Breo on-treatment start date will be defined as the randomisation date and Relvar/Breo Treatment Stop Date will be defined as the latest treatment stop date (from the study treatment compliance eCRF log and treatment discontinuation eCRF page) for the participant. These dates will be used to determine whether a measurement is run-in, on or post-treatment. (See Section 10.3.1 Study Phases). Study conclusion is defined as completion or withdrawal, as applicable.
• Duration of exposure to study drug will be calculated as:
  ○ Duration of Exposure (days) = Treatment Stop Date – Randomisation Date + 1
• Duration of post-treatment time spent in the study will be calculated as:
  ○ Duration of Post-Treatment Study Time (days) = Study Conclusion Date – Treatment Stop Date
• Duration of total time spent in the study will be calculated as:
  ○ Duration of Study Time (days) = Study Conclusion Date – Randomisation Date + 1
• Years exposed will be calculated as:
  ○ Last treatment stop date - Randomisation Date +1 / 365.25.
  ○ Total Years Exposed will be the sum of the year exposed per treatment arm.

10.5.3. Efficacy

10.5.3.1. ELLIPTA Device Sensor Assessments

Percentage of ELLIPTA doses taken (daily adherence) Endpoint
Overview of Calculation

1. Create a dataset (Observed Data A) to calculate the monthly observed percentage of ELLIPTA adherence values (from month 1 to month 6) accounting for the following,
  a. number of days adherent to ELLIPTA (as prescribed)
  b. number of days post ELLLIPTA maintenance sensor permanent discontinuation
  c. the intermittent missing daily adherence data due to device incident.
  d. Non-adherent days (i.e. none of the above and those days with more than one dose in 24-hour period).

Percentage of ELLIPTA doses taken (daily adherence) Endpoint

2. Duplicate the observed monthly adherence values dataset (Observed Dataset A). Using the values in the duplicate dataset (Dataset B), impute the month where the sensor was permanently discontinued before the end of that month (and therefore presents a monthly adherence rate based on partly observed sensor data for that month) as missing unless the participant is a study completer.

3. Using each of the two observed datasets (Observed Dataset A and Observed Dataset B), create four separate imputed datasets (J2R-Dataset A, J2R-Dataset B, MAR-Dataset A, MAR-Dataset B) that account for the two imputation methods (J2R or MAR) that may be applied to participants' data after discontinuation of the maintenance sensor, ELLIPTA or withdrawal from study. Imputation will be carried out using observed monthly adherence rates for months 1 to 6. 1000 draws will be used. Completely missing intermediate monthly values will be assumed MAR. The multiple imputation will be implemented using the methods described in Carpenter, 2013, using the macros (Part1A, Part1B, Part2A and Part2B) available from https://missingdata.lshtm.ac.uk/2017/04/06/gsk-five-macros/ using seeds documented in the RAP for the respective endpoint.

4. The Observed Datasets (A and B), imputed datasets (J2R-Dataset A, J2R-Dataset B, MAR-Dataset A, MAR-Dataset B) and the timing of the intercurrent events; permanent discontinuation of the ELLIPTA maintenance sensor; permanent discontinuation of ELLIPTA treatment and withdrawal from study; will be used to create an analysis dataset (Dataset C) that identifies the proportion of each month to be assigned as observed data, J2R imputed data, MAR imputed data, or no data. The strategy for handling intercurrent events is described in Section 7.1.4 Strategy for Intercurrent (Post-Randomisation) Events.

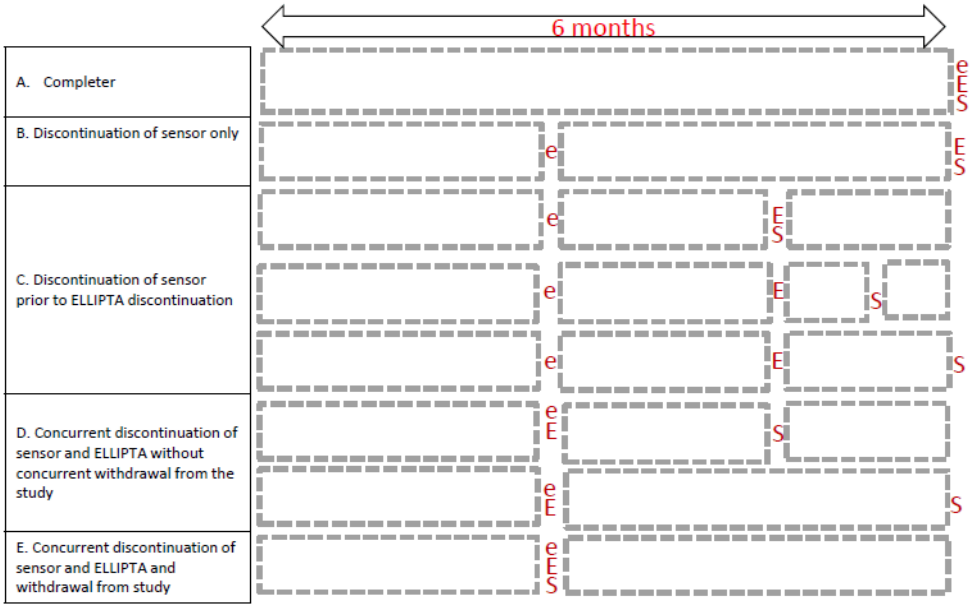
   Within each imputation draw, for each missing month, the observed and any imputed data will be combined to provide a percentage adherence value. The values for months 4 to 6, months 1-3 and months 1-6, will be combined to create the value for the respective primary and secondary endpoint analyses and the weight to be assigned to each participant.

5. Analyse using Multiple Imputation macro Part3
   a. Perform ANCOVA on the endpoint for each imputed dataset to obtain treatment effect estimate and standard error
   b. Combine estimates across imputations using Rubin's rules

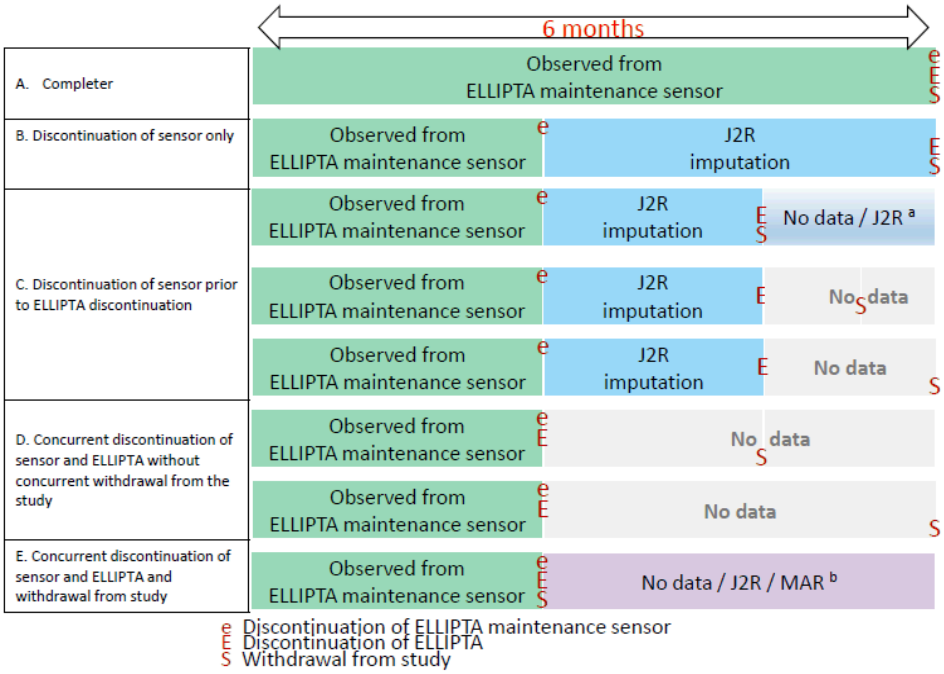
Percentage of ELLIPTA doses taken (daily adherence) Endpoint

The intercurrent events identified as part of the primary endpoint estimand and derivation are detailed in full in Section 7.2.1.3 Strategy for Intercurrent (Post-Randomisation) Events. Below are two schematics of the intercurrent event patterns and their estimation rules.

Intercurrent Event Patterns



Intercurrent Event 'Estimation Rules' 1-4



a. No data if withdrawal related to ELLIPTA; J2R imputation if withdrawal not related to ELLIPTA

b. No data if withdrawal related to ELLIPTA; J2R imputation if withdrawal related to CIS; MAR imputation if withdrawal not related to ELLIPTA or CIS

Percentage of ELLIPTA doses taken (daily adherence) Endpoint
Intercurrent Events related to Relvar/Breo or CIS
In order to implement the intercurrent event strategy detailed in Section 7.1.4 Strategy for Intercurrent (Post-Randomisation) Events, it is necessary to determine if and when the reasons for permanent discontinuations related to CIS or ELLIPTA Relvar/Breo treatment occur. The date and reason for permanently withdrawing from ELLIPTA treatment will be determined from the study treatment (Relvar/Breo ELLIPTA) discontinuation page of the eCRF. ELLIPTA discontinuation reasons classified as not related to ELLIPTA are as follows: • AE - not treatment related (determine from the AE that lead to withdrawal to treatment if study treatment related, on the AE eCRF page) • Protocol deviation - not related to study treatment • Participant reached protocol defined stopping criteria - not related to study treatment • Study closed/terminated • Lost to follow-up • Investigator discretion - not related to study treatment • Decision by participant or proxy - not related to study treatment ELLIPTA discontinuation reasons classified as related to ELLIPTA are as follows: • AE - treatment related (determine from the AE that lead to withdrawal to treatment if study treatment related, on the AE eCRF page) • Lack of efficacy • Protocol deviation - related to study treatment • Participant reached protocol defined stopping criteria (except pregnancy) - related to study treatment • Investigator discretion - related to study treatment • Decision by participant or proxy - related to study treatment The date and reason for withdrawing from the study will be determined from the study conclusion page of the eCRF. Study discontinuation reasons classified as related to CIS are as follows: • Withdrew consent – dissatisfaction with the connected inhaler system (CIS)

Percentage of ELLIPTA doses taken (daily adherence) Endpoint

Monthly Percentage of ELLIPTA doses taken (daily adherence) - Calculation

STEP 1: Creating the observed adherence dataset (Observed Dataset A)

To determine the monthly observed percentage of ELLIPTA adherence values (Observed Dataset A) the following should be applied for each month:

For Baseline Analysis Month, for each participant create a count of each of the following types of Days
D1 = Adherence recorded
D2 = Device incident
D3 = Post discontinuation of maintenance Sensor
D4 = Non-adherent (including those imputed as non-adherent)

- D5=D1 + D2 + D3 + D4, i.e. The total number of days within the Baseline Analysis Month; the total number of days between Beginning Timepoint and Ending Timepoint as defined in Table 5 in Section 10.2 Appendix 2: Assessment Windows.

For Analysis Month 1, 2, 3, 4 and 5, for each participant create a count of each of the following types of days:

D1 = Adherence recorded
D2 = Device incident
D3 = Post discontinuation of maintenance Sensor
D4 = Non-adherent (including those imputed as non-adherent)
D5 = D1 + D2 + D3 + D4, i.e. The total number of days within the Analysis Month; the total number of days between Beginning Timepoint and Ending Timepoint as defined in Table 5 in Section 10.2 Appendix 2: Assessment Windows.

For Analysis Month 6, for each participant create a count of each of the following types of days:

D1 = Adherence recorded
D2 = Device incident
D3 = Post discontinuation of maintenance sensor
D4 = Non-adherent (including those imputed as non-adherent)
D5 = D1 + D2 + D3 + D4, i.e. the total number of days within Analysis Month 6; the total number of days between Beginning Timepoint and Ending Timepoint as defined in Table 5 in Section 10.2 Appendix 2: Assessment Windows.

The following observations from the sensor and eCRF will be required to determine the above Days and the differences between missing at random due to device/sensor incident and non-adherent days.

- Device malfunction date
- Sensor malfunction date
- Permanent discontinuation of maintenance sensor
- First and last individual sensor synchronisation dates

The first and last individual sensor synchronisation dates will be provided in the sensor dataset. These dates will be used to assess whether missing observations are due to non-adherent days or data being missing at random due to device/sensor malfunction.

For each Analysis Month, the Observed adherence for that month will be calculated as follows:

Percentage of ELLIPTA doses taken (daily adherence) Endpoint

$$Monthly\ observed\ maintenance\ adherence\ (\%) = \left(\frac{D1}{D5 - D2 - D3}\right) x100$$

STEP 2: Creating the modified observed adherence dataset (Observed Dataset B)

The Observed Dataset A will be duplicated. Using the values in the duplicate dataset (Observed Dataset B) the Analysis Month where the maintenance sensor was permanently discontinued before the end of that month (and therefore presents a monthly adherence rate based on partly observed sensor data for that month) will be imputed as missing; i.e.in Dataset B, if within an Analysis Month (D3>0 and D3<D5) then set monthly value for that Analysis Month to missing. (Note: unless the participant is a completer in which case do not set the value to missing for that Analysis Month)

STEP 3: Creating the reference imputed datasets under MAR and J2R method

Using each of the two observed datasets (Observed Dataset A and Observed Dataset B) monthly values, create four separate reference imputed datasets (J2R-Dataset A, J2R-Dataset B, MAR-Dataset A, MAR-Dataset B) that account for the two imputation methods (J2R or MAR). Completely missing intermediate monthly values will be assumed MAR.

The multiple imputation will be implemented using the methods described in Carpenter, 2013 using macros, Part1A, Part1B, Part2A and Part2B (available from https://missingdata.lshtm.ac.uk/2017/04/06/gsk-five-macros/). The seeds are documented at the end of Section 10.5.3.1. and 1000 draws will be used in the relevant macros parameters.

Due to the range of the monthly adherence percentages being limited between 0 and 100, the multiple imputation process can generate percentages outside the possible range of values (< 0% or > 100%). A cap will be put in place where values imputed < 0 will be set as 0 and values imputed as > 100 set as 100.

STEP 4: Creating the Monthly Analysis values dataset

For each month within each participant create a count of each of the following durations based on intercurrent events: Let,
m1 = maintenance sensor still in use
m2 = maintenance sensor discontinued, but ELLIPTA Relvar/Breo not discontinued
m3 = ELLIPTA Relvar/Breo discontinued (includes days post withdrawal from the study). Note, if participant is a completer then for Analysis Month 6, m3=0.
m4 = m1 + m2 + m3

Calculate the proportion of days the sensor was still in use from the total number of days ELLIPTA was in use within a month, m1/(m1+m2)
Calculate the proportion of days the sensor was discontinued from the total number of days ELLIPTA was in use within a month, m2/(m1+m2)

Set participants monthly values to observed, MARA, MARB, J2RA, J2RB imputation, no data each with an m1, m2, m3 and m4 duration.

Percentage of ELLIPTA doses taken (daily adherence) Endpoint

Examples include to following;

- A participant who prematurely discontinues sensor after 15 days of Analysis Month 5 and concurrently discontinues ELLIPTA maintenance therapy and study withdrawal after 10 days of Analysis Month 6

Subject Id	Draw	Month	A	B	J2RA	J2RB	MARA	MARB	m1	m2	m3	m4
X	1	1	77	77	77	77	77	77	28	0	0	28
X	1	2	82	82	82	82	82	82	28	0	0	28
X	1	3	87	87	87	87	87	87	28	0	0	28
X	1	4	77	77	77	77	77	77	28	0	0	28
X	1	5	71	.	71	77	71	78	15	13	0	28
X	1	6	.	.	80	79	77	76	0	10	18	28

- A participant who concurrently prematurely discontinues sensor, ELLIPTA maintenance therapy and study withdrawal after 15 days of Analysis Month 5

Subject Id	Draw	Month	A	B	J2RA	J2RB	MARA	MARB	m1	m2	m3	m4
X	1	1	77	77	77	77	77	77	28	0	0	28
X	1	2	80	80	80	80	80	80	28	0	0	28
X	1	3	79	79	79	79	79	79	28	0	0	28
X	1	4	75	75	75	75	75	75	28	0	0	28
X	1	5	83	.	83	77	83	79	15	0	13	28
X	1	6	.	.	77	77	75	80	0	0	28	28

- A participant who completes the study after 26 days in Analysis Month 6

Subject Id	Draw	Month	A	B	J2RA	J2RB	MARA	MARB	m1	m2	m3	m4
X	1	1	77	77	77	77	77	77	28	0	0	28
X	1	2	82	82	82	82	82	82	28	0	0	28
X	1	3	87	87	87	87	87	87	28	0	0	28
X	1	4	77	77	77	77	77	77	28	0	0	28
X	1	5	80	80	80	80	80	80	28	0	0	28
X	1	6	82	82	82	82	82	82	15	11	0	26

- If the sensor is in use for at least a day within a month, m1>0 then let the analysis value be a combined value (weighted average) of the J2RA observed and J2RB imputed values, by taking a proportion of each value based on the proportion of days sensor was still in use and discontinued whilst on ELLIPTA respectively;

  Analysis value = m1/m1+m2 x (value from J2RA) + m2/m1+m2 x (value from J2RB)

  Note the weight is, m1 + m2

- Else if the sensor was not used in the month, m1=0 then let the analysis value be the imputed value,

  Analysis value = value from J2RA dataset (which is the imputed value)

Implement special cases of J2R post-discontinuation of ELLIPTA by identifying participants where ELLIPTA is prematurely discontinued and the participant concurrently withdraws from the study, and ELLIPTA discontinuation reason is not related to ELLIPTA:

Percentage of ELLIPTA doses taken (daily adherence) Endpoint

- If the sensor is in use for at least a day within a month, m1>0 then let the analysis value be a combined value (weighted average) of the J2RA observed and J2RB imputed values, by taking a proportion of each value based on the proportion of days the sensor is in use and not in use in that month

  Analysis value = m1/m4 x (value from J2RA) + (m2+m3)/m4 x (value from J2RB)

  Note the weight is, m4

- Else if the sensor was not used in the month, m1=0 then let the analysis value be the imputed value,

  Analysis value = value from J2RA dataset (which is the imputed value)

Implement special case of MAR post-discontinuation of ELLIPTA by identify participants where ELLIPTA is prematurely discontinued and the participant concurrently discontinues the maintenance eSensor and concurrently withdraws from the study, and ELLIPTA discontinuation reason is not related to ELLIPTA and study withdrawal is not related to CIS.

Where ELLIPTA has not been discontinued after the sensor but on the same day, m2=0.

- If the sensor is in use for at least a day within a month, m1>0 then let the analysis value be a combined value (weighted average) of the J2RA observed and MARB imputed values, by taking a proportion of each value based on the proportion of days the ELLIPTA was in use and not in use in that month

  Analysis Value = m1/m4 x (value from J2RA) + m3/m4 x (value from MARB)
- Else

  Analysis Value = m1/m4 x (value from J2RA) + m3/m4 x (value from MARA)

Note the weights are m4

STEP 5: Primary and Secondary Percentage of ELLIPTA doses taken Endpoints calculation

The calculations presented in the previous steps support the final derivation of the following primary and secondary endpoints, the percentage of ELLIPTA doses taken between

- the beginning of Month 4 and the end of Month 6
- the beginning of Month 1 and the end of Month 6
- the beginning of Month 1 and the end of Month 3

For participants who complete the study treatment (i.e. no premature discontinuation of ELLIPTA Relvar/Breo) during the endpoint period of interest:

Analysis Endpoint is the average of monthly Analysis Values over the number of months in the endpoint period of interest, i.e.

- Month 4 to Month 6
- Month 1 to Month 6
- Month 1 to Month 3

For participants who prematurely discontinue ELLIPTA during the endpoint period of interest for reasons related to ELLIPTA, then the weight is the total duration on ELLIPTA within the endpoint period of interest and applied to each analysis month based on the duration within that month. This weight should be applied to each monthly Analysis value within the period of interest and results summed together to produce the final endpoint/response variable for modelling within macro Part 3.

Percentage of ELLIPTA doses taken (daily adherence) Endpoint

Note the weight is, total duration of ELLIPTA use within the period of interest . The proportion of weight to apply per monthly Analysis value is m1+m2/total duration of ELLIPTA use within the period of interest

For participants who prematurely discontinue ELLIPTA during the endpoint period of interest for reasons not related to ELLIPTA or CIS, or just related to CIS, the MAR or J2R imputation assumes participants would have continued taking ELLIPTA until the end of the period of interest. The weight is the total duration within the endpoint period of interest. This weight will be applied to each monthly Analysis value within the period of interest and results summed together to produce the final endpoint/response variable for modelling within macro Part 3.

Note the weight is, total expected ELLIPTA duration within the period of interest. The proportion of weight to apply per monthly Analysis value is m1+m2+m3/ Total expected ELLIPTA duration within the period of interest.

Percentage of ELLIPTA doses taken (daily adherence) – Sensitivity Analysis

Sensitivity analyses will be performed estimating the treatment effect by utilizing a generalized linear model (GLM) and not running the multiple imputation process. The model will follow a binomial distribution with the logit link function.

The sensitivity analyses will be performed for the following primary and secondary endpoints relating to the percentage of ELLIPTA doses taken between

- the beginning of Month 4 and the end of Month 6
- the beginning of Month 1 and the end of Month 6
- the beginning of Month 1 and the end of Month 3

Model assumptions will be checked by using standardised residual plots. Missing data will be assumed to be MAR.

The weighting strategy is to be applied as detailed above.

Percentage of ELLIPTA doses taken (daily adherence) Endpoint

Seeds for Multiple Imputations Macros

Seeds for all planned MI analyses were determined in advance using the following SAS code and documented within this RAP prior to unblinding:

```
data temp;
  do i = 1 to 6;
    number=round(10000*ranuni(0),1);
   output;
  end;
run;
proc print;
run;
```

Part 1B Macro Seed for Parameter Estimation Using Bayesian MCMC Procedure

Endpoint	Input Dataset	Macro Seed
Percentage of Daily Adherence	Observed Dataset A	2124
	Observed Dataset B	5071

Part 2B Macro Seeds for Multiple Imputation of Datasets

Endpoint	Multiple Imputation Method	Macro Seed	Output Dataset
Percentage of Daily Adherence	MAR	8517	MAR Dataset A
	J2R	6888	J2R Dataset A
	MAR	6388	MAR Dataset B
	J2R	8674	J2R Dataset B

10.5.3.2. MDI Device Sensor Assessments

Percentage of Rescue Free Days Endpoint

Overview of Calculation

1. Create a dataset (Observed Data A) to calculate the monthly observed percentage of MDI rescue free days values (from month 1 to month 6) accounting for the following,
    a. number of days MDI rescue medication was used (at least once per day)
    b. number of days post MDI rescue use sensor permanent discontinuation
    c. the intermittent missing daily MDI rescue use data due to device incident
    d. MDI Rescue free days (i.e. none of the above).

2. Duplicate the observed monthly MDI rescue free values dataset (Observed Dataset A). Using the values in the duplicate dataset (Dataset B), impute the month where the sensor was permanently discontinued before the end of that month (and therefore presents a monthly adherence rate based on partly observed sensor data for that month) as missing unless the participant is a study completer.

3. Using each of the two observed datasets (Observed Dataset A and Observed Dataset B), create four separate imputed datasets (J2R-Dataset A, J2R-Dataset B, MAR-Dataset A, MAR-Dataset B) that account for the two imputation methods (J2R or MAR) that may be applied to participants data after discontinuation of the MDI rescue sensor or withdrawal from study. Imputation will be carried out using observed monthly MDI rescue free rates for months 1 to 6. 1000 draws will be used. Completely missing intermediate monthly values will be assumed MAR. The multiple imputation will be implemented using the methods described in Carpenter, 2013, using the macros (Part1A, Part1B, Part2A and Part2B) available from https://missingdata.lshtm.ac.uk/2017/04/06/gsk-five-macros/ using seeds documented in the RAP for the respective endpoint.

4. The Observed Datasets (A and B), imputed datasets (J2R-Dataset A, J2R-Dataset B, MAR-Dataset A, MAR-Dataset B) and the timing of the intercurrent events; permanent discontinuation of the MDI rescue sensor and withdrawal from study; will be used to create an analysis dataset (Dataset C) that identifies the proportion of each month to be assigned as observed data, J2R imputed data or MAR imputed data. The strategy for handling intercurrent events is described in Section 7.2.2.3 Strategy for Intercurrent (Post-Randomisation) Events.

    Within each imputation draw, for each missing month, the observed and any imputed data will be combined to provide a percentage of rescue free days value. The values for months 4 to 6 will be combined to create the value for the respective secondary endpoint analysis and the weight to be assigned to each participant.

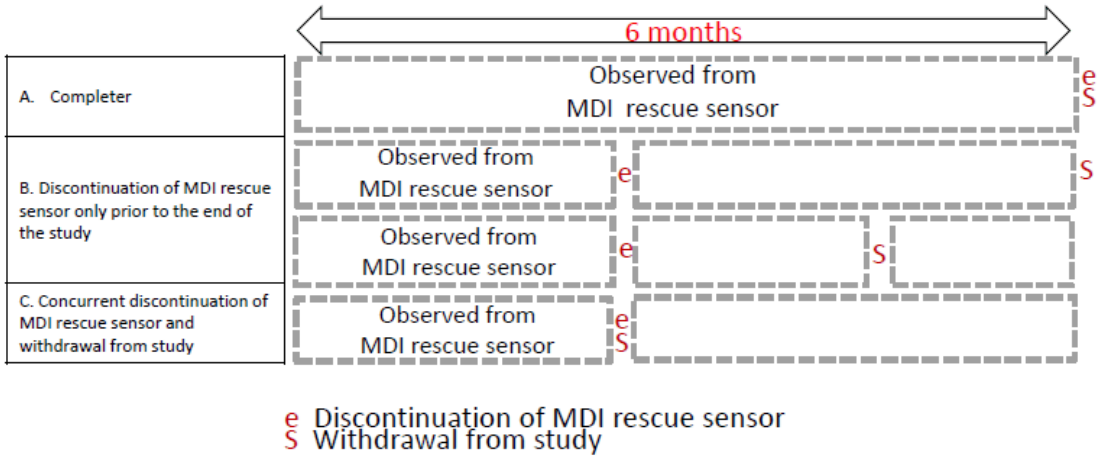
5. Analyse using Multiple Imputation macro Part3

a. Perform ANCOVA on the endpoint for each imputed dataset to obtain treatment effect estimate and standard error
b. Combine estimates across imputations using Rubin's rules

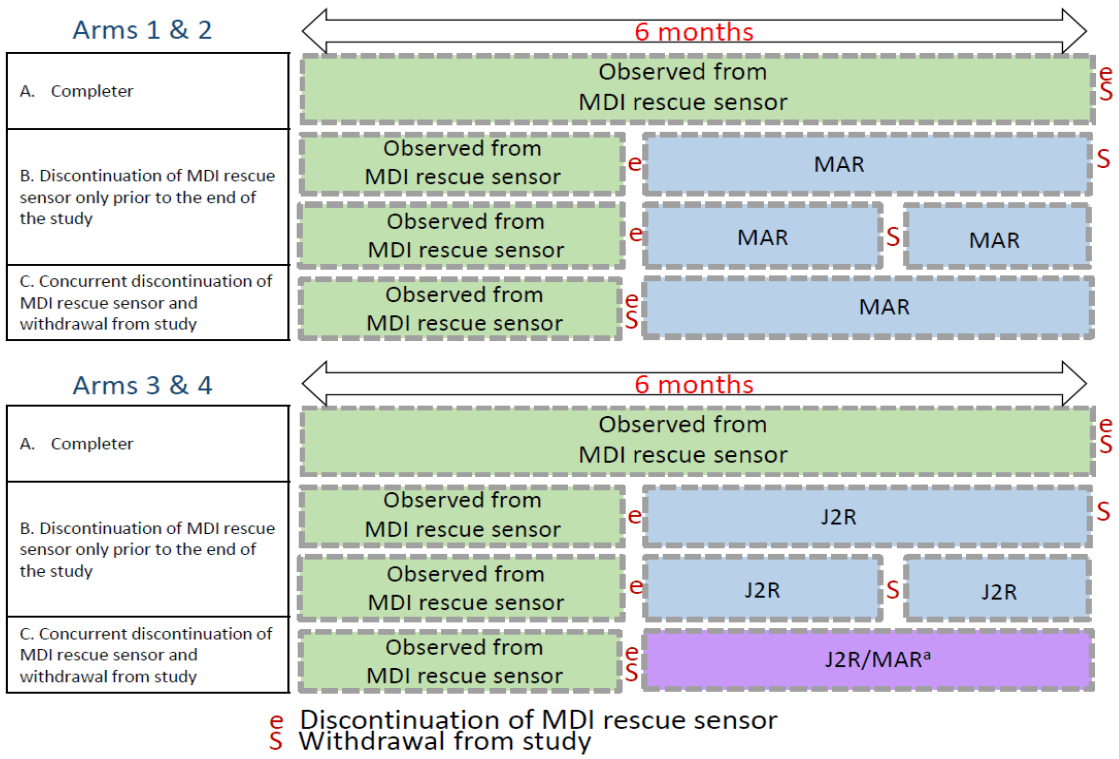
Percentage of Rescue Free Days Endpoint

The intercurrent events identified as part of this secondary endpoint estimand and derivation are detailed in full in Section 7.2.2.3 Strategy for Intercurrent (Post-Randomisation) Events. Below are two schematics of the intercurrent event patterns and their estimation rules.

Intercurrent Event Patterns



Intercurrent Event 'Estimation Rules' 1-4



a. J2R imputation if withdrawal related to CIS; MAR imputation if withdrawal not related to CIS

Percentage of Rescue Free Days Endpoint
Intercurrent Events related to CIS
In order to implement the intercurrent event strategy detailed in Section 7.2.2.3 Strategy for Intercurrent (Post-Randomisation) Events, it is necessary to determine if and when the reasons for permanent discontinuations related to CIS occur. The date and reason for withdrawing from the study will be determined from the study conclusion page of the eCRF. Study discontinuation reasons classified as related to CIS are as follows: • Withdrew consent – dissatisfaction with the connected inhaler system (CIS)

Percentage of Rescue Free Days Endpoint
Monthly Percentage of Rescue Free Days - Calculation
STEP 1: Creating the observed adherence dataset (Observed Dataset A) To determine the monthly observed percentage of rescue free days values (Observed Dataset A) the following should be applied for each month: For Baseline Analysis Month, for each participant create a count of each of the following types of Days D1 = Rescue use recorded D2 = Device incident D3 = Post discontinuation of MDI rescue sensor D4 = MDI rescue free D5=D1 + D2 + D3 + D4, i.e. The total number of days within the Baseline Analysis Month; the total number of days between Beginning Timepoint and Ending Timepoint as defined in Table 5 in Section 10.2 Appendix 2: Assessment Windows. For Analysis Month 1, 2, 3, 4 and 5, for each participant create a count of each of the following types of days: D1 = Rescue use recorded D2 = Device incident D3 = Post discontinuation of MDI rescue sensor D4 = MDI rescue free D5 = D1 + D2 + D3 + D4, i.e. The total number of days within the Analysis Month; the total number of days between Beginning Timepoint and Ending Timepoint as defined in Table 5 in Section 10.2 Appendix 2: Assessment Windows. For Analysis Month 6, for each participant create a count of each of the following types of days: D1 = Rescue use recorded D2 = Device incident D3 = Post discontinuation of MDI rescue sensor D4 = MDI rescue free D5 = D1 + D2 + D3 + D4, i.e. the total number of days within Analysis Month 6; the total number of days between Beginning Timepoint and Ending Timepoint as defined in Table 5 in Section 10.2 Appendix 2: Assessment Windows.

Percentage of Rescue Free Days Endpoint

The following observations from the sensor and eCRF will be required to determine the above Days and the differences between missing at random due to device/sensor incident and non-adherent days.

- Device malfunction date
- Sensor malfunction date
- Permanent discontinuation of MDI rescue sensor
- First and last individual sensor synchronisation dates

The first and last individual sensor synchronisation dates will be provided in the sensor dataset. These dates will be used to assess whether missing observations are due to rescue free days or data being missing at random due to device/sensor malfunction.

For each Analysis Month, the Observed MDI rescue free days (%) for that month will be calculated as follows:

$$Monthly\ observed\ MDI\ rescue\ free\ days\ (\%) = \left(\frac{D4}{D5 - D2 - D3}\right) x100$$

STEP 2: Creating the modified observed MDI rescue free dataset (Observed Dataset B)

The Observed Dataset A will be duplicated. Using the values in the duplicate dataset (Observed Dataset B) the Analysis Month where the MDI rescue sensor was permanently discontinued before the end of that month (and therefore presents a monthly rescue free rate based on partly observed sensor data for that month) will be imputed as missing; i.e.in Dataset B, if within an Analysis Month (D3>0 and D3<D5) then set monthly value for that Analysis Month to missing. (Note: unless the participant is a completer in which case do not set the value to missing for that Analysis Month).

STEP 3: Creating the reference imputed datasets under MAR and J2R method

Using each of the two observed datasets (Observed Dataset A and Observed Dataset B) monthly values, create four separate reference imputed datasets (J2R-Dataset A, J2R-Dataset B, MAR-Dataset A, MAR-Dataset B) that account for the two imputation methods (J2R or MAR). Completely missing intermediate monthly values will be assumed MAR.

The multiple imputation will be implemented using the methods described in Carpenter, 2013 using macros, Part1A, Part1B, Part2A and Part2B (available from https://missingdata.lshtm.ac.uk/2017/04/06/gsk-five-macros/). The seeds are documented at the end of Section 10.5.3.2 and 1000 draws will be used in the relevant macros parameters.

Due to the range of the rescue free days percentages being limited between 0 and 100, the multiple imputation process can generate percentages outside the possible range of values (< 0% or > 100%). A cap will be put in place where values imputed < 0 will be set as 0 and values imputed as > 100 set as 100.

STEP 4: Creating the Monthly Analysis values dataset

For each month within each participant create a count of each of the following durations based on intercurrent events: Let,
r1 = MDI rescue sensor still in use

Percentage of Rescue Free Days Endpoint

r2 = MDI rescue sensor discontinued but MDI rescue use ongoing until study withdrawal
r3 = MDI rescue discontinued at study withdrawal (includes days post withdrawal from the study). Note, if participant is a completer then for Analysis Month 6, r3=0.
r4 = r1 + r2 + r3
Note: it is assumed that MDI rescue use is not discontinued until permanent discontinuation of the study. Therefore, discontinuation date of MDI rescue use is the same date as permanent discontinuation of study

Set participants monthly values to observed, MARA, MARB, J2RA, J2RB imputation, no data each with a r1, r2, r3 duration.

Examples include to following;

- A participant who prematurely discontinues sensor after 20 days of Analysis Month 5 and withdraws from study after 5 days of Analysis Month 6

Subject Id	Draw	Month	A	B	J2RA	J2RB	MARA	MARB	r1	r2	r3	r4
X	1	1	77	77	77	77	77	77	28	0	0	28
X	1	2	82	82	82	82	82	82	28	0	0	28
X	1	3	87	87	87	87	87	87	28	0	0	28
X	1	4	77	77	77	77	77	77	28	0	0	28
X	1	5	71	.	71	77	71	78	20	8	0	28
X	1	6	.	.	80	79	77	76	0	5	23	28

- A participant who concurrently prematurely discontinues sensor and withdraws from study after 20 days of Analysis Month 5

Subject Id	Draw	Month	A	B	J2RA	J2RB	MARA	MARB	r1	r2	r3	r4
X	1	1	77	77	77	77	77	77	28	0	0	28
X	1	2	80	80	80	80	80	80	28	0	0	28
X	1	3	79	79	79	79	79	79	28	0	0	28
X	1	4	75	75	75	75	75	75	28	0	0	28
X	1	5	83	.	83	77	83	79	20	0	8	28
X	1	6	.	.	77	77	75	80	0	0	28	28

- A participant who completes the study after 27 days in Analysis Month 6

Subject Id	Draw	Month	A	B	J2RA	J2RB	MARA	MARB	r1	r2	r3	r4
X	1	1	77	77	77	77	77	77	28	0	0	28
X	1	2	82	82	82	82	82	82	28	0	0	28
X	1	3	87	87	87	87	87	87	28	0	0	28
X	1	4	77	77	77	77	77	77	28	0	0	28
X	1	5	80	80	80	80	80	80	28	0	0	28
X	1	6	82	82	82	82	82	82	15	12	0	27

For Arms 1 and 2,

- If the sensor is in use for at least a day within a month, r1>0 then let the analysis value be a combined value (weighted average) of the J2RA observed and MARB imputed values, by taking a proportion of each value based on the proportion of days the sensor is in use and not in use in that month

Percentage of Rescue Free Days Endpoint

Analysis value = r1/r4 x (value from J2RA) + (r2+r3)/r4 x (value from MARB)
Note the weight is, r4

- Else if the sensor was not used in the month, r1=0 then let the analysis value be the imputed value,
  Analysis value = value from J2RA dataset (which is the imputed value)

Implement special case of MAR post-early discontinuation of study by identifying participants where the MDI rescue sensor is prematurely discontinued and the participant concurrently withdraws from the study. Where study withdrawal has not been discontinued after the sensor but on the same day, r2=0.

- If the sensor is in use for at least a day within a month, r1>0 then let the analysis value be a combined value (weighted average) of the J2RA observed and MARB imputed values, by taking a proportion of each value based on the proportion of days the MDI rescue was in use and not in use in that month
  Analysis Value = r1/r4 x (value from J2RA) + r3/r4 x (value from MARB)

Note the weights are r4

- Else if the sensor was not used in the month, r1=0 then let the analysis value be the imputed value,
  Analysis value = value from MARA dataset (which is the imputed value)

For Arm 3 and 4,

- If the sensor is in use for at least a day within a month, r1>0 then let the analysis value be a combined value (weighted average) of the J2RA observed and J2RB imputed values, by taking a proportion of each value based on the proportion of days the MDI sensor is in use and not in use in that month
  Analysis value = r1/r4 x (value from J2RA) + (r2+r3)/r4 x (value from J2RB)
  Note the weight is, r4

- Else if the sensor was not used in the month, r1=0 then let the analysis value be the imputed value,
  Analysis value = value from J2RA dataset (which is the imputed value)

Implement special case of MAR post-early discontinuation of study by identifying participants where the MDI rescue sensor is prematurely discontinued and the participant concurrently withdraws from the study and study withdrawal reason is <u>not</u> related to CIS. Where study withdrawal has not been discontinued after the sensor but on the same day, r2=0.

- If the sensor is in use for at least a day within a month, r1>0 then let the analysis value be a combined value (weighted average) of the J2RA observed and MARB imputed values, by taking a proportion of each value based on the proportion of days the MDI rescue was in use and not in use in that month
  Analysis Value = r1/r4 x (value from J2RA) + r3/r4 x (value from MARB)

Note the weights are r4

- Else if the sensor was not used in the month, r1=0 then let the analysis value be the imputed value,
  Analysis value = value from MARA dataset (which is the imputed value)

Implement special case of J2R post-early discontinuation of study by identifying participants where the MDI rescue sensor is prematurely discontinued and the participant concurrently withdraws from the study and study withdrawal reason <u>is</u> related to CIS. Where study withdrawal has not been discontinued after the sensor but on the same day, r2=0.

Percentage of Rescue Free Days Endpoint

- If the sensor is in use for at least a day within a month, r1>0 then let the analysis value be a combined value (weighted average) of the J2RA observed and J2RB imputed values, by taking a proportion of each value based on the proportion of days the MDI rescue was in use and not in use in that month

  Analysis Value = r1/r4 x (value from J2RA) + r3/r4 x (value from J2RB)

Note the weights are r4

- Else if the sensor was not used in the month, r1=0 then let the analysis value be the imputed value,

  Analysis value = value from J2RA dataset (which is the imputed value

STEP 5: Secondary Endpoint Percentage of Rescue Free Days Endpoint calculation

The calculations presented in the previous steps support the final derivation of the following secondary endpoint, the percentage of rescue free days between

- the beginning of Month 4 and the end of Month 6

For participants who complete the study during the endpoint period of interest:

Analysis Endpoint is the average of monthly Analysis Values over the number of months in the endpoint period of interest, i.e.

- Month 4 to Month 6

For participants who prematurely discontinue the study during the endpoint period of interest for reasons related or not related to CIS, the MAR or J2R imputation assumes participants would have continued in the study until the end of the period of interest. The weight is the total duration within the endpoint period of interest. This weight will be applied to each month within the period of interest and results summed together to produce the final endpoint/response variable for modelling within macro Part 3.

Note the weight is, total expected study duration within the period of interest. The proportion of weight to apply per monthly Analysis value is r1+r2+r3/ Total expected study duration within the period of interest.

Percentage of Rescue Free Days Endpoint

Seeds for Multiple Imputations Macros

Seeds for all planned MI analyses were determined in advance using the following SAS code and documented within this RAP prior to unblinding:

```
data temp;
  do i = 1 to 6;
    number=round(10000*ranuni(0),1);
   output;
  end;
run;
proc print;
run;
```

Part 1B Macro Seed for Parameter Estimation Using Bayesian MCMC Procedure

Endpoint	Input Dataset	Macro Seed
Percentage of Rescue Free Days	Observed Dataset A	9170
	Observed Dataset B	5337

Part 2B Macro Seeds for Multiple Imputation of Datasets

Endpoint	Multiple Imputation Method	Macro Seed	Output Dataset
Percentage of Rescue Free Days	MAR	2553	MAR Dataset A
	J2R	8350	J2R Dataset A
	MAR	4380	MAR Dataset B
	J2R	2045	J2R Dataset B

10.5.3.3. Patient Reported Outcomes

Asthma Control Test (ACT)

The ACT is a validated self-administered questionnaire utilising 5 questions to assess asthma control during the past 4 weeks on a 5-point categorical scale (1 to 5).

By answering all 5 questions, a participant with asthma can obtain a score that may range between 5 and 25, with higher scores indicating better control. An ACT total score of 5 to 19 suggests that the participant's asthma is unlikely to be well controlled. A score of 20 to 25 suggests that the participant's asthma is likely to be well controlled. The minimally important difference (MID) for ACT is 3 [Schatz, 2009].

The total score is calculated as the sum of the scores from all 5 questions [Nathan,2004], provided all scores are non-missing; if any individual scores are missing then the overall score will be set to missing. The ACT total scores calculated using the electronic version on the ePRO device will be used; i.e. total scores will not be rederived from the individual question responses.

ACT will be completed on an ePRO device at the clinical study site and at the times detailed in Appendix 1: Schedule of Activities.

Asthma Symptom Utility Index (ASUI)

The ASUI is a 10-item self-administered questionnaire with 4 questions on asthma symptoms (Cough, wheeze, shortness of breath, awakening at night) and 1 question about the side effects of asthma medications [Revicki, 1998].

For each symptom, there are 2 dimensions; frequency and severity. The questionnaire is based on a 2-week patient recall of symptoms with response options of 0 to 4 for frequency (not at all, 1 to 3 days, 4 to 7 days, and 8 to 14 days) and severity (not applicable, mild, moderate and severe).

ASUI score ranges from 0 (worst possible symptoms) to 1 (no symptoms) and the MID of the ASUI is considered to be 0.09 [Bime, 2012]. If the response to any question is missing then the ASUI is also set to missing.

A multi-attributable utility theory was used to construct a model for calculating ASUI utilities from individual patient responses [Revicki, 1998]. The multi-attributable utility function is:

$$ASUI = 1.200 \times (s_1 \times s_2 \times s_3 \times s_4 \times s_5) - 0.200$$

where ASUI is the utility of the symptom state on a scale where the best state (no symptoms) has a score of 1 and worst possible symptoms (severe symptoms for 8 to 14 days) has a score of 0; and i_s is the score for the level on symptom *i*. The table below shows the coefficients for calculating the ASUI scores:

	Symptom (Attribute)				
Level, d	Cough, S_1	Wheeze, S_2	Dyspnoea, S_3	Awaken at Night, S_4	Medication Side Effects, S_5
1 None	1.0	1.0	1.0	1.0	1.0
2 Mild, 1-3	0.985	0.962	0.946	0.955	0.970
3 Mild, 4-7	0.963	0.940	0.920	0.931	0.954
4 Mild, 8-14	0.935	0.913	0.885	0.899	0.930
5 Moderate, 1-3	0.955	0.913	0.892	0.909	0.924
6 Moderate, 4-7	0.920	0.886	0.860	0.880	0.900
7 Moderate, 8-14	0.875	0.851	0.818	0.845	0.862
8 Severe, 1-3	0.863	0.810	0.771	0.821	0.824
9 Severe, 4-7	0.813	0.772	0.729	0.781	0.789
10 Severe, 8-14	0.751	0.729	0.681	0.734	0.730

ASUI will be completed on an ePRO device at the clinical study site and at the times detailed in Appendix 1: Schedule of Activities.

St. George's Respiratory Questionnaire (SGRQ)

The St. George's Respiratory Questionnaire is a well-established instrument, comprising a 50-item questionnaire designed to measure Quality of Life in patients with diseases of airway obstruction, measuring symptoms, impact, and activity.

The questions are designed to be self-completed by the participant with a recall over the past 4 weeks [Jones, 1992].

Scores are expressed as the percentage of overall impairment with 100 equalling to the worst possible health status and 0 indicating the best possible health status.

Scoring in each domain of the SGRQ (Symptoms, Activity, Impacts) and the Total score are described in the St George's Respiratory Questionnaire Manuel (Version 2.3, 2009).

SGRQ will be completed on an ePRO device at the clinical study site and at the times detailed in Appendix 1: Schedule of Activities.

Patient Activation Measure (PAM-13)

Patient Activation Measure will be used to assess the knowledge, skills and confidence a person has in managing their own health and health care.

The PAM contains a series of 13 statements designed to assess the extent of a patient's activation. These statements are about beliefs, confidence in the management of health-related tasks and self-assessed knowledge. Patients are asked to rate the degree to which they agree or disagree with each statement. These answers are combined to provide a single score of between 0 and 100, which represents the patients' concept of themselves as an active manager of their health and health care. There is no specified timeframe on which responses should be based, the questionnaire is suitable to be used to measure changes in activation over time and can be performed before and after an intervention [Hibbard, 2004].

The 13 items have four possible response options: (1) disagree strongly, (2) disagree, (3) agree and (4) agree strongly, and an additional "Not applicable" option. The total PAM score is then calculated by dividing the raw score over the number of items answered (not including the non-applicable items) and multiplied by 13. This score is then transformed to a scale with a range of 0-100 based on calibration tables and proprietary PAM algorithm (http://www.insigniahealth.com/). The score will be provided for analysis.

Medication Adherence Report Scale for Asthma (MARS-A)

The MARS-A is a 10-item questionnaire where medication use is rated on a 5-point Likert scale (1 indicating 'always' to 5 indicating 'never'). It has been validated as a self-reported measure of adherence with ICS for patients with asthma, and includes generic ("I use it regularly every day") and lung condition-specific questions about medication use ("I only use it when I feel breathless") [Cohen, 2009].

The MARS-A 10-Score will be calculated for each participant as the sum of scores for each of the ten questions divided by the number of non-missing responses to the ten questions.

If some responses are missing the MARS-A 10-score is calculated as follows for each participant:

- If eight or more of the questions have been answered, the missing responses for that participant will be imputed to the average score

- If less than eight of the questions have been answered, the overall MARS-A 10-score for that participant will be set to missing

MARS-A will be completed on an ePRO device at the clinical study site and at the times detailed in Appendix 1: Schedule of Activities.

Beliefs in Medicine Questionnaire (BMQ)

The BMQ questionnaire consists of the BMQ Specific, which measures perceptions of specific medicines, and the BMQ General, which measures more general beliefs about medicines. All items are scored on a 5-point Likert scale ranging from Strongly Disagree (1) to Strongly Agree (5).

The BMQ Specific questionnaire is formed of the 6 item Necessity and 12 item Concern scales, and the General questionnaire is formed of the 4 item Benefit, 5 item Harm and 3 item Overuse scales.

CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.

[redacted]

Scores obtained for individual items within scales are summed together to provide a total score. The BMQ Specific and General will be completed on an ePRO device at the clinical study site and at the times detailed in Appendix 1: Schedule of Activities.

Biomarkers

PEF and FeNO

- Participants should not use their rescue medication for at least 6 hours before each FeNO and PEF assessment, unless essential for clinical need. Participants should also withhold ICS/LABA for (1 dosing interval) approximately 12-24 hours prior to FeNO and PEF assessment.

- PEF and FeNO will be taken in triplicate at the times detailed in Appendix 1: Schedule of Activities. All 3 measures will be recorded in the eCRF.

- The maximum value from the 3 measures taken at each visit will be used in the calculation of the FeNO and PEF endpoints.

Severe Asthma Exacerbations

General

Missing onset or resolution dates will be handled as follows:

- Single event with missing onset and/or resolution dates:
  - (a) Missing onset date: set onset date = study treatment start date
  - (b) Missing resolution date: set resolution date = study treatment stop date
  - (c) Both missing: imputed per both (a) and (b)
- Multiple events, one event with some missing onset/resolution dates; on the assumption any partial date information does not occur during the other events:
  - (a) Missing onset date: set onset date = max[(resolution date of the nearest previous event) + 1 day, study treatment start date]
  - (b) Missing resolution date: set resolution date = min[(onset date of the nearest subsequent event) - 1 day, study treatment stop date]
  - (c) Both missing: determine the largest gap between study treatment start date and first event onset date, between first event resolution date and next event(s) onset dates (if any), between last event resolution date and study treatment stop date. If there is more than one gap which is the largest, then take the first occurrence. Then impute as follows:

    onset date = (onset date of largest gap) + 1 day

    resolution date = (resolution date of largest gap) + 1 day

10.5.4. Safety

Adverse Events
• Adverse events will be coded using the current MedDRA coding dictionary at the time of reporting providing a Preferred Term (PT) and a System Organ Class (SOC) for analysis and reporting.
ADRs and SAEs of Special Interest
ADR and SAE groups of special interest have been defined as SAEs which are included in specified areas of interest for Relvar/Breo. They are identified by groupings of preferred terms based on the Medical Dictionary for Regulatory Activities (MedDRA) dictionary version used in each reporting effort. Groupings or subgroups may be defined, based on relevant combination of preferred terms, or on Standardised MedDRA queries (SMQs). SAEs of special interest will be confirmed prior to final data, based on the MedDRA version in use at the time

10.6. Appendix 6: Reporting Standards for Missing Data

10.6.1. Premature Withdrawals

Element	Reporting Detail
General	• Participant study completion (as specified in the protocol) is defined as completing all visits of the study including the follow-up phone contact. • Withdrawn participants will not be replaced in the study. • All available data from participants who are withdrawn from the study will be included in listings and where possible any available data from withdrawn participants will be included in summaries or analyses, unless otherwise specified.

10.6.2. Handling of Missing Data

Element	Reporting Detail
General	• Missing data occurs when any requested data is not provided, leading to blank fields on the collection instrument: o These data will be indicated by the use of a “blank” in participant listing displays. If all data for a specific visit are missing, the visit will be excluded from the display. o Answers such as “Not applicable” and “Not evaluable” are not considered to be missing data and will be displayed as such.
MMRM Analysis	• All the available assessments taken at scheduled visits will be included in the repeated measures models in which missing data are not explicitly imputed but the correlation between visits for all participants is used to adjust the estimate of treatment effect considering any missing data.
Rescue Free Days Endpoint	• Handling of missing sensor data is detailed in Section 7.2.2.3 Strategy for Intercurrent (Post-Randomisation) Events, as well Section 10.5.3.2 MDI Device Sensor Assessments.
ACT	• Handling of missing ACT data is detailed in Section 7.2.3.3 Strategy for Intercurrent (Post-Randomisation) Events.
Other PROs	• Handling of missing PRO data is detailed in Section 7.3.3.4 Strategy for Intercurrent (Post-Randomisation) Events, as well in Section 10.5.3.3 Patient Reported Outcomes.

10.6.3. Handling of Partial Dates

Element	Reporting Detail
General	• Partial dates will be displayed as captured in participant listing displays.
Adverse Events	• The eCRF does not allow partial dates to be captured for AEs. All dates will either be complete or missing. • Completely missing start or end dates will remain missing, with no imputation applied. • Where AE onset dates are missing then the AE will be considered on-treatment.
Concomitant Medications	• The eCRF allows partial dates to be captured for concomitant medications. • Partial dates for any concomitant medications recorded in the eCRF will be imputed using the following convention: o If the partial date is a start date, a '01' will be used for the day and 'Jan' will be used for the month o If the partial date is a stop date, a '28/29/30/31' will be used for the day (dependent on the month and year) and 'Dec' will be used for the month.

Element	Reporting Detail
	• The answers to the questions “Taken Prior to Study?” and “Ongoing?” which are recorded in the eCRF will also be taken into consideration to determine if the medication was started pre-treatment or continued post-treatment. In each case, should the answers suggest a different classification than the dates, the medication will be summarized in all possible classifications (pre-/during/post-treatment) in which it could conceivably have been taken.
Exacerbations	• Exacerbations are treated in the same way as AEs.

10.7. Appendix 7: Abbreviations & Trade Marks

10.7.1. Abbreviations

Abbreviation	Description
ACT	Asthma Control Test
ADaM	Analysis Data Model
ADR	Adverse Drug Reaction
AE	Adverse Event
ANCOVA	Analysis of Covariance
A&R	Analysis and Reporting
ASUI	Asthma Symptom Utility Index
ATC	Anatomical Therapeutical Chemical
BMQ	Beliefs in Medicine Questionnaire
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
CIS	Connected Inhaler System
CS	Clinical Statistics
CSR	Clinical Study Report
DBF	Database Freeze
DBR	Database Release
DOB	Date of Birth
DP	Decimal Places
DM	Data Management
DPI	Dry powder inhaler
eCRF	Electronic Case Record Form
ER	Emergency Room
EW	Early Withdrawal
FeNO	Fractional exhaled Nitric Oxide
GLM	Generalized Linear Model
GSK	GlaxoSmithKline
HCP	Healthcare Professional
HCRU	Health Care Resource Utilization
IA	Interim Analysis
ICH	International Conference on Harmonization
ICF	Informed Consent Form
ICS	Inhaled Corticosteroid
IDSL	Integrated Data Standards Library
ITT	Intent-To-Treat
J2R	Jump to reference
LABA	Long-Acting Beta2-Agonist
MAR	Missing At Random
MARS-A	Medication Adherence Report Scale for Asthma
MDI	Metered dose inhaler
MMRM	Mixed Model Repeated Measures
PAM	Patient Activation Measure
PDMP	Protocol Deviation Management Plan
PEF	Peak Expiratory Flow
PRO	Patient Reported Outcomes
PT	Preferred Term

Abbreviation	Description
QC	Quality Control
RAP	Reporting & Analysis Plan
RFD	Rescue Free Day
RAMOS	Randomisation & Medication Ordering System
SAC	Statistical Analysis Complete
SAE	Serious Adverse Event
S&P	Statistics and Programming
SD	Standard Deviation
SDL	Source Data Lock
SDTM	Study Data Tabulation Model
SGRQ	St. Georges Respiratory Questionnaire
SI	System Independent
SMQ	Standardised MedDRA Queries
SOC	System Organ Class
TRU	Total Rescue Use
SOP	Standard Operation Procedure
TA	Therapeutic Area
TFL	Tables, Figures & Listings

10.7.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
BREO
ELLIPTA
RELVAR

Trademarks not owned by the GlaxoSmithKline Group of Companies
ACT
ASUI
BMQ
MARS-A
MedDRA
PAM-13
RAMOS NG
SAS
SGRQ

10.8. Appendix 8: List of Data Displays

10.8.1. Data Display Numbering

The following numbering will be applied for RAP generated displays:

Section	Tables	Figures
Study Population	1.01 to 1.44	1.01 to 1.02
Efficacy	2.01 to 2.41	2.01 to 2.22
Safety	3.01 to 3.29	None
Section	**Listings**	
ICH Listings	1 to 19	
Other Listings	20 to 44	

10.8.2. Mock Example Shell Referencing

Non IDSL specifications will be referenced as indicated and if required example mock-up displays provided in Appendix 9: Example Mock Shells for Data Displays: Example Mock Shells for Data Displays.

Section	Figure	Table	Listing
Study Population	POP_Fn	POP_Tn	POP_Ln
Efficacy	EFF_Fn	EFF_Tn	EFF_Ln
Safety	Not applicable	SAFE_Tn	SAFE_Ln

NOTES:

- Non-Standard displays are indicated in the 'IDSL / Example Shell' or 'Programming Notes' column as '[Non-Standard] + Reference.'

10.8.3. Deliverables

Delivery [Priority] [1]	Description
SAC [2]	Final Statistical Analysis Complete
DRY RUN [1]	Dry Run

NOTES:

1. Indicates priority (i.e. order) in which displays will be generated for the reporting effort

10.8.4. Study Population Tables

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
1.1.	Screened	IDSL_SP1	Summary of Subject Populations	See Section 4 for population details	SAC [2] DRY RUN [1]
1.2.	Enrolled	IDSL_ES6	Summary of Screening Status and Reasons for Screen Failure		SAC [2] DRY RUN [1]
1.3.	Enrolled	IDSL_ES6	Summary of Run-in Status and Reasons for Run-In Failure		SAC [2] DRY RUN [1]
1.4.	ITT	POP_T1	Summary of Attendance at Each Visit	Note: Visit 2/3/4 subjects may be randomised or re-entered into run-in up 3 times if ACT ≥ 20. Note: Visits 6/7/8/9 are Healthcare Professional Dashboard reviews for Arm 1 and Arm 3 .	SAC [2] DRY RUN [1]
1.5.	ITT	IDSL_ES1	Summary of Subject Disposition for the Subject Conclusion Record		SAC [2] DRY RUN [1]
1.6.	ITT	IDSL_ES4	Summary of Subject Disposition at Each Study Epoch		SAC [2] DRY RUN [1]
1.7.	ITT	IDSL_SD1	Summary of Treatment Status and Reasons for Discontinuation of Study Treatment		SAC [2] DRY RUN [1]
1.8.	ITT	POP_T2	Summary of Relvar/Breo ELLIPTA Sensor Status		SAC [2] DRY RUN [1]

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
1.9.	ITT	POP_T2	Summary of Salbutamol MDI Sensor Status		SAC [2] DRY RUN [1]
1.10.	ITT	POP_T3	Summary of App Status		SAC [2] DRY RUN [1]
1.11.	Enrolled	IDSL_NS1	Summary of Number of Subjects Enrolled by Country and Site ID	Disclosure display Add "No Treatment" column Do by page by country to help fit all columns in one width.	SAC [2] DRY RUN [1]
1.12.	ITT	IDSL_NS1	Summary of Number of Subjects Enrolled by Country and Site ID	Do by page by country for consistency with above display	SAC [2] DRY RUN [1]
1.13.	ITT	IDSL_IE1	Summary of Inclusion/Exclusion Criteria Deviations		SAC [2] DRY RUN [1]
1.14.	ITT	IDSL_DV1	Summary of Important Protocol Deviations		SAC [2] DRY RUN [1]
Demographic and Baseline Characteristics					
1.15.	ITT	IDSL_DM1	Summary of Demographic Characteristics	Include, Gender, Age (years), Age group categories: 18-64, 65-84 and >=85, Ethnicity, Height, Weight, BMI	SAC [2] DRY RUN [1]
1.16.	ITT	IDSL_DM1	Summary of Demographic Characteristics by Country		SAC [2] DRY RUN [1]
1.17.	Enrolled	IDSL_DM11	Summary of Age ranges	Disclosure displays / Categories: 18-64, 65-84 and >=85. Include "No Treatment" column	SAC [2] DRY RUN [1]

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
1.18.	ITT	IDSL_DM5	Summary of Race and Racial Combinations		SAC [2] DRY RUN [1]
1.19.	ITT	IDSL_DM6	Summary of Race and Racial Combination Details		SAC [2] DRY RUN [1]
Medical Conditions					
1.20.	ITT	IDSL_MH4	Summary of Current Medical Conditions		SAC [2] DRY RUN [1]
1.21.	ITT	IDSL_MH4	Summary of Past Medical Conditions		SAC [2] DRY RUN [1]
1.22.	ITT	IDSL_FH1	Summary of Family History of Cardiovascular Risk Factors		SAC [2] DRY RUN [1]
1.23.	ITT	IDSL_SU1	Summary of Substance Use at Screening	Include Smoking History, for the Current and Former Smokers include Years smoked, Cigarettes/Day, Smoking Pack Years	SAC [2] DRY RUN [1]
Disease Characteristics					
1.24.	ITT	POP_T4	Summary of Asthma Duration at Screening		SAC [2] DRY RUN [1]
1.25.	ITT	POP_T5	Summary of Exacerbation History at Screening		SAC [2] DRY RUN [1]
1.26.	ITT	POP_T6	Summary of Screening and Randomisation Peak Expiratory Flow (PEF)	Summarize using the maximum value at visit	SAC [2] DRY RUN [1]

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
1.27.	ITT	POP_T6	Summary of Screening and Randomisation Peak Expiratory Flow (PEF) by Country	Summarize using the maximum value at visit	SAC [2] DRY RUN [1]
1.28.	ITT	POP_T6	Summary of Screening and Randomisation Fractional Exhaled Nitric Oxide (FeNO)	Summarize using the maximum value at visit	SAC [2] DRY RUN [1]
Concomitant Medications					
1.29.	ITT	IDSL_CM1	Summary of Concomitant Medications Taken in the Run-in, Medications Given for Severe Exacerbation		SAC [2] DRY RUN [1]
1.30.	ITT	IDSL_CM1	Summary of On-Treatment Asthma Concomitant Medications, Medications Given for Severe Exacerbation		SAC [2] DRY RUN [1]
1.31.	ITT	IDSL_CM1	Summary of On-Treatment Asthma Concomitant Medications		SAC [2] DRY RUN [1]
1.32.	ITT	IDSL_CM1	Summary of Post-Treatment Asthma Concomitant Medications		SAC [2] DRY RUN [1]
1.33.	ITT	IDSL_CM1	Summary of Run-in Treatment Asthma Concomitant Medications		SAC [2] DRY RUN [1]
1.34.	ITT	IDSL_CM1	Summary of On-Treatment Non-Asthma Concomitant Medications		SAC [2] DRY RUN [1]
1.35.	ITT	IDSL_CM1	Summary of Post-Treatment Non-Asthma Concomitant Medications		SAC [2] DRY RUN [1]
1.36.	ITT	IDSL_CM1	Summary of Run-in Treatment Non-Asthma Concomitant Medications		SAC [2] DRY RUN [1]

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
1.37.	ITT	IDSL_CM1	Summary of Asthma Concomitant Medications Taken Prior to Screening	Ensure the observations dates are pre-screening visit 1 (there is a specific prior conmeds page in eCRF	SAC [2] DRY RUN [1]
Exposure and Treatment Compliance					
1.38.	ITT	POP_T7	Summary of Exposure to Study Medication	Post-randomisation treatment exposure	SAC [2] DRY RUN [1]
1.39.	ITT	POP_T8	Summary of the Frequency of Puffs Per Day – ELLIPTA Sensor	Programming Note: Repeat for Months 2, 3, 4, 5, 6, Months 4-6, Months 1-6 and Months 1-3.Frequency of puffs per day over the baseline and on-treatment period as defined in the Assessment Windows of RAP	SAC [2] DRY RUN [1]
1.40.	ITT	POP_T8	Summary of the Frequency of Puffs Per Day – MDI Sensor	Programming Note: Repeat for Months 2, 3, 4, 5, 6, Months 4-6, Months 1-6 and Months 1-3.Frequency of puffs per day over the baseline and on-treatment period as defined in the Assessment Windows of RAP	SAC [2] DRY RUN [1]

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
1.41.	ITT	POP_T9	Summary of Treatment Compliance	Post-randomisation compliance Note: Treatment compliance = (Total number of inhalation taken / Expected Inhalation x (Stop date - Start date + 1)) x 100 where Total Number of Inhalations Taken is the total number of doses taken from all inhalers, Expected Inhalations is equal to 1 and Start Date and Stop Date are the earliest treatment start date on or post randomisation and the latest treatment stop date recorded for all the inhalers.	SAC [2] DRY RUN [1]
Others					
1.42.	ITT	POP_T10	Summary of Incidence of Preferred Time of Dosing over the Treatment Period		SAC [2] DRY RUN [1]
1.43.	ITT	POP_T11	Summary of HCP Dashboard Review by Visit	Note: Visits 6/7/8/9 are Healthcare Professional Dashboard reviews for Arm 1 and Arm 3 [1] Action taken – Email/Text/Phone Contact	SAC [2] DRY RUN [1]
1.44.	ITT	POP_T12	Summary of Prior Prescription Details		SAC [2] DRY RUN [1]

10.8.5. Study Population Figures

Study Population Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Relvar/Breo ELLIPTA Adherence					
1.1.	ITT	POP_F1	Frequency of ELLIPTA Puffs Per Day– ELLIPTA Sensor	Programming Note: Repeat for Period: Month 1, 2, 3, 4, 5, 6, Month 4-6, Month 1-3, Month 1-6.	SAC [2] DRY RUN [1]
1.2.	ITT	POP_F1	Frequency of MDI Puffs Per Day – MDI Sensor	Programming Note: Repeat for Period: Month 1, 2, 3, 4, 5, 6, Month 4-6, Month 1-3, Month 1-6.	SAC [2] DRY RUN [1]

10.8.6. Efficacy Tables

Efficacy Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Relvar/Breo ELLIPTA Adherence					
2.1.	ITT	EFF_T1	Summary of Monthly Percentage of ELLIPTA doses taken (daily adherence) between the beginning of month 1 and the end of month 6 as determined by the maintenance sensor – Observed Data	Use the observed monthly values (month 1, 2, 3, 4, 5, 6) [1] Baseline adherence is calculated using up to the last 28 days of daily adherence data during the run-in period.	SAC [2] DRY RUN [1]

Efficacy Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.2.	ITT	EFF_T2	Summary of Statistical Analysis of Percentage of ELLIPTA doses taken (daily adherence) between the beginning of month 4 and the end of month 6 as determined by the maintenance sensor	Present comparisons Arm 1,2,3,4 v Arm 5	SAC [2] DRY RUN [1]
2.3.	ITT	EFF_T2	Summary of Statistical Analysis of Percentage of ELLIPTA doses taken (daily adherence) between the beginning of month 4 and the end of month 6 as determined by the maintenance sensor – Generalised Linear Model (Sensitivity Analysis)	Present comparisons Arm 1,2,3,4 v Arm 5	SAC [2]
2.4.	ITT	EFF_T3	Summary of Statistical Analysis of Percentage of ELLIPTA doses taken (daily adherence) between the beginning of month 4 and the end of month 6 as determined by the maintenance sensor by Baseline ACT Total Score Group	Subgroup analysis output Update footer with interaction between treatment group arm and baseline ACT Total Score Group	SAC [2] DRY RUN [1]
2.5.	ITT	EFF_T3	Summary of Statistical Analysis of Percentage of ELLIPTA doses taken (daily adherence) between the beginning of month 4 and the end of month 6 as determined by the maintenance sensor by Age Group	Subgroup analysis output Update footer with interaction between treatment group arm and baseline ACT Total Score Group	SAC [2] DRY RUN [1]
2.6.	ITT	EFF_T4	Summary of Statistical Analysis of Percentage of ELLIPTA doses taken (daily adherence) between the beginning of month 1 and the end of month 3 as determined by the maintenance sensor	Present comparisons Arms 1,2,3,4 v Arm 5	SAC [2] DRY RUN [1]
2.7.	ITT	EFF_T4	Summary of Statistical Analysis of Percentage of ELLIPTA doses taken (daily adherence) between the beginning of month 1 and the end of month 3 as determined by the maintenance sensor – Generalised Linear Model (Sensitivity Analysis)	Present comparisons Arm 1,2,3,4 v Arm 5	SAC [2]

Efficacy Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.8.	ITT	EFF_T4	Summary of Statistical Analysis of Percentage of ELLIPTA doses taken (daily adherence) between the beginning of month 1 and the end of month 6 as determined by the maintenance sensor	Present comparisons Arms 1,2,3,4 v Arm 5	SAC [2] DRY RUN [1]
2.9.	ITT	EFF_T4	Summary of Statistical Analysis of Percentage of ELLIPTA doses taken (daily adherence) between the beginning of month 1 and the end of month 6 as determined by the maintenance sensor – Generalised Linear Model (Sensitivity Analysis)	Present comparisons Arm 1,2,3,4 v Arm 5	SAC [2]
2.10.	ITT	EFF_T5	Summary of Statistical Analysis of Percentage of ELLIPTA doses taken (daily adherence) between the beginning of month 4 and the end of month 6 as determined by the maintenance sensor – Impact of Feedback of Sensor Data to HCP	Present comparisons Arm 1 v 2, Arm 3 v 4	SAC [2] DRY RUN [1]
2.11.	ITT	EFF_T6	Summary of Statistical Analysis of Percentage of ELLIPTA doses taken (daily adherence) between the beginning of month 4 and the end of month 6 as determined by the maintenance sensor – Impact of Feedback on Rescue Medication Use	Present comparisons Arm 1 v 3, Arm 2 v 4	SAC [2] DRY RUN [1]
Salbutamol MDI Rescue Medication Use					
2.12.	ITT	EFF_T1	Summary of Monthly Percentage of Rescue Free Days between the beginning of month 1 and then end of month 6 as determined by the rescue medication sensor – Observed Data	Use the observed monthly values (month 1, 2, 3, 4, 5, 6) [1] Baseline rescue free use is calculated using up to the last 28 days of daily rescue use data during the run-in period.	SAC [2] DRY RUN [1]
2.13.	ITT	EFF_T4	Summary of Statistical Analysis of Percentage of Rescue Free Days between the beginning of month 4 and the end of month 6 as determined by the maintenance sensor	Present comparisons Arms 1,2,3,4 v Arm 5	SAC [2] DRY RUN [1]

Efficacy Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.14.	ITT	EFF_T1	Summary of Total Rescue Medication Use as determined by the maintenance sensor		SAC [2] DRY RUN [1]
Asthma Control Test (ACT)					
2.15.	ITT	EFF_T1	Summary of Asthma Control Test (ACT) Total Score	Programming Note: Add screening visit score. [1] Baseline ACT total score is taken at Randomisation visit.	SAC [2] DRY RUN [1]
2.16.	ITT	EFF_T4	Summary of the Statistical Analysis of Change from Baseline (Randomisation) in ACT Total Score at Month 6		SAC [2] DRY RUN [1]
2.17.	ITT	EFF_T12	Summary of Percentage of Subjects Who Have Either an ACT Total Score >= 20 and/ or >= 3 Point Increase from Baseline in ACT Total Score	See SLS T2.1	SAC [2] DRY RUN [1]
2.18.	ITT	EFF_T13	Summary of the Statistical Analysis of Percentage of Patients Who Have an ACT Total Score of >=20 at Month 6		SAC [2] DRY RUN [1]
2.19.	ITT	EFF_T13	Summary of the Statistical Analysis of Percentage of Patients with an Increase from Baseline ≥3 in ACT Total Score at Month 6		SAC [2] DRY RUN [1]
2.20.	ITT	EFF_T13	Summary of the Statistical Analysis of Percentage of Patients Who Have Either an ACT Total Score of ≥ 20 and/or an Increase from Baseline of ≥ 3 in ACT Total Score at Month 6		SAC [2] DRY RUN [1]
Unscheduled Health Care Utilisation					
2.21.	ITT	EFF_T14	Summary of Unscheduled Asthma Related Healthcare Utilisation During the Study		SAC [2] DRY RUN [1]
2.22.	ITT	EFF_T22	Summary of Primary Care Visits relating to HCP Dashboard Review		SAC [2] DRY RUN [1]

Efficacy Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Severe On-treatment Exacerbations					
2.23.	ITT	EFF_T15	Summary of Severe On-Treatment and Post-Treatment Asthma Exacerbations	Exacerbation duration and rates will only be determined from those events that have dates of onset and resolution Include a total column	SAC [2] DRY RUN [1]
Asthma Symptom Utility Index (ASUI)					
2.24.	ITT	EFF_T1	Summary of Asthma Symptom Utility Index (ASUI) Score	Programming Note: Add screening visit score. Decimal places need to be increased by 2 dp for all values. [1] Baseline ASUI total score is taken at Randomisation visit.Note:	SAC [2] DRY RUN [1]
2.25.	ITT	EFF_T16	Summary of Statistical Analysis of Percentage of Patients Meeting a Responder Threshold of ≥ 0.09 Points Improvement (Increase) from Baseline (Randomisation) for the ASUI Total Score at Visit 10 (Month 6)		SAC [2] DRY RUN [1]
2.26.	ITT	EFF_T4	Summary of Statistical Analysis of Change from Baseline (Randomisation) in Asthma Symptom Utility Index (ASUI) Score at Visit 10 (Month 6)		SAC [2] DRY RUN [1]
St. George's Respiratory Questionnaire (SGRQ)					
2.27.	ITT	EFF_T1	Summary of St. George's Respiratory Questionnaire (SGRQ) Total Score	Programming Note: Add screening visit score. [1] Baseline SGRQ total score is taken at Randomisation visit.	SAC [2] DRY RUN [1]

Efficacy Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.28.	ITT	EFF_T13	Statistical Analysis of Percentage of Patients Meeting a Responder Threshold of ≥ 4 Points Improvement (Decrease) from Baseline (Randomisation) for the SGRQ Total Score at Visit 10 (Month 6)		SAC [2] DRY RUN [1]
2.29.	ITT	EFF_T4	Summary of Statistical Analysis of Change from Baseline (Randomisation) in St. George's Respiratory Questionnaire (SGRQ) at Visit 10 (Month 6)		SAC [2] DRY RUN [1]
Patient Activation Measure (PAM-13)					
2.30.	ITT	EFF_T1	Summary of Patient Activation Measure (PAM) 13 Total Score	Programming Note: Add randomisation visit score. [1] Baseline PAM-13 total score is taken at Screening visit.	SAC [2] DRY RUN [1]
Medication Adherence Rating Scale Asthma (MARS-A)					
2.31.	ITT	EFF_T1	Summary of Medication Adherence Report Scale-Asthma (MARS-A) Total Score	Programming Note: Add randomisation visit score. [1] Baseline MARS-A total score is taken at Screening visit.	SAC [2] DRY RUN [1]
Beliefs about Medicines (BMQ)					
2.32.	ITT	EFF_T1	Summary of BMQ General Benefit Total Score	Programming Note: Add randomisation visit score. [1] Baseline BMQ total score is taken at Screening visit.	SAC [2] DRY RUN [1]
2.33.	ITT	EFF_T1	Summary of BMQ General Harm Total Score	Programming Note: Add randomisation visit score. [1] Baseline BMQ total score is taken at Screening visit.	SAC [2] DRY RUN [1]

Efficacy Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.34.	ITT	EFF_T1	Summary of BMQ General Overuse Total Score	Programming Note: Add randomisation visit score. [1] Baseline BMQ total score is taken at Screening visit.	SAC [2] DRY RUN [1]
2.35.	ITT	EFF_T1	Summary of BMQ Specific Necessity Total Score	Programming Note: Add randomisation visit score. [1] Baseline BMQ total score is taken at Screening visit.	SAC [2] DRY RUN [1]
2.36.	ITT	EFF_T1	Summary of BMQ Specific Concern Total Score	Programming Note: Add randomisation visit score. [1] Baseline BMQ total score is taken at Screening visit.	SAC [2] DRY RUN [1]
Medical Device Incidents					
2.37.	ITT	EFF_T21	Summary of Medical Device Incidents (Sensors)		SAC [2] DRY RUN [1]
Fractional Exhaled Nitric Oxide (FeNO) and Peak Expiratory Flow (PEF)					
2.38.	ITT	EFF_T1	Summary of Fractional Exhaled Nitric Oxide (FeNO)	Programming Note: Add screening visit reading. [1] Baseline FeNO readings are taken at Randomisation visit.	SAC [2] DRY RUN [1]
2.39.	ITT	EFF_T23	Summary of Change from Baseline (Randomisation) in Fractional Exhaled Nitric Oxide (FeNO) at Month 6 (Visit 10) by Percentage of ELLIPTA doses taken (daily adherence) between the beginning of Month 4 and the end of Month 6 Group	The adherence observations should be those taken from the analysis dataset holding the observed % values. These should be grouped in quantiles using the 25th, 50th and 75th percentiles as the data group boundaries.	SAC [2] DRY RUN [1]

Efficacy Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.40.	ITT	EFF_T1	Summary of Peak Expiratory Flow (PEF)	Programming Note: Add screening visit reading. [1] Baseline FeNO readings are taken at Randomisation visit.	SAC [2] DRY RUN [1]
2.41.	ITT	EFF_T23	Summary of Change from Baseline (Randomisation) in Peak Expiratory Flow (PEF) at Month 6 (Visit 10) by Percentage of ELLIPTA doses taken (daily adherence) between the beginning of Month 4 and the end of Month 6 Group	The adherence observations should be those taken from the analysis dataset holding the observed % values. These should be grouped in quantiles using the 25th, 50th and 75th percentiles as the data group boundaries	SAC [2] DRY RUN [1]

10.8.7. Efficacy Figures

Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Relvar/Breo ELLIPTA Adherence					
2.1.	ITT	EFF_F5	Box plot of Monthly Percentage of ELLIPTA doses taken (daily adherence) as determined by the maintenance sensor – Observed Data	Month 1, 2, 3, 4, 5, and 6, ave month 1-3, ave month 4-6, ave month 1-6 across the x-axis. Monthly observed % value on the y-axis. Present each treatment over each month, off-set from one another	SAC [2] DRY RUN [1]

Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.2.	ITT	EFF_F3	Adjusted Treatment Differences for Percentage of ELLIPTA doses taken (daily adherence) between the beginning of month 4 and the end of month 6 as determined by the maintenance sensor – Comparisons Arm 1,2,3,4 v Arm 5	ANCOVA Primary endpoint analysis Present "Treatment Arm Difference (95% CI) versus Arm 5" on y-axis and "Treatment Arms" Arm 1, Arm 2, Arm 3 and Arm 4 on the x-axis.	SAC [2] DRY RUN [1]
2.3.	ITT	EFF_F4	Summary of Interaction Tests for Percentage of ELLIPTA doses taken (daily adherence) between the beginning of month 4 and the end of month 6 as determined by the maintenance sensor - – Comparisons Arm 1,2,3,4 v Arm 5	Footer: the results displays are from an ANCOVA adjusted for randomised treatment arm, baseline adherence, duration of run-in (visits), country, gender [1] age (years), covariate, and two-way interaction between randomised treatment arm and covariate [2] covariate, two-way interaction between randomised treatment group and covariate.	SAC [2] DRY RUN [1]
2.4.	ITT	EFF_F2	Scatter Plot of Percentage of ELLIPTA doses taken (daily adherence) between the beginning of month 4 and the end of month 6 as determined by the maintenance sensor (Observed values) by Age	Requires the primary endpoint observed value, each treatment arm presented with a unique symbol/pattern	SAC [2] DRY RUN [1]
2.5.	ITT	EFF_F2	Scatter Plot of Percentage of ELLIPTA doses taken (daily adherence) between the beginning of month 4 and the end of month 6 as determined by the maintenance sensor (Observed values) by Baseline ACT Total Score	Requires the primary endpoint observed value, each treatment arm presented with a unique symbol/pattern	SAC [2] DRY RUN [1]

Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.6.	ITT	EFF_F3	Adjusted Treatment Differences for Percentage of ELLIPTA doses taken (daily adherence) between the beginning of month 4 and the end of month 6 as determined by the maintenance sensor – Impact of Feedback of Sensor Data to HCP	ANCOVA Present comparisons Arm 1 v 2, Arm 3 v 4 Present "Treatment Arm Difference (95% CI)" on y-axis and "Treatment Arms" "Arm 1 vs Arm 2" and "Arm 3 vs Arm 4" on the x-axis	SAC [2] DRY RUN [1]
2.7.	ITT	EFF_F3	Adjusted Treatment Differences for Percentage of ELLIPTA doses taken (daily adherence) between the beginning of month 4 and the end of month 6 as determined by the maintenance sensor – Impact of Feedback on Rescue Medication Use	ANCOVA Present comparisons Arm 1 v 3, Arm 2 v 4 Present "Treatment Arm Difference (95% CI)" on y-axis and "Treatment Arms" "Arm 1 vs Arm 3" and "Arm 2 vs Arm 4" on the x-axis	SAC [2] DRY RUN [1]
2.8.	ITT	EFF_F3	Adjusted Treatment Differences for Percentage of ELLIPTA doses taken (daily adherence) between the beginning of month 1 and the end of month 3 as determined by the maintenance sensor – Comparisons Arm 1,2,3,4 v Arm 5	ANCOVA Present comparisons Arms 1,2,3,4 v Arm 5 Present "Treatment Arm Difference (95% CI) versus Arm 5" on y-axis and "Treatment Arms" Arm 1, Arm 2, Arm 3 and Arm 4 on the x-axis.	SAC [2] DRY RUN [1]
2.9.	ITT	EFF_F3	Adjusted Treatment Differences for Percentage of ELLIPTA doses taken (daily adherence) between the beginning of month 1 and the end of month 6 as determined by the maintenance sensor – Comparisons Arm 1,2,3,4 v Arm 5	ANCOVA Present comparisons Arms 1,2,3,4 v Arm 5 Present "Treatment Arm Difference (95% CI) versus Arm 5" on y-axis and "Treatment Arms" Arm 1, Arm 2, Arm 3 and Arm 4 on the x-axis.	SAC [2] DRY RUN [1]

Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Salbutamol MDI Rescue Medication Use					
2.10.	ITT	EFF_F5	Box plot of Monthly Percentage of Rescue Free Days as determined by the rescue medication MDI sensor	Month 1, 2, 3, 4, 5, and 6, ave month 4-6 across the x-axis. Monthly observed % value on the y-axis. Present each treatment over each month, off-set from one another	SAC [2] DRY RUN [1]
2.11.	ITT	EFF_F3	Adjusted Treatment Differences for Percentage of Rescue Free Days between the beginning of month 4 and the end of month 6 as determined by the rescue medication MDI sensor – Comparisons Arm 1,2,3,4 v Arm 5	ANCOVA Present "Treatment Arm Difference (95% CI) versus Arm 5" on y-axis and "Treatment Arms" Arm 1, Arm 2, Arm 3 and Arm 4 on the x-axis.	SAC [2] DRY RUN [1]
Asthma Control Test (ACT)					
2.12.	ITT	EFF_F3	Summary of ACT Total Score	Present "ACT Total Score (Mean± SD)" on y-axis and "Visit" on x-axis Baseline, Visit 5 (Month 1), Visit 10 (Month 6). Present mean ACT Total Score ± SD separately for treatment group at each visit, connecting the means with a solid line. Distinguish the treatment groups by different line types. [1] Baseline FeNO readings are taken at Randomisation visit.	SAC [2] DRY RUN [1]

Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.13.	ITT	EFF_F3	Summary of Statistical Analysis for Change from Baseline (Randomisation) in ACT Total Score at Month 6	(MMRM) Present "Treatment Arm Difference (95% CI) versus Arm 5" on y-axis and "Visit" on x-axis Visit 5 (Month 1), Visit 10 (Month 6). Present Difference and 95% CI change from baseline in treatment arm difference and CI separately for treatment group at each visit. Distinguish the treatment groups by different line types.	SAC [2] DRY RUN [1]
2.14.	ITT	EFF_F1	Forest Plot for Odds Ratio of Percentage of Subjects Who Have Either an ACT Total Score >= 20 and/or Increase from Baseline of >= 3 in ACT Total Score at Visit 10 (Month 6)	See example display for full visual. Present each treatment comparison per page. Within the plot Favours Arm 5 should on the left and Favour Arm x on the right per page. Three odds ratios should be presented, one for each of the ACT responder models – • ACT Total Score of >=20 • ACT Total Score Increase from Baseline ≥3 • ACT Total Score of ≥ 20 and/or an Increase from Baseline of ≥ 3	SAC [2] DRY RUN [1]

Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Asthma Symptom Utility Index (ASUI)					
2.15.	ITT	EFF_F3	Summary of ASUI Total Score	Present "ASUI Total Score (Mean ± SD)" on y-axis and "Visit" on x-axis Baseline, Visit 5 (Month 1), Visit 10 (Month 6). Present mean ASUI Total Score ± SD separately for treatment group at each visit, connecting the means with a solid line. Distinguish the treatment groups by different line types. Note: Baseline ASUI total score is taken at Randomisation visit.	SAC [2] DRY RUN [1]
2.16.	ITT	EFF_F3	Summary of Statistical Analysis for Change from Baseline (Randomisation) in ASUI Total Score at Visit 10 (Month 6)	(MMRM) Present "Treatment Arm Difference (95% CI) versus Arm 5" on y-axis and "Visit" on x-axis Visit 5 (Month 1), Visit 10 (Month 6). Present Difference and 95% CI change from baseline in treatment arm difference and CI separately for treatment group at each visit. Distinguish the treatment groups by different line types.	SAC [2] DRY RUN [1]
2.17.	ITT	EFF_F1	Forest Plot for Odds Ratio of Percentage of Patients Meeting a Responder Threshold of ≥ 0.09 Points Improvement from Baseline (Randomisation) for the ASUI Total Score at Visit 10 (Month 6)	See example display for full visual. Present each treatment comparison per page. Within the plot Favours Arm 5 should on the left and Favour Arm x on the right per page. Odds ratio should be presented for logistic reg. analysis • ASUI	SAC [2] DRY RUN [1]

Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
St. George's Respiratory Questionnaire (SGRQ)					
2.18.	ITT	EFF_F3	Summary of SGRQ Total Score	Present "SGRQ Total Score (Mean ± SD)" on y-axis and "Visit" on x-axis Baseline, Visit 5 (Month 1), Visit 10 (Month 6). Present mean SGRQ Total Score ± SD separately for treatment group at each visit, connecting the means with a solid line. Distinguish the treatment groups by different line types. Note: Baseline SGRQ total score is taken at Randomisation visit.	SAC [2] DRY RUN [1]
2.19.	ITT	EFF_F3	Summary of Statistical Analysis for Change from Baseline (Randomisation) in SGRQ Total Score at Visit 10 (Month 6)	(MMRM) Present "Treatment Arm Difference (95% CI) versus Arm 5" on y-axis and "Visit" on x-axis Visit 5 (Month 1), Visit 10 (Month 6). Present Difference and 95% CI change from baseline in treatment arm difference and CI separately for treatment group at each visit. Distinguish the treatment groups by different line types.	SAC [2] DRY RUN [1]
2.20.	ITT	EFF_F1	Forest Plot for Odds Ratio of Percentage of Patients Meeting a Responder Threshold of ≥ 4 Points Improvement from Baseline (Randomisation) for the SGRQ Total Score at Visit 10 (Month 6)	See example display for full visual. Present each treatment comparison per page. Within the plot Favours Arm 5 should on the left and Favour Arm x on the right per page. Odds ratio should be presented, for logistic reg. analysis • SGRQ	SAC [2] DRY RUN [1]

Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Fractional Exhaled Nitric Oxide (FeNO) and Peak Expiratory Flow (PEF)					
2.21.	ITT	EFF_F2	Scatter Plot of Percentage of ELLIPTA doses taken (daily adherence) between the beginning of month 4 and the end of month 6 as determined by the maintenance sensor (observed values) by Change from Baseline (Randomisation) in FeNO at Month 6 (Visit 10)	Requires the primary endpoint observed value, each treatment arm presented with a unique symbol/pattern	SAC [2] DRY RUN [1]
2.22.	ITT	EFF_F2	Scatter Plot of Percentage of ELLIPTA doses taken (daily adherence) between the beginning of month 4 and the end of month 6 as determined by the maintenance sensor (observed values) by Change from Baseline (Randomisation) in PEF at Month 6 (Visit 10)	Requires the primary endpoint observed value, each treatment arm presented with a unique symbol/pattern	SAC [2] DRY RUN [1]

10.8.8. Safety Tables

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Adverse Events (AEs)					
3.1.	ITT	SAFE_T1	Overview of On-Treatment and Post-Treatment Non-Serious AEs leading to Withdrawal, Non-Serious ADRs and SAEs	Include total column	SAC [2] DRY RUN [1]
3.2.	ITT	SAFE_T1	Overview of Run-In Treatment Non-Serious AEs leading to Withdrawal, Non-Serious ADRs and SAEs	Include total column	SAC [2] DRY RUN [1]

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.3.	Not in ITT	SAFE_T1	Overview of Run-In Treatment Non-Serious AEs leading to Withdrawal, Non-Serious ADRs and SAEs for Subjects not in ITT	Total column only	SAC [2] DRY RUN [1]
3.4.	ITT	IDSL_AE15	Summary of Common (>=1%) Non-serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences)	Include total column. Do not apply rounding. Footnote: Non-serious Adverse Events includes non-serious ADRs and non-serious AEs leading to withdrawal Disclosure table.	SAC [2] DRY RUN [1]
3.5.	ITT	IDSL_AE15	Summary of Common (>=1%) Run-In Treatment Non-Serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences)	Include total column only. Do not apply rounding. Footnote: Non-serious Adverse Events includes non-serious ADRs and non-serious AEs leading to withdrawal Disclosure table.	SAC [2] DRY RUN [1]
3.6.	Not in ITT	IDSL_AE15	Summary of Common (>=1%) Run-In Treatment Non-Serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences) for Subjects not in ITT	Include total column only. Do not apply rounding. Footnote: Non-serious Adverse Events includes non-serious ADRs and non-serious	SAC [2] DRY RUN [1]

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
				AEs leading to withdrawal Disclosure table.	
Adverse Drug Reactions (ADRs)					
3.7.	ITT	IDSL_AE1	Summary of On-Treatment Adverse Drug Reactions	Include total column. All ADRs (Non-serious and Serious)	SAC [2] DRY RUN [1]
3.8.	ITT	IDSL_AE1	Summary of Post-Treatment Adverse Drug Reactions	Include total column. All ADRs (Non-serious and Serious)	SAC [2] DRY RUN [1]
3.9.	ITT	IDSL_AE1	Summary of On-Treatment Serious Adverse Drug Reactions	Include total column	SAC [2] DRY RUN [1]
3.10.	ITT	IDSL_AE1	Summary of Post-Treatment Serious Adverse Drug Reactions	Include total column	SAC [2] DRY RUN [1]
3.11.	ITT	IDSL_AE1	Summary of On-Treatment Non-Serious Adverse Drug Reactions	Include total column	SAC [2] DRY RUN [1]
3.12.	ITT	IDSL_AE1	Summary of Post-Treatment Non-Serious Adverse Drug Reactions	Include total column	SAC [2] DRY RUN [1]

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Serious Adverse Events (SAEs)					
3.13.	ITT	IDSL_AE16	Summary of Serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences)	Include total column	SAC [2] DRY RUN [1]
3.14.	ITT	IDSL_AE16	Summary of Run-In Treatment Serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences)	Include total column	SAC [2] DRY RUN [1]
3.15.	Not in ITT	IDSL_AE16	Summary of Run-In Treatment Serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences) for Subjects not in ITT	Include total column	SAC [2] DRY RUN [1]
3.16.	ITT	IDSL_AE1	Summary of On-Treatment Serious Adverse Events	Include total column	SAC [2] DRY RUN [1]
3.17.	ITT	IDSL_AE1	Summary of Post-Treatment Serious Adverse Events	Include total column	SAC [2] DRY RUN [1]
Adverse Events leading to Withdrawal					
3.18.	ITT	IDSL_AE1	Summary of All On-treatment or Post-Treatment Adverse Events Leading to Permanent Discontinuation of Study Drug or Withdrawal from Study	Footnote: All Adverse Events includes ADRs, SAEs and Non-serious AEs leading to withdrawal Include total column	SAC [2] DRY RUN [1]

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.19.	ITT	IDSL_AE1	Summary of All On-treatment or Post-Treatment Serious Adverse Events Leading to Permanent Discontinuation of Study Drug or Withdrawal from Study	Include total column	SAC [2] DRY RUN [1]
3.20.	ITT	IDSL_AE1	Summary of On-treatment or Post-Treatment Non-Serious Adverse Events Leading to Permanent Discontinuation of Study Drug or Withdrawal from Study	Include total column	SAC [2] DRY RUN [1]
3.21.	ITT	IDSL_AE1	Summary of On-treatment or Post-Treatment Adverse Drug Reactions Leading to Permanent Discontinuation of Study Drug or Withdrawal from Study	Include total column	SAC [2] DRY RUN [1]
Adverse Events of Special Interest					
3.22.	ITT	IDSL_AE1	Summary of On-Treatment Non-Serious Adverse Drug Reactions of Special Interest	Footnote: [1] This special interest group/subgroup was defined using Special MedDRA Queries Include total column	SAC [2] DRY RUN [1]
3.23.	ITT	IDSL_AE1	Summary of On-Treatment Serious Adverse Drug Reactions of Special Interest	Footnote: [1] This special interest group/subgroup was defined using Special MedDRA Queries Include total column	SAC [2] DRY RUN [1]

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.24.	ITT	IDSL_AE1	Summary of On-Treatment Adverse Drug Reactions of Special Interest	Footnote: [1] This special interest group/subgroup was defined using Special MedDRA Queries Include total column	SAC [2] DRY RUN [1]
3.25.	ITT	IDSL_AE1	Summary of On-Treatment Serious Adverse Events of Special Interest	Footnote: [1] This special interest group/subgroup was defined using Special MedDRA Queries Include total column	SAC [2] DRY RUN [1]
Most Commonly Reported Events/Reactions					
3.26.	ITT	SAFE_T2	Top Ten Most Commonly Reported On-Treatment Adverse Events Per Treatment Group	Footnote: All Adverse Events includes ADRs, SAEs and Non-serious AEs leading to withdrawal Include total column	SAC [2] DRY RUN [1]
3.27.	ITT	SAFE_T2	Top Ten Most Commonly Reported On-Treatment Adverse Drug Reactions Per Treatment Group	ADRs only Include total column	SAC [2] DRY RUN [1]

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Plain Language Summary Displays					
3.28.	ITT	IDSL_AE15	Summary of Common (>=1%) Serious Drug-Related Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences)	Include total column	SAC [2] DRY RUN [1]
3.29.	ITT	IDSL_AE15	Summary of Common (>=1%) Non-Serious Drug-Related Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences)	Footnote: Non-serious Adverse Events includes non-serious ADRs and non-serious AEs leading to withdrawal Include total column	SAC [2] DRY RUN [1]

10.8.9. ICH Listings

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
1.	Screened	IDSL_ES7	Listing of Reasons for Screen Failure		SAC [2]
2.	Enrolled	IDSL_ES7	Listing of Reasons for Run-in Failure		SAC [2]
3.	Screened	IDSL_ES9	Listing of Subjects Who Were Rescreened		SAC [2]
4.	ITT	IDSL_ES2	Listing of Reasons for Study Withdrawal		SAC [2]
5.	ITT	IDSL_SD2	Listing of Reasons for Study Treatment Discontinuation		SAC [2]
6.	ITT	IDSL_TA1	Listing of Planned and Actual Treatments	Planned arm is determine from the RANDALL dataset and Actual treatment arm received determine from the eCRF data	SAC [2]
Exposure					
7.	ITT	IDSL_EX3	Listing of Exposure		SAC [2]
Protocol Deviations					
8.	ITT	IDSL_DV2	Listing of Important Protocol Deviations		SAC [2]
9.	ITT	IDSL_IE3	Listing of Subjects with Inclusion/Exclusion Criteria Deviations		SAC [2]
Demographic and Baseline Characteristics					
10.	ITT	IDSL_DM2	Listing of Demographic Characteristics	Include Height, Weight, BMI in the listing	SAC [2]
11.	ITT	IDSL_DM9	Listing of Race		SAC [2]

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Adverse Events					
12.	ITT	IDSL_AE8	Listing of All Adverse Events	Footnote: All Adverse Events includes ADRs, SAEs and Non-serious AEs leading to withdrawal	SAC [2]
13.	ITT	IDSL_AE7	Listing of Subject Numbers for Individual Adverse Events		SAC [2]
14.	ITT	IDSL_AE2	Listing of Relationship Between Adverse Event System Organ Class, Preferred Term and Verbatim Text		SAC [2]
15.	Not in ITT	IDSL_AE8	Listing of All Adverse Events for Subjects not in Intent-to-Treat Population	Footnote: All Adverse Events includes ADRs, SAEs and Non-serious AEs leading to withdrawal	SAC [2]
Serious and Other Significant Adverse Events					
16.	ITT	IDSL_AE8	Listing of Fatal Serious Adverse Events	Fatal and Non-Fatal SAEs are combined into a single listing for ClinPharm studies (i.e., “Listing of Serious Adverse Events”).	SAC [2]
17.	ITT	IDSL_AE8	Listing of Non-Fatal Serious Adverse Events	Fatal and Non-Fatal SAEs are combined into a single listing for ClinPharm studies (i.e., “Listing of Serious Adverse Events”).	SAC [2]
18.	ITT	IDSL_AE14	Listing of Reasons for Considering as a Serious Adverse Event		SAC [2]
19.	ITT	IDSL_AE8	Listing of All Adverse Events Leading to Withdrawal from Study / Permanent Discontinuation of Study Treatment	Footnote: All Adverse Events includes ADRs, SAEs and Non-serious AEs leading to withdrawal	SAC []

10.8.10. Non-ICH Listings

Non-ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Study Population					
20.	Enrolled	POP_L1	Listing of Subjects Screened but Not in the Intent-to-Treat Population		SAC [2]
21.	ITT	POP_L2	Listing of Subjects by Country		SAC [2]
22.	ITT	POP_L3	Listing of Family History of Cardiovascular Risk Factors		SAC [2]
23.	ITT	IDSL_SU2	Listing of Substance Use		SAC [2]
24.	ITT	POP_L4	Listing of Asthma History		SAC [2]
25.	ITT	POP_L5	Listing of Prescription Details		SAC [2]
26.	ITT	POP_L6	Listing of Preferred time of dosing		SAC [2]
27.	ITT	POP_L7	Listing of HCP Dashboard Review		SAC [2]
28.	ITT	POP_L8	Listing of Treatment Compliance		SAC [2]
Medical Conditions					
29.	ITT	IDSL_MH2	Listing of Medical Conditions		SAC [2]

Non-ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Concomitant Medications					
30.	ITT	IDSL_CM3	Listing of Concomitant Medications	Note: IDSL shell in development. Required for ClinPharm studies instead of a corresponding table. Not required for studies where a table is produced.	SAC [2]
31.	ITT	IDSL_CM6	Relationship between ATC Level 1, Ingredient and Verbatim Text		SAC [2]
Adverse Events of Special Interest					
32.	ITT	SAFE_L1	Listing of Adverse Event of Special Interest Group, Subgroup, Sub-SMQ and Preferred Term		SAC [2]
Device Malfunction					
33.	Enrolled	SAFE_L2	Listing of Relvar/Breo Ellipta Sensor Status		SAC [2]
34.	Enrolled	SAFE_L3	Listing of Salbutamol MDI Sensor Status		SAC [2]
35.	ITT	SAFE_L4	Listing of Sensor App Status		SAC [2]
36.	ITT	SAFE_L5	Listing of Device Malfunction		SAC [2]

Non-ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Efficacy					
37.	ITT	EFF_L1	Listing of Relvar/Breo ELLIPTA Adherence		SAC [2]
38.	ITT	EFF_L2	Listing of Salbutamol MDI Rescue Free Days and Total Rescue Use		SAC [2]
39.	ITT	EFF_L3	Listing of Patient Reported Outcome Questionnaire Total Scores – ACT, ASUI, MARS-A, PAM-13 and SGRQ		SAC [2]
40.	ITT	EFF_L3	Listing of Patient Reported Outcome Questionnaire Total Scores – BMQ	Replace the different questionnaire headings with the separate scales of the BMQ general and specific	SAC [2]
41.	ITT	EFF_L4	Listing of Severe Asthma Exacerbations		SAC [2]
42.	ITT	EFF_L5	Listing of Unscheduled Asthma Related Healthcare Utilisation		SAC [2]
43.	ITT	EFF_L11	Listing of Peak Expiratory Flow (PEF) and Fractional Exhaled Nitric Oxide (FeNO) Results		SAC [2]
Cardiovascular Events (Patient profiles)					
44.	Enrolled	IDSL_DEATH	Listing of All Cause Deaths		SAC [2]

10.9. Appendix 9: Example Mock Shells for Data Displays

STUDY POPULATION TABLES

POP_T1
Protocol: 207040
Population: Intent-to-Treat

Table 1.4
Summary of Attendance at Each Visit

Visit	Arm 1 (N=XXX)	Arm 2 (N=XXX)	Arm 3 (N=XXX)	Arm 4 (N=XXX)	Arm 5 (N=XXX)	Total (N=XXX)
Visit 1 (Screening)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)
Visit 2 (Run-In)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)
Visit 3 (Run-In)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)
Visit 4 (Run-In)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)
Visit 5 (Month 1)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)
Visit 6 (Month 2)	xxx (xxx%)	N/A	xxx (xxx%)	N/A	N/A	xxx (xxx%)
Visit 7 (Month 3)	xxx (xxx%)	N/A	xxx (xxx%)	N/A	N/A	xxx (xxx%)
Visit 8 (Month 4)	xxx (xxx%)	N/A	xxx (xxx%)	N/A	N/A	xxx (xxx%)
Visit 9 (Month 5)	xxx (xxx%)	N/A	xxx (xxx%)	N/A	N/A	xxx (xxx%)
Visit 10 (Month 6)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)
Visit 11 (Follow-Up)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)
Early Withdrawal	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)

Note: Visit 2/3/4 subjects may be randomised or re-entered into run-in up 3 times if ACT ≥ 20.
Note: Visits 6/7/8/9 are Healthcare Professional Dashboard reviews for Arm 1 and Arm 3.

POP_T2
Protocol: 207040
Population: Intent-to-Treat

Table 1.8
Summary of Relvar/Breo ELLIPTA Sensor Status

	Arm 1 (N=XXX)	Arm 2 (N=XXX)	Arm 3 (N=XXX)	Arm 4 (N=XXX)	Arm 5 (N=XXX)	Total (N=XXX)
Number of Subjects who Activated a Sensor	xxx	xxx	xxx	xxx	xxx	xxx
Number of Sensors Activated	xxx	xxx	xxx	xxx	xxx	xxx
Was the Sensor Returned?						
Yes	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)
No	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)
Reason sensor was not returned						
Lost	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)
Subject Lost to Follow-up	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)
Other	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)
Did the sensor malfunction?						
Yes	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)
No	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)
Did the subject permanently stop using their activated sensor during the Study						
Yes	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)
No	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)

POP_T2
Protocol: 207040
Population: Intent-to-Treat

Table 1.8
Summary of Relvar/Breo ELLIPTA Sensor Status

	Arm 1 (N=XXX)	Arm 2 (N=XXX)	Arm 3 (N=XXX)	Arm 4 (N=XXX)	Arm 5 (N=XXX)	Total (N=XXX)
Did the subject permanently stop using sensors from the study						
Yes	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)
No	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)

Note: Did the subject permanently stop using their activated sensor during the Study – How many activated sensors the subject permanently stopped using during the study.
Note: Did the subject permanently stop using sensors from the study - These the number of subjects who did not activate a new sensor after permanently stopping their previous sensor while still on the study.

POP_T2
Protocol: 207040
Population: Intent-to-Treat

Table 1.9
Summary of Salbutamol MDI Sensor Status

Programming note: Repeat as per Table 1.xxx

POP_T3
Protocol: 207040
Population: Intent-to-Treat

Table 1.10
Summary of App Status

	Arm 1 (N=XXX)	Arm 2 (N=XXX)	Arm 3 (N=XXX)	Arm 4 (N=XXX)	Arm 5 (N=XXX)	Total (N=XXX)
Did subject permanently discontinue form the Sensor App during the study?						
n	xxx	xxx	xxx	xxx	xxx	xxx
No	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)
Yes	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)

Note: As reported by data collected in the eCRF.

POP_T4
Protocol: 207040
Population: Intent-to-Treat

Table 1.24
Summary of Asthma Duration at Screening

	Arm 1 (N=XXX)	Arm 2 (N=XXX)	Arm 3 (N=XXX)	Arm 4 (N=XXX)	Arm 5 (N=XXX)	Total (N=XXX)
Duration of Asthma						
n	xxx	xxx	xxx	xxx	xxx	xxx
< 6 months	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)
>= 6 month to < 1 year	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)
>= 1 year to < 5 years	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)
>= 5 years to < 10 years	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)
>= 10 years	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)

Example : POP_T5
Protocol : 207040
Population : Intent-to-Treat

Table 1.25
Summary of Asthma Exacerbation History at Screening

	Arm 1 (N=xxx)	Arm 2 (N=xxx)	Arm 3 (N=xxx)	Arm 4 (N=xxx)	Arm 5 (N=xxx)	Total (N=xxx)
Total number of exacerbations during the 12 months prior to screening						
n	xx	xx	xx	xx	xx	xx
0	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
1	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
>1	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
Number of exacerbations during the 12 months prior to screening						
n	xx	xx	xx	xx	xx	xx
Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
SD	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Min.	xx	xx	xx	xx	xx	xx
Max.	xx	xx	xx	xx	xx	xx

Note: Number of severe asthma exacerbations reported in the 12 months prior to Screening (Visit 1)

POP_T5
Protocol: 207040
Population: Intent-to-Treat

Table 1.25
Summary of Asthma Exacerbation History at Screening

	Arm 1 (N=xxx)	Arm 2 (N=xxx)	Arm 3 (N=xxx)	Arm 4 (N=xxx)	Arm 5 (N=xxx)	Total (N=xxx)
Did not require oral/systemic corticosteroids (not involving hospitalisation)						
n	xx	xx	xx	xx	xx	xx
0	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
1	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
> 1	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
Required oral/systemic corticosteroids (not involving hospitalisation)						
n	xx	xx	xx	xx	xx	xx
0	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
1	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
> 1	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
Required hospitalisation						
n	xx	xx	xx	xx	xx	xx
0	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
1	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
> 1	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)

Note: Number of severe asthma exacerbations reported in the 12 months prior to Screening (Visit 1).

Example: POP_T6
Protocol: 207040
Population: Intent-to-Treat

Table 1.26
Summary of Screening and Baseline (Randomisation) Peak Expiratory Flow (PEF)

		Arm 1 (N=XXX)	Arm 2 (N=XXX)	Arm 3 (N=XXX)	Arm 4 (N=XXX)	Arm 5 (N=XXX)	Total (N=XXX)
Screening Pre-bronchodilator PEF (L/min)	n	xxx	xxx	xxx	xxx	xxx	xxx
	Mean	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x
	SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	Median	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x
	Min.	xx	xx	xx	xx	xx	xx
	Max.	xxx	xxx	xxx	xxx	xxx	xxx
Baseline Pre-bronchodilator PEF (L/min)	n	xxx	xxx	xxx	xxx	xxx	xxx
	Mean	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x
	SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	Median	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x
	Min.	xx	xx	xx	xx	xx	xx
	Max.	xxx	xxx	xxx	xxx	xxx	xxx

Example: POP_T6
Protocol: 207040
Population: Intent-to-Treat

Table 1.27
Summary of Screening and Baseline (Randomisation) Peak Expiratory Flow (PEF) by Country

Country: xxxxxx

Programming note: Repeat on subsequent pages by Country in alphabetical order.

Example: POP_T6
Protocol:207040
Population: Intent-to-Treat

Table 1.28
Summary of Screening and Baseline (Randomisation) Exhaled Nitric Oxide (FeNO)

		Arm 1 (N=xx)	Arm 2 (N=xx)	Arm 3 (N=xx)	Arm 4 (N=xx)	Arm 5 (N=xx)	Total (N=xx)
Screening FeNO (ppb)	n	xxx	xxx	xxx	xxx	xxx	xxx
	Mean	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x
	SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	Median	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x
	Min.	xx	xx	xx	xx	xx	xx
	Max.	xxx	xxx	xxx	xxx	xxx	xxx
Baseline FeNO (ppb)	n	xxx	xxx	xxx	xxx	xxx	xxx
	Mean	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x
	SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	Median	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x
	Min.	xx	xx	xx	xx	xx	xx
	Max.	xxx	xxx	xxx	xxx	xxx	xxx

Example: POP_T7:
Protocol: 207040
Population: Intent-to-Treat

Table 1.38
Summary of Exposure to Study Medication

Overall		Arm 1 (N=xx)	Arm 2 (N=xx)	Arm 3 (N=xx)	Arm 4 (N=xx)	Arm 5 (N=xx)	Total (N=xx)
Exposure (days) [1]	N	xxx	xxx	xxx	xxx	xxx	xxx
	Mean	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x
	SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	Median	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x
	Min.	xx	xx	xx	xx	xx	xx
	Max.	xxx	xxx	xxx	xxx	xxx	xxx
Total Subject Years (years)		xxx	xxx	xxx	xxx	xxx	xxx
Range of Exposure	<= 6 weeks	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)
	<= 12 weeks	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)
	<= 18 weeks	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)
	<= 24 weeks	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)
	> 24 weeks	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)

[1] Exposure to study medication = treatment stop date – randomisation date + 1, regardless of dosage modification.

Example POP_T8
Protocol: 207040
Population: Intent-to-Treat

Table 1.39
Summary of the Frequency of Puffs Per Day – ELLIPTA Relvar/Breo Sensor

Period		Arm 1 (N=xx)	Arm 2 (N=xx)	Arm 3 (N=xx)	Arm 4 (N=xx)	Arm 5 (N=xx)	Total (N=xx)
Baseline	Number of subjects	xx	xx	xx	xx	xx	xx
	Number of subject days	xx	xx	xx	xx	xx	xx
	0 per day [1]	xx (%)	xx (%)	xx (%)	xx (%)	xx (%)	xx (%)
	1 per day	xx (%)	xx (%)	xx (%)	xx (%)	xx (%)	xx (%)
	2 per day	xx (%)	xx (%)	xx (%)	xx (%)	xx (%)	xx (%)
	3 per day	xx (%)	xx (%)	xx (%)	xx (%)	xx (%)	xx (%)
	4 per day	xx (%)	xx (%)	xx (%)	xx (%)	xx (%)	xx (%)
	>=5 per day	xx (%)	xx (%)	xx (%)	xx (%)	xx (%)	xx (%)
Month 1	Number of subjects	xx	xx	xx	xx	xx	xx
	Number of subject days	xx	xx	xx	xx	xx	xx
	0 per day [1]	xx (%)	xx (%)	xx (%)	xx (%)	xx (%)	xx (%)
	1 per day	xx (%)	xx (%)	xx (%)	xx (%)	xx (%)	xx (%)
	2 per day	xx (%)	xx (%)	xx (%)	xx (%)	xx (%)	xx (%)
	3 per day	xx (%)	xx (%)	xx (%)	xx (%)	xx (%)	xx (%)
	4 per day	xx (%)	xx (%)	xx (%)	xx (%)	xx (%)	xx (%)
	>=5 per day	xx (%)	xx (%)	xx (%)	xx (%)	xx (%)	xx (%)

.....

Note: Number of subject days are number of days a subject has contributed to in that time period
[1]: 0 per day can constitute of: No puffs recorded, Device Incidents, or Post discontinuation of ELLIPTA maintenance sensor

Programming Note: Repeat for Months 2, 3, 4, 5, 6, Months 4-6, Months 1-6 and Months 1-3.

Example POP_T8
Protocol: 207040
Population: Intent-to-Treat

Table 1.40
Summary of the Frequency of Puffs Per Day – MDI Sensor

Period		Arm 1 (N=xx)	Arm 2 (N=xx)	Arm 3 (N=xx)	Arm 4 (N=xx)	Arm 5 (N=xx)	Total (N=xx)
Baseline	Number of subjects	xx	xx	xx	xx	xx	xx
	Number of subject days	xx	xx	xx	xx	xx	xx
	0 per day [1]	xx (%)	xx (%)	xx (%)	xx (%)	xx (%)	xx (%)
	1 per day	xx (%)	xx (%)	xx (%)	xx (%)	xx (%)	xx (%)
	2 per day	xx (%)	xx (%)	xx (%)	xx (%)	xx (%)	xx (%)
	3 per day	xx (%)	xx (%)	xx (%)	xx (%)	xx (%)	xx (%)
	4 per day	xx (%)	xx (%)	xx (%)	xx (%)	xx (%)	xx (%)
	5 per day	xx (%)	xx (%)	xx (%)	xx (%)	xx (%)	xx (%)
	6 per day	xx (%)	xx (%)	xx (%)	xx (%)	xx (%)	xx (%)
	7 per day	xx (%)	xx (%)	xx (%)	xx (%)	xx (%)	xx (%)
	8 per day	xx (%)	xx (%)	xx (%)	xx (%)	xx (%)	xx (%)
	>=9 per day	xx (%)	xx (%)	xx (%)	xx (%)	xx (%)	xx (%)
Month 1	Number of subjects	xx	xx	xx	xx	xx	xx
	Number of subject days	xx	xx	xx	xx	xx	xx
	0 per day [1]	xx (%)	xx (%)	xx (%)	xx (%)	xx (%)	xx (%)
	1 per day	xx (%)	xx (%)	xx (%)	xx (%)	xx (%)	xx (%)
	2 per day	xx (%)	xx (%)	xx (%)	xx (%)	xx (%)	xx (%)
	3 per day	xx (%)	xx (%)	xx (%)	xx (%)	xx (%)	xx (%)
	4 per day	xx (%)	xx (%)	xx (%)	xx (%)	xx (%)	xx (%)
	5 per day	xx (%)	xx (%)	xx (%)	xx (%)	xx (%)	xx (%)
.....	.....	....					

Note: Number of subject days are number of days a subject has contributed to in that time period
[1]: 0 per day can constitute of: No puffs recorded, Device Incidents, or Post discontinuation of MDI maintenance sensor
Programming Note: Repeat for Months 2, 3, 4, 5, 6 and Months 4-6.

Example POP_T9
Protocol:207040
Population: Intent-to-Treat

Table 1.41
Summary of Treatment Compliance

Overall Compliance (%)	Arm 1 (N=xx)	Arm 2 (N=xx)	Arm 3 (N=xx)	Arm 4 (N=xx)	Arm 5 (N=xx)	Total (N=xx)
n	xxx	xxx	xxx	xxx	xxx	xxx
Mean	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x
SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
Median	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x
Min.	xx	xx	xx	xx	xx	xx
Max.	xxx	xxx	xxx	xxx	xxx	xxx
< 80%	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)
80% - < 100%	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)
100% - < 120%	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)
>=120%	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)

Example POP_T10
Protocol:207040
Population: Intent-to-Treat

Table 1.42
Summary of Incidence of Preferred Time of Dosing Over the Treatment Period

%	Arm 1 (N=xxx)	Arm 2 (N=xxx)	Arm 3 (N=xxx)	Arm 4 (N=xxx)	Arm 5 (N=xxx)
n	xxx	xxx	xxx	xxx	xxx
Mean	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x
SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
Median	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x
Min.	xx	xx	xx	xx	xx
Max.	xxx	xxx	xxx	xxx	xxx

Note: A subject is considered as having taken their dose at their preferred time if the actuation time from the Relvar/Breo ELLIPTA sensor is recorded ±1 hour of their preferred time as captured on the eCRF at screening

Example POP_T11
Protocol:207040
Population: Intent-to-Treat

Table 1.43
Summary of HCP Dashboard Review by Visit

Visit: Visit 5

Actions taken post review	Arm 1 (N=xxx)	Arm 3 (N=xxx)
n	xxx	xxx
No action taken	xxx (xx%)	xxx (xx%)
Action Taken	xxx (xx%)	xxx (xx%)
Discuss adherence	xxx (xx%)	xxx (xx%)
Discuss rescue medication	xxx (xx%)	xxx (xx%)
Subject was called in for an unscheduled clinic visit	xxx (xx%)	xxx (xx%)
Other	xxx (xx%)	xxx (xx%)

Programming note: Repeat subsequent pages by visits 6,7,8, 9 and 10 and Unscheduled

Example: POP_T12
Protocol: 207040
Population: Intent-to-Treat

Table 1.44
Summary of Asthma Maintenance Therapy Prescription Details in the Previous 12 Months

	Arm 1 (N=xxx)	Arm 2 (N=xxx)	Arm 3 (N=xxx)	Arm 4 (N=xxx)	Arm 5 (N=xxx)
Actual number of prescriptions requested in previous 12 months					
n	xx	xx	xx	xx	xx
Mean	xx.x	xx.x	xx.x	xx.x	xx.x
SD	x.xx	x.xx	x.xx	x.xx	x.xx
Median	xx.x	xx.x	xx.x	xx.x	xx.x
Min.	xx	xx	xx	xx	xx
Max.	xx	xx	xx	xx	xx
Number of prescriptions requested/prescribed to be 100% compliant in previous 12 months					
n	xx	xx	xx	xx	xx
Mean	xx.x	xx.x	xx.x	xx.x	xx.x
SD	x.xx	x.xx	x.xx	x.xx	x.xx
Median	xx.x	xx.x	xx.x	xx.x	xx.x
Min.	xx	xx	xx	xx	xx
Max.	xx	xx	xx	xx	xx
Prescription Compliance in previous 12 months (%)					
n	xx	xx	xx	xx	xx
Mean	xx.x	xx.x	xx.x	xx.x	xx.x
SD	x.xx	x.xx	x.xx	x.xx	x.xx
Median	xx.x	xx.x	xx.x	xx.x	xx.x
Min.	xx	xx	xx	xx	xx
Max.	xx	xx	xx	xx	xx

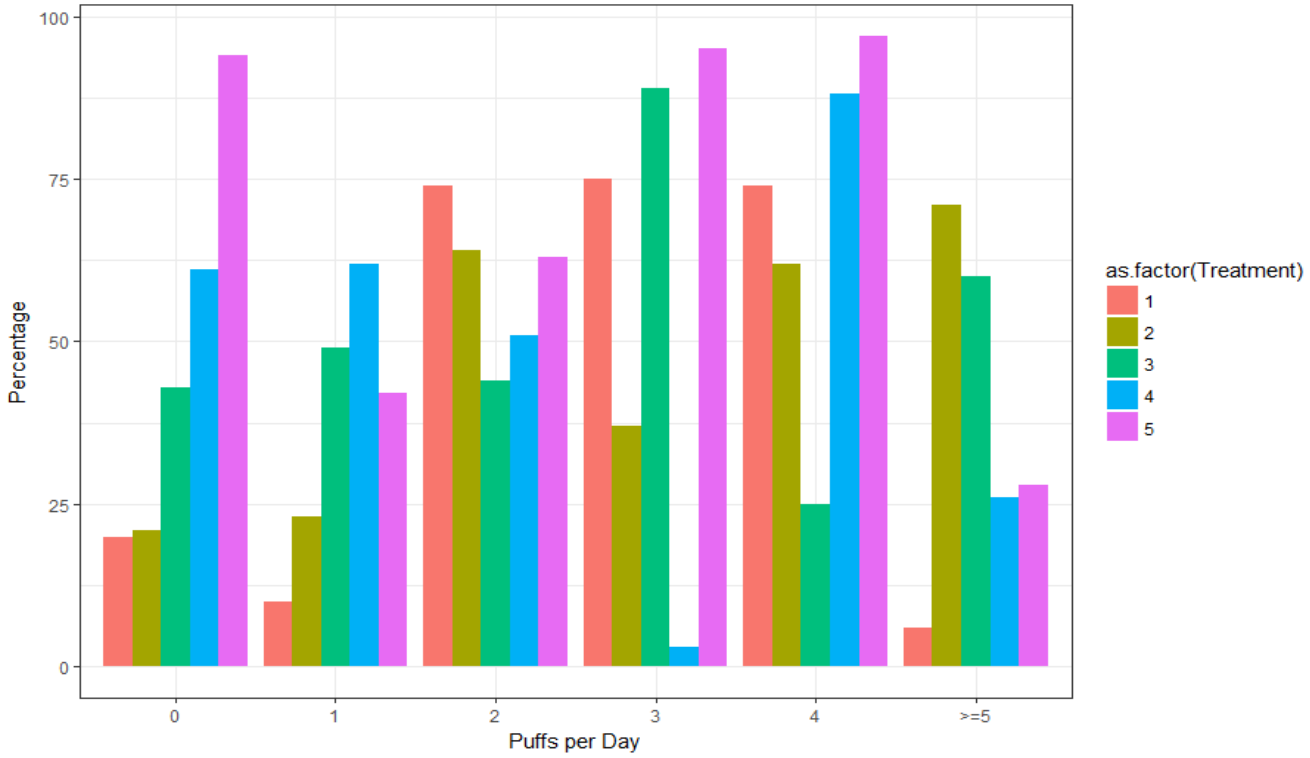
Note: Prescription compliance is calculated as 100*(Actual number of prescriptions)/(Number of prescriptions requested/prescribed to be 100% compliant)

STUDY POPULATION FIGURES

Example : POP_F1
Protocol : 207040
Population : Intent-to-Treat

Figure 1.02
Frequency of ELLIPTA Puffs Per Day

Period: Baseline



Note: 0 Puffs per day can constitute of: No puffs recorded, Device Incidents, or Post discontinuation of ELLIPTA maintenance sensor
Programming Note: Repeat for Period: Month 1, 2, 3, 4, 5, 6, Month 4-6, Month 1-3, Month 1-6.

EFFICACY TABLES

Example : EFF_T1
Protocol : 207040
Population : Intent-to-Treat

Table 2.01
Summary of Monthly Percentage of ELLIPTA doses taken (daily adherence) between the beginning of month 1 and end of month 6 as determined by the maintenance sensor – Observed Monthly Data

Month		Arm 1 (N=xxx)	Arm 2 (N=xxx)	Arm 3 (N=xxx)	Arm 4 (N=xxx)	Arm 5 (N=xxx)
Baseline (%)	n	xx	xx	xx	xx	xx
	Mean	xx.x	xx.x	xx.x	xx.x	xx.x
	SD	x.xx	x.xx	x.xx	x.xx	x.xx
	Median	xx.x	xx.x	xx.x	xx.x	xx.x
	Min.	xx	xx	xx	xx	xx
	Max.	xx	xx	xx	xx	xx
Month 1 (%)	n	xx	xx	xx	xx	xx
	Mean	xx.x	xx.x	xx.x	xx.x	xx.x
	SD	x.xx	x.xx	x.xx	x.xx	x.xx
	Median	xx.x	xx.x	xx.x	xx.x	xx.x
	Min.	xx	xx	xx	xx	xx
	Max.	xx	xx	xx	xx	xx
Average Month 1 to 6 (%)	n	xx	xx	xx	xx	xx
	Mean	xx.x	xx.x	xx.x	xx.x	xx.x
	SD	x.xx	x.xx	x.xx	x.xx	x.xx
	Median	xx.x	xx.x	xx.x	xx.x	xx.x
	Min.	xx	xx	xx	xx	xx
	Max.	xx	xx	xx	xx	xx

Programming note: Continue table to include all monthly timelines (month2, month 3, month 4, month 5, month 6, average month 4-6, average month 1-3, average month 1-6)

Example : EFF_T2
Protocol : 207040
Population : Intent-to-Treat

Table 2.02

Summary of Statistical Analysis of Percentage of ELLIPTA doses taken (daily adherence) between the beginning of month 4 and the end of month 6 as determined by the maintenance sensor

Month 4 to 6 (%)	Arm 1 (N=xxx)	Arm 2 (N=xxx)	Arm 3 (N=xxx)	Arm 4 (N=xxx)	Arm 5 (N=xxx)
n	xx	xx	xx	xx	xx
LS Mean (Std Error)	xx.x	xx.x	xx.x	xx.x	xx.x
CIS Arm vs Arm 5					
Difference	xx.x	xx.x	xx.x	xx.x	
95% C.I.	(x.xx, x.xx)	(x.xx, x.xx)	(x.xx, x.xx)	(x.xx, x.xx)	
p-value	xx.xxx	xx.xxx	xx.xxx	xx.xxx	

[1] Monthly adherence values were weighted by amount of observed data available and time on ELLIPTA between month 4 and 6

Example : EFF_T3
Protocol : 207040
Population : Intent-to-Treat

Table 2.xx

Summary of Statistical Analysis of Percentage of ELLIPTA doses taken (daily adherence) between the beginning of month 4 and the end of month 6 as determined by the maintenance sensor by Baseline ACT Total Score Group

Table 2.xx

Summary of Statistical Analysis of Percentage of ELLIPTA doses taken (daily adherence) between the beginning of month 4 and the end of month 6 as determined by the maintenance sensor by Age Group

Example : EFF_T4
Protocol : 207040
Population : Intent-to-Treat

Table 2.xx

Summary of Statistical Analysis of Percentage of ELLIPTA doses taken (daily adherence) between the beginning of month 1 and the end of month 3 as determined by the maintenance sensor

Month 1 to 3 (%)	Arm 1 (N=xxx)	Arm 2 (N=xxx)	Arm 3 (N=xxx)	Arm 4 (N=xxx)	Arm 5 (N=xxx)
n	xx	xx	xx	xx	xx
LS Mean (Std Error)	xx.x	xx.x	xx.x	xx.x	xx.x
CIS Arm vs Arm 5					
Difference	xx.x	xx.x	xx.x	xx.x	
95% C.I.	(x.xx, x.xx)	(x.xx, x.xx)	(x.xx, x.xx)	(x.xx, x.xx)	
p-value	xx.xxx	xx.xxx	xx.xxx	xx.xxx	

Example : EFF_T4
Protocol : 207040
Population : Intent-to-Treat

Table 2.xx
Summary of Statistical Analysis of Percentage of ELLIPTA doses taken (daily adherence) between the beginning of month 1 and the end of month 6 as determined by the maintenance sensor

Month 1 to 6 (%)	Arm 1 (N=xxx)	Arm 2 (N=xxx)	Arm 3 (N=xxx)	Arm 4 (N=xxx)	Arm 5 (N=xxx)
n	xx	xx	xx	xx	xx
LS Mean (Std Error)	xx.x	xx.x	xx.x	xx.x	xx.x
CIS Arm vs Arm 5					
Difference	xx.x	xx.x	xx.x	xx.x	
95% C.I.	(x.xx, x.xx)	(x.xx, x.xx)	(x.xx, x.xx)	(x.xx, x.xx)	
p-value	xx.xxx	xx.xxx	xx.xxx	xx.xxx	

Example : EFF_T5
Protocol : 207040
Population : Intent-to-Treat

Table 2.xx

Summary of Statistical Analysis of Percentage of ELLIPTA doses taken (daily adherence) between the beginning of month 4 and the end of month 6 as determined by the maintenance sensor – Impact of Feedback of Sensor Data to HCP

Month 4 to 6 (%)	Arm 1 (N=xxx)	Arm 2 (N=xxx)	Arm 3 (N=xxx)	Arm 4 (N=xxx)	Arm 5 (N=xxx)
n	xx	xx	xx	xx	xx
LS Mean (Std Error)	xx.x	xx.x	xx.x	xx.x	xx.x
CIS Arm 1 vs Arm 2					
Difference	xx.x				
95% C.I.	(x.xx, x.xx)				
p-value	xx.xxx				
CIS Arm 3 vs Arm 4					
Difference			xx.x		
95% C.I.			(x.xx, x.xx)		
p-value			xx.xxx		

Example : EFF_T6
Protocol : 207040
Population : Intent-to-Treat

Table 2.xx

Summary of Statistical Analysis of Percentage of ELLIPTA doses taken (daily adherence) between the beginning of month 4 and the end of month 6 as determined by the maintenance sensor – Impact of Feedback on Rescue Medication Use

Month 4 to 6 (%)	Arm 1 (N=xxx)	Arm 2 (N=xxx)	Arm 3 (N=xxx)	Arm 4 (N=xxx)	Arm 5 (N=xxx)
n	xx	xx	xx	xx	xx
LS Mean (Std Error)	xx.x	xx.x	xx.x	xx.x	xx.x
CIS Arm 1 vs Arm 3					
Difference	xx.x				
95% C.I.	(x.xx, x.xx)				
p-value	xx.xxx				
CIS Arm 2 vs Arm 4		xx.x			
Difference		(x.xx, x.xx)			
95% C.I.		xx.xxx			
p-value					

Example : EFF_T1
Protocol : 207040
Population : Intent-to-Treat

Table 2.xx

Summary of Monthly Percentage of Rescue Free Days between the beginning of month 1 and then end of month 6 as determine by the MDI rescue medication sensor – Observed Data

Month		Arm 1 (N=xxx)	Arm 2 (N=xxx)	Arm 3 (N=xxx)	Arm 4 (N=xxx)	Arm 5 (N=xxx)
Baseline (%)	n	xx	xx	xx	xx	xx
	Mean	xx.x	xx.x	xx.x	xx.x	xx.x
	SD	x.xx	x.xx	x.xx	x.xx	x.xx
	Median	xx.x	xx.x	xx.x	xx.x	xx.x
	Min.	xx	xx	xx	xx	xx
	Max.	xx	xx	xx	xx	xx
Month 1 (%)	n	xx	xx	xx	xx	xx
	Mean	xx.x	xx.x	xx.x	xx.x	xx.x
	SD	x.xx	x.xx	x.xx	x.xx	x.xx
	Median	xx.x	xx.x	xx.x	xx.x	xx.x
	Min.	xx	xx	xx	xx	xx
	Max.	xx	xx	xx	xx	xx
Average Month 1 to 6 (%)	n	xx	xx	xx	xx	xx
	Mean	xx.x	xx.x	xx.x	xx.x	xx.x
	SD	x.xx	x.xx	x.xx	x.xx	x.xx
	Median	xx.x	xx.x	xx.x	xx.x	xx.x
	Min.	xx	xx	xx	xx	xx
	Max.	xx	xx	xx	xx	xx

Programming note: Continue table to include all monthly timelines (month 2, month 3, month 4, month 5, month 6, average month 4-6)

Example : EFF_T4
Protocol : 207040
Population : Intent-to-Treat

Table 2.xx

Summary of Statistical Analysis of Percentage of Rescue Free Days between the beginning of month 4 and then end of month 6 as determine by the MDI rescue medication sensor

Month 4 to 6 (%)	Arm 1 (N=xxx)	Arm 2 (N=xxx)	Arm 3 (N=xxx)	Arm 4 (N=xxx)	Arm 5 (N=xxx)
n	xx	xx	xx	xx	xx
LS Mean (Std Error)	xx.x	xx.x	xx.x	xx.x	xx.x
CIS Arm vs Arm 5					
Difference	xx.x	xx.x	xx.x	xx.x	
95% C.I.	(x.xx, x.xx)	(x.xx, x.xx)	(x.xx, x.xx)	(x.xx, x.xx)	
p-value	xx.xxx	xx.xxx	xx.xxx	xx.xxx	

[1] Monthly adherence values were weighted by amount of observed data available and time on ELLIPTA between month 4 and 6

Example : EFF_T1
Protocol : 207040
Population : Intent-to-Treat

Table 2.xx

Summary of Total Rescue Use as Determined by the Maintenance Sensor

Month		Arm 1 (N=xxx)	Arm 2 (N=xxx)	Arm 3 (N=xxx)	Arm 4 (N=xxx)	Arm 5 (N=xxx)
Baseline	n	xx	xx	xx	xx	xx
	Mean	xx.x	xx.x	xx.x	xx.x	xx.x
	SD	x.xx	x.xx	x.xx	x.xx	x.xx
	Median	xx.x	xx.x	xx.x	xx.x	xx.x
	Min.	xx	xx	xx	xx	xx
	Max.	xx	xx	xx	xx	xx
Month 1	n	xx	xx	xx	xx	xx
	Mean	xx.x	xx.x	xx.x	xx.x	xx.x
	SD	x.xx	x.xx	x.xx	x.xx	x.xx
	Median	xx.x	xx.x	xx.x	xx.x	xx.x
	Min.	xx	xx	xx	xx	xx
	Max.	xx	xx	xx	xx	xx
Average Month 1 to 6	n	xx	xx	xx	xx	xx
	Mean	xx.x	xx.x	xx.x	xx.x	xx.x
	SD	x.xx	x.xx	x.xx	x.xx	x.xx
	Median	xx.x	xx.x	xx.x	xx.x	xx.x
	Min.	xx	xx	xx	xx	xx
	Max.	xx	xx	xx	xx	xx

Programming note: Continue table to include all monthly timelines (month 2, month 3, month 4, month 5, month 6, average month 4-6)

Example : EFF_T1
Protocol : 207040
Population : Intent-to-Treat

Table 2.xx
Summary of Asthma Control Test (ACT) Total Score

Visit		Arm 1 (N=xxx)	Arm 2 (N=xxx)	Arm 3 (N=xxx)	Arm 4 (N=xxx)	Arm 5 (N=xxx)
Baseline [1]	n	xx	xx	xx	xx	xx
	Mean	xx.x	xx.x	xx.x	xx.x	xx.x
	SD	x.xx	x.xx	x.xx	x.xx	x.xx
	Median	xx.x	xx.x	xx.x	xx.x	xx.x
	Min.	xx	xx	xx	xx	xx
	Max.	xx	xx	xx	xx	xx
Visit 5 (Month 1)	n	xx	xx	xx	xx	xx
	Mean	xx.x	xx.x	xx.x	xx.x	xx.x
	SD	x.xx	x.xx	x.xx	x.xx	x.xx
	Median	xx.x	xx.x	xx.x	xx.x	xx.x
	Min.	xx	xx	xx	xx	xx
	Max.	xx	xx	xx	xx	xx
Change from Baseline at Visit 5 (Month 1)	n	xx	xx	xx	xx	xx
	Mean	xx.x	xx.x	xx.x	xx.x	xx.x
	SD	x.xx	x.xx	x.xx	x.xx	x.xx
	Median	xx.x	xx.x	xx.x	xx.x	xx.x

[1] Baseline ACT total score is taken at randomisation visit.
Programming note: repeat for Visit 10 (Month 6), Change from Baseline at Visit 10 (Month 6), Early Withdrawal, Change from Baseline at Early withdrawal

Example : EFF_T4
Protocol : 207040
Population: Intent-to-Treat

Table 2.xx
Summary of the Statistical Analysis of Change from Baseline (Randomisation) in ACT Total Score at Visit 10 (Month 6)

	Arm 1 (N=xxx)	Arm 2 (N=xxx)	Arm 3 N=xxx)	Arm 4 (N=xxx)	Arm 5 (N=xxx)
n	xx	xx	xx	xx	xx
LS Mean Change (SE)	xx.xx (x.xxx)	xx.xx (x.xxx)	xx.xx (x.xxx)	xx.xx (x.xxx)	xx.xx (x.xxx)
CIS Arm vs. Arm 5					
Difference	xx.x	xx.x	xx.x	xx.x	
95% CI	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)	
p-value	x.xxx	x.xxx	x.xxx	x.xxx	

Note: The analysis method was an MMRM adjusted for randomised treatment arm, (visit), baseline ACT total score, randomised treatment arm-by-visit interaction, baseline ACT total score-by-visit interaction, gender, age, country and subject fitted as a random factor.
Note: The Restricted Maximum Likelihood (REML) estimation approach was used with a default covariance structure of unstructured.

Programming note: Should computational issues be encountered when using an unstructured covariance structure, other structures including AR1 and CS should be considered and the second footnote updated as appropriate.

Example : EFF_T12
Protocol : 207040
Population : Intent-to-Treat

Table 2.xx
Summary of Percentage of Subjects Who Have Either an ACT Total Score of >= 20 and/or >= 3 Point Increase from Baseline (Randomisation) in ACT Total Score

Visit		Arm 1 (N=xxx)	Arm 2 (N=xxx)	Arm 3 (N=xxx)	Arm 4 (N=xxx)	Arm 5 (N=xxx)
Visit 5 (Month 1)	n	xxx	xxx	xxx	xxx	xxx
	ACT Total Score >= 20 and/or >= 3 Point Increase from Baseline	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)
	ACT Total Score >= 20	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)
	>= 3 Point Increase from Baseline	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)
Visit 10 (Month 6)	n	xxx	xxx	xxx	xxx	xxx
	ACT Total Score >= 20 and/or >= 3 Point Increase from Baseline	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)
	ACT Total Score >= 20	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)
	>= 3 Point Increase from Baseline	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)

Example : EFF_T13
Protocol : 207040
Population : Intent-to-Treat

Table 2.xx
Summary of the Statistical Analysis of Percentage of Subjects Who Have an ACT Total Score of ≥ 20 at Visit 10 (Month 6)

	Arm 1 (N=xxx)	Arm 2 (N=xxx)	Arm 3 (N=xxx)	Arm 4 (N=xxx)	Arm 5 (N=xxx)
n	xxx	xxx	xxx	xxx	xxx
Responder [1]	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)
Non-Responder	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)
CIS Arm v Arm 5					
Adjusted Odds Ratio	x.xx	x.xx	x.xx	x.xx	
95% C.I.	(x.xx, x.xx)	(x.xx, x.xx)	(x.xx, x.xx)	(x.xx, x.xx)	
p-value	x.xx	x.xx	x.xx	x.xx	

[1] Responder is defined as an ACT total score >= 20.
Note: The analysis method was logistic regression adjusted for randomised treatment arm, baseline ACT total score, country, gender and age

Example : EFF_T13
Protocol : 207040
Population : Intent-to-Treat

Table 2.xx

Summary of the Statistical Analysis of Percentage of Subjects with an Increase from Baseline (Randomisation) ≥3 in ACT Total Score at Visit 10 (Month 6)

	Arm 1 (N=xxx)	Arm 2 (N=xxx)	Arm 3 (N=xxx)	Arm 4 (N=xxx)	Arm 5 (N=xxx)
n	xxx	xxx	xxx	xxx	xxx
Responder [1]	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)
Non-Responder	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)
CIS Arm v Arm 5					
Adjusted Odds Ratio	x.xx	x.xx	x.xx	x.xx	
95% C.I.	(x.xx, x.xx)	(x.xx, x.xx)	(x.xx, x.xx)	(x.xx, x.xx)	
p-value	x.xx	x.xx	x.xx	x.xx	

[1] Responder is defined as an increase from baseline of >= 3 in ACT total score.
Note: The analysis method was logistic regression adjusted for randomised treatment arm, baseline ACT total score, country, gender and age

Example : EFF_T13
Protocol : 207040
Population : Intent-to-Treat

Table 2.xx
Summary of the Statistical Analysis of Percentage of Subjects Who Have Either an ACT Total Score of >=20 and/or an Increase from Baseline (Randomisation) of >=3 in ACT Total Score at Visit 10 (Month 6)

	Arm 1 (N=xxx)	Arm 2 (N=xxx)	Arm 3 (N=xxx)	Arm 4 (N=xxx)	Arm 5 (N=xxx)
n	xxx	xxx	xxx	xxx	xxx
Responder [1]	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)
Non-Responder	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)
CIS Arm v Arm 5					
Adjusted Odds Ratio	x.xx	x.xx	x.xx	x.xx	
95% C.I.	(x.xx, x.xx)	(x.xx, x.xx)	(x.xx, x.xx)	(x.xx, x.xx)	
p-value	x.xx	x.xx	x.xx	x.xx	

[1] Responder is defined as an ACT total score >= 20 and/or an increase from baseline of >= 3.
Note: The analysis method was logistic regression adjusted for randomised treatment arm, baseline ACT total score, country, gender and age

Example : EFF_T14
Protocol : 207040
Population : Intent-to-Treat

Table 2.xx
Summary of Unscheduled Asthma Related Healthcare Resource Utilisation During the Study

		Arm 1 (N=XXX)	Arm 2 (N=XXX)	Arm 3 (N=XXX)	Arm 4 (N=XXX)	Arm 5 (N=XXX)
Had unscheduled healthcare utilisation	n (%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)
Number of telephone calls	n	xxx	xxx	xxx	xxx	xxx
	0	xxx (%)	xxx (%)	xxx (%)	xxx (%)	xxx (%)
	1	xxx (%)	xxx (%)	xxx (%)	xxx (%)	xxx (%)
	2	xxx (%)	xxx (%)	xxx (%)	xxx (%)	xxx (%)
	3	xxx (%)	xxx (%)	xxx (%)	xxx (%)	xxx (%)
	>3	xxx (%)	xxx (%)	xxx (%)	xxx (%)	xxx (%)
	Total [1]	xxx	xxx	xxx	xxx	xxx
Number of home visits (Day)	n	xxx	xxx	xxx	xxx	xxx
	0	xxx (%)	xxx (%)	xxx (%)	xxx (%)	xxx (%)
	1	xxx (%)	xxx (%)	xxx (%)	xxx (%)	xxx (%)
	2	xxx (%)	xxx (%)	xxx (%)	xxx (%)	xxx (%)
	3	xxx (%)	xxx (%)	xxx (%)	xxx (%)	xxx (%)
	>3	xxx (%)	xxx (%)	xxx (%)	xxx (%)	xxx (%)
	Total [1]	xxx	xxx	xxx	xxx	xxx

[1] Total number of days/contacts across all subjects.

Example : EFF_T14
Protocol : 207040
Population : Intent-to-Treat

Table 2.xx
Summary of Unscheduled Asthma Related Healthcare Resource Utilisation During the Study

		Arm 1 (N=XXX)	Arm 2 (N=XXX)	Arm 3 (N=XXX)	Arm 4 (N=XXX)	Arm 5 (N=XXX)
Number of home visits (Night)	n	xxx	xxx	xxx	xxx	xxx
	0	xxx (%)	xxx (%)	xxx (%)	xxx (%)	xxx (%)
	1	xxx (%)	xxx (%)	xxx (%)	xxx (%)	xxx (%)
	2	xxx (%)	xxx (%)	xxx (%)	xxx (%)	xxx (%)
	3	xxx (%)	xxx (%)	xxx (%)	xxx (%)	xxx (%)
	>3	xxx (%)	xxx (%)	xxx (%)	xxx (%)	xxx (%)
	Total [1]	xxx	xxx	xxx	xxx	xxx
Number of office/practice visits	n	xxx	xxx	xxx	xxx	xxx
	0	xxx (%)	xxx (%)	xxx (%)	xxx (%)	xxx (%)
	1	xxx (%)	xxx (%)	xxx (%)	xxx (%)	xxx (%)
	2	xxx (%)	xxx (%)	xxx (%)	xxx (%)	xxx (%)
	3	xxx (%)	xxx (%)	xxx (%)	xxx (%)	xxx (%)
	>3	xxx (%)	xxx (%)	xxx (%)	xxx (%)	xxx (%)
	Total [1]	xxx	xxx	xxx	xxx	xxx
Number of urgent care/outpatient visits	n	Xxx	xxx	xxx	xxx	xxx
	0	xxx (%)	xxx (%)	xxx (%)	xxx (%)	xxx (%)
	1	xxx (%)	xxx (%)	xxx (%)	xxx (%)	xxx (%)
	2	xxx (%)	xxx (%)	xxx (%)	xxx (%)	xxx (%)
	3	xxx (%)	xxx (%)	xxx (%)	xxx (%)	xxx (%)
	>3	xxx (%)	xxx (%)	xxx (%)	xxx (%)	xxx (%)
	Total [1]	xxx	xxx	xxx	xxx	xxx

[1] Total number of days/ contacts across all subjects.

Example : EFF_T14
Protocol : 207040
Population : Intent-to-Treat

Table 2.xx
Summary of Unscheduled Asthma Related Healthcare Resource Utilisation During the Study

		Arm 1 (N=XXX)	Arm 2 (N=XXX)	Arm 3 (N=XXX)	Arm 4 (N=XXX)	Arm 5 (N=XXX)
Number of emergency room visits	n	xxx	xxx	xxx	xxx	xxx
	0	xxx (%)	xxx (%)	xxx (%)	xxx (%)	xxx (%)
	1	xxx (%)	xxx (%)	xxx (%)	xxx (%)	xxx (%)
	2	xxx (%)	xxx (%)	xxx (%)	xxx (%)	xxx (%)
	3	xxx (%)	xxx (%)	xxx (%)	xxx (%)	xxx (%)
	>3	xxx (%)	xxx (%)	xxx (%)	xxx (%)	xxx (%)
	Total [1]	xxx	xxx	xxx	xxx	xxx
Number of days inpatient hospitalisation days	n	xxx	xxx	xxx	xxx	xxx
	0	xxx (%)	xxx (%)	xxx (%)	xxx (%)	xxx (%)
	1	xxx (%)	xxx (%)	xxx (%)	xxx (%)	xxx (%)
	2	xxx (%)	xxx (%)	xxx (%)	xxx (%)	xxx (%)
	3	xxx (%)	xxx (%)	xxx (%)	xxx (%)	xxx (%)
	>3	xxx (%)	xxx (%)	xxx (%)	xxx (%)	xxx (%)
	Total [1]	xxx	xxx	xxx	xxx	xxx

[1] Total number of days/ contacts across all subjects.

Example : EFF_T22
Protocol : 207040
Population : Intent-to-Treat

Table 2.xx
Summary of Primary Care Visits relating to HCP Dashboard Review

	Arm 1 (N=XXX)	Arm 2 (N=XXX)	Arm 3 (N=XXX)	Arm 4 (N=XXX)	Arm 5 (N=XXX)
Number of Subjects called in for an unscheduled clinic visit	xx	xx	xx	xx	xx
Number of unscheduled clinic visits	xx	xx	xx	xx	xx

Example : EFF_T15
Protocol : 207040
Population : Intent-to-Treat

Table 2.xx
Summary of Severe On-Treatment and Post-Treatment Asthma Exacerbations

Time: On-Treatment

	Arm 1 (N=xxx)	Arm 2 (N=xxx)	Arm 3 (N=xxx)	Arm 4 (N=xxx)	Arm 5 (N=xxx)	Total (N=xxx)
No. of subjects with one or more severe asthma exacerbation	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
Total no. of severe asthma exacerbations	xx	xx	xx	xx	xx	xx
Number of severe asthma exacerbations per subject						
0	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
1	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
> 1	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
Duration of severe asthma exacerbation (days) [1]						
n	xx	xx	xx	xx	xx	xx
Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
SD	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Min.	xx	xx	xx	xx	xx	xx
Max.	xx	xx	xx	xx	xx	xx

[1] Summary only includes exacerbations for which a date of onset and resolution were provided in the eCRF.
Programming Note: Repeat for Post-Treatment

Example : EFF_T15
Protocol : 207040
Population : Intent-to-Treat

Table 2.xx
Summary of Severe On-Treatment and Post-Treatment Asthma Exacerbations

Time: On-Treatment

	Arm 1 (N=xxx)	Arm 2 (N=xxx)	Arm 3 (N=xxx)	Arm 4 (N=xxx)	Arm 5 (N=xxx)	Total (N=xxx)
No. of subjects with an exacerbation outcome						
Resolved	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
Fatal	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
Not resolved	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
No. of subjects with exacerbations:						
Requiring use of systemic/oral corticosteroids	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
Leading to hospitalisation	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
Requiring emergency room visit	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
No. of subjects with exacerbations requiring intubation	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
No. of subjects with exacerbations leading to withdrawal from study	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
Annual severe asthma exacerbation rate [1]						
n	xx	xx	xx	xx	xx	xx
Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
SD	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Min.	xx	xx	xx	xx	xx	xx
Max.	xx	xx	xx	xx	xx	xx

[1] Summary only includes exacerbations for which a date of onset and resolution were provided in the eCRF..

Example EFF_T1
Protocol : 207040
Population : Intent-to-Treat

Table 2.xx
Summary of Asthma Symptom Utility Index (ASUI) Score

Visit		Arm 1 (N=xxx)	Arm 2 (N=xxx)	Arm 3 (N=xxx)	Arm 4 (N=xxx)	Arm 5 (N=xxx)
Baseline [1]	n	xx	xx	xx	xx	xx
	Mean	xx.x	xx.x	xx.x	xx.x	xx.x
	SD	x.xx	x.xx	x.xx	x.xx	x.xx
	Median	xx.x	xx.x	xx.x	xx.x	xx.x
	Min.	xx	xx	xx	xx	xx
	Max.	xx	xx	xx	xx	xx
Visit 5 (Month 1)	n	xx	xx	xx	xx	xx
	Mean	xx.x	xx.x	xx.x	xx.x	xx.x
	SD	x.xx	x.xx	x.xx	x.xx	x.xx
	Median	xx.x	xx.x	xx.x	xx.x	xx.x
	Min.	xx	xx	xx	xx	xx
	Max.	xx	xx	xx	xx	xx
Change from Baseline at Visit 5 (Month 1)	n	xx	xx	xx	xx	xx
	Mean	xx.x	xx.x	xx.x	xx.x	xx.x
	SD	x.xx	x.xx	x.xx	x.xx	x.xx
	Median	xx.x	xx.x	xx.x	xx.x	xx.x
	Min.	xx	xx	xx	xx	xx
	Max.	xx	xx	xx	xx	xx

[1] Baseline ASUI total score is taken at randomisation visit.
Programming note: repeat, Visit 10 (Month 6), Change from Baseline at Visit 10 (Month 6), Early Withdrawal

Example EFF_T16
Protocol : 207040
Population : Intent-to-Treat

Table 2.xx
Summary of Statistical Analysis of Percentage of Subjects Meeting a Responder Threshold of 0.09 Points Improvement (Increase) from Baseline (Randomisation) for the ASUI Total Score at Visit 10 (Month 6)

	Arm 1 (N=xxx)	Arm 2 (N=xxx)	Arm 3 (N=xxx)	Arm 4 (N=xxx)	Arm 5 (N=xxx)
n	xxx	xxx	xxx	xxx	xxx
Responder [1]	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)
Non-Responder	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)
CIS Arm v Arm 5					
Adjusted Odds Ratio	x.xx	x.xx	x.xx	x.xx	
95% C.I.	(x.xx, x.xx)	(x.xx, x.xx)	(x.xx, x.xx)	(x.xx, x.xx)	
p-value	x.xx	x.xx	x.xx	x.xx	

[1] Responder is defined as an ASUI total score >= 0.09 points increase from baseline.
Note: The analysis method was logistic regression adjusted for randomised treatment arm, baseline ASUI total score, country, gender and age

Example : EFF_T4
Protocol : 207040
Population: Intent-to-Treat

Table 2.xx
Summary of the Statistical Analysis of Change from Baseline (Randomisation) in Asthma Symptom Utility Index (ASUI) Total Score at Visit 10 (Month 6)

	Arm 1 (N=xxx)	Arm 2 (N=xxx)	Arm 3 N=xxx)	Arm 4 (N=xxx)	Arm 5 (N=xxx)
n	xx	xx	xx	xx	xx
LS Mean Change (SE)	xx.xx (x.xxx)	xx.xx (x.xxx)	xx.xx (x.xxx)	xx.xx (x.xxx)	xx.xx (x.xxx)
CIS Arm vs. Arm 5					
Difference	xx.x	xx.x	xx.x	xx.x	
95% CI	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)	
p-value	x.xxx	x.xxx	x.xxx	x.xxx	

Note: The analysis method was an MMRM adjusted for randomised treatment arm, visit, baseline ASUI total score, randomised treatment arm-by-visit interaction, baseline ASUI total score-by-visit interaction, gender, age, country and subject fitted as a random factor.
Note: The Restricted Maximum Likelihood (REML) estimation approach was used with a default covariance structure of unstructured.

Programming note: Should computational issues be encountered when using an unstructured covariance structure, other structures including AR1 and CS should be considered and the second footnote updated as appropriate.

Example : EFF_T1
Protocol : 207040
Population : Intent-to-Treat

Table 2.xx
Summary of St. George's Respiratory Questionnaire (SGRQ) Total Score

Visit		Arm 1 (N=xxx)	Arm 2 (N=xxx)	Arm 3 (N=xxx)	Arm 4 (N=xxx)	Arm 5 (N=xxx)
Baseline [1]	n	xx	xx	xx	xx	xx
	Mean	xx.x	xx.x	xx.x	xx.x	xx.x
	SD	x.xx	x.xx	x.xx	x.xx	x.xx
	Median	xx.x	xx.x	xx.x	xx.x	xx.x
	Min.	xx	xx	xx	xx	xx
	Max.	xx	xx	xx	xx	xx
Visit 5 (Month 1)	n	xx	xx	xx	xx	xx
	Mean	xx.x	xx.x	xx.x	xx.x	xx.x
	SD	x.xx	x.xx	x.xx	x.xx	x.xx
	Median	xx.x	xx.x	xx.x	xx.x	xx.x
	Min.	xx	xx	xx	xx	xx
	Max.	xx	xx	xx	xx	xx
Change from Baseline at Visit 5 (Month 1)	n	xx	xx	xx	xx	xx
	Mean	xx.x	xx.x	xx.x	xx.x	xx.x
	SD	x.xx	x.xx	x.xx	x.xx	x.xx
	Median	xx.x	xx.x	xx.x	xx.x	xx.x
	Min.	xx	xx	xx	xx	xx
	Max.	xx	xx	xx	xx	xx

[1] Baseline SGRQ total score is taken at randomisation visit
Programming note: repeat for Visit 10 (Month 6), Change from Baseline at Visit 10 (Month 6), Early Withdrawal

Example : EFF_T13
Protocol : 207040
Population : Intent-to-Treat

Table 2.xx
Summary of the Statistical Analysis of Percentage of Subjects Meeting a Responder Threshold of ≥4 Points Improvement (Decrease) from Baseline (Randomisation) for the SGRQ Total Score at Visit 10 (Month 6)

	Arm 1 (N=xxx)	Arm 2 (N=xxx)	Arm 3 (N=xxx)	Arm 4 (N=xxx)	Arm 5 (N=xxx)
n	xxx	xxx	xxx	xxx	xxx
Responder [1]	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)
Non-Responder	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)
CIS Arm v Arm 5					
Adjusted Odds Ratio	x.xx	x.xx	x.xx	x.xx	
95% C.I.	(x.xx, x.xx)	(x.xx, x.xx)	(x.xx, x.xx)	(x.xx, x.xx)	
p-value	x.xx	x.xx	x.xx	x.xx	

[1] Responder is defined as SGRQ total score >= 4 points decrease from baseline.
Note: The analysis method was logistic regression adjusted for randomised treatment arm, baseline SGRQ total score, country, gender and age

Example : EFF_T
Protocol : 207040
Population : Intent-to-Treat

Table 2.xx
Summary of the Statistical Analysis of Change from Baseline (Randomisation) in SGRQ at Visit 10 (Month 6)

	Arm 1 (N=xxx)	Arm 2 (N=xxx)	Arm 3 N=xxx)	Arm 4 (N=xxx)	Arm 5 (N=xxx)
n	xx	xx	xx	xx	xx
LS Mean Change (SE)	xx.xx (x.xxx)	xx.xx (x.xxx)	xx.xx (x.xxx)	xx.xx (x.xxx)	xx.xx (x.xxx)
CIS Arm vs. Arm 5					
Difference	xx.x	xx.x	xx.x	xx.x	
95% CI	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)	
p-value	x.xxx	x.xxx	x.xxx	x.xxx	

Note: The analysis method was an MMRM adjusted for randomised treatment arm, visit, baseline SGRQ total score, randomised treatment arm-by-visit interaction, baseline SGRQ total score-by-visit interaction, gender, age, country and subject fitted as a random factor.
Note: The Restricted Maximum Likelihood (REML) estimation approach was used with a default covariance structure of unstructured.

Programming note: Should computational issues be encountered when using an unstructured covariance structure, other structures including AR1 and CS should be considered and the second footnote updated as appropriate.

Example : EFF_T1
Protocol : 207040
Population : Intent-to-Treat

Table 2.xx
Summary of Patient Activation Measure (PAM) 13 Total Score

Visit		Arm 1 (N=xxx)	Arm 2 (N=xxx)	Arm 3 (N=xxx)	Arm 4 (N=xxx)	Arm 5 (N=xxx)
Baseline [1]	n	xx	xx	xx	xx	xx
	Mean	xx.x	xx.x	xx.x	xx.x	xx.x
	SD	x.xx	x.xx	x.xx	x.xx	x.xx
	Median	xx.x	xx.x	xx.x	xx.x	xx.x
	Min.	xx	xx	xx	xx	xx
	Max.	xx	xx	xx	xx	xx
Visit 5 (month 1)	n	xx	xx	xx	xx	xx
	Mean	xx.x	xx.x	xx.x	xx.x	xx.x
	SD	x.xx	x.xx	x.xx	x.xx	x.xx
	Median	xx.x	xx.x	xx.x	xx.x	xx.x
	Min.	xx	xx	xx	xx	xx
	Max.	xx	xx	xx	xx	xx

[1] Baseline PAM-13 total score is taken from Screening Visit
Programming note: repeat for Randomisation Visit, Change from Baseline at Visit 5 (Month 1), Visit 10 (Month 6), Change from Baseline at Visit 10 (Month 6), Early Withdrawal

Note: The total PAM score is calculated by dividing the raw score over the number of items answered and multiplied by 13. This score is then transformed to a scale within a range of 0-100 based on calibration tables and proprietary PAM algorithm.

Example : EFF_T28
Protocol : 207040
Population : Intent-to-Treat

Table 2.xx
Summary of Medication Adherence Report Scale - Asthma (MARS-A) Total Score

Visit		Arm 1 (N=xxx)	Arm 2 (N=xxx)	Arm 3 (N=xxx)	Arm 4 (N=xxx)	Arm 5 (N=xxx)
Baseline [1]	n	xx	xx	xx	xx	xx
	Mean	xx.x	xx.x	xx.x	xx.x	xx.x
	SD	x.xx	x.xx	x.xx	x.xx	x.xx
	Median	xx.x	xx.x	xx.x	xx.x	xx.x
	Min.	xx	xx	xx	xx	xx
	Max.	xx	xx	xx	xx	xx
Visit 5 (Month 1)	n	xx	xx	xx	xx	xx
	Mean	xx.x	xx.x	xx.x	xx.x	xx.x
	SD	x.xx	x.xx	x.xx	x.xx	x.xx
	Median	xx.x	xx.x	xx.x	xx.x	xx.x
	Min.	xx	xx	xx	xx	xx
	Max.	xx	xx	xx	xx	xx

[1] Baseline MARS-A 10 total score is taken from screening visit.
Note: MARS-A 10 Total Score is based on the mean score across all ten questions per visit.

Programming note: repeat for Randomisation visit, Change from Baseline at Visit 5 (Month 1), Visit 10 (Month 6), Change from Baseline at Visit 10 (Month 6), Early Withdrawal

EFF_T19
Protocol:207040
Population: Intent-to-Treat

Table 2.xx
Summary of Beliefs in Medicine Questionnaire (BMQ) General Benefit Total Score

Visit		Arm 1 (N=xxx)	Arm 2 (N=xxx)	Arm 3 (N=xxx)	Arm 4 (N=xxx)	Arm 5 (N=xxx)
Baseline [1]	n	xx	xx	xx	xx	xx
	Mean	xx.x	xx.x	xx.x	xx.x	xx.x
	SD	x.xx	x.xx	x.xx	x.xx	x.xx
	Median	xx.x	xx.x	xx.x	xx.x	xx.x
	Min.	xx	xx	xx	xx	xx
	Max.	xx	xx	xx	xx	xx
Visit 5 (Month 1)	n	xx	xx	xx	xx	xx
	Mean	xx.x	xx.x	xx.x	xx.x	xx.x
	SD	x.xx	x.xx	x.xx	x.xx	x.xx
	Median	xx.x	xx.x	xx.x	xx.x	xx.x
	Min.	xx	xx	xx	xx	xx
	Max.	xx	xx	xx	xx	xx

[1] Baseline BMQ total score is taken from screening visit.
Note: BMQ Score is based on the total score across all items within the BMQ measure

Programming note: repeat for Randomisation visit, Change from Baseline at Visit 5 (Month 1), Visit 10 (Month 6), Change from Baseline at Visit 10 (Month 6), Early Withdrawal

Repeat for:
Table 2.28 Summary of Beliefs in Medicine Questionnaire (BMQ) General Harm Total Score
Programming note: Use the items as presented in RAP
Table:2.29 Summary of Beliefs in Medicine Questionnaire (BMQ) General Overuse Total Score
Programming note: Use the items as presented in RAP
Table:2.30 Summary of Beliefs in Medicine Questionnaire (BMQ) Specific Necessity Total Score
Programming note: Use the items as presented in RAP
Table:2.31 Summary of Beliefs in Medicine Questionnaire (BMQ) Specific Concern Total Score
Programming note: Use the items as presented in RAP

EFF_T21
Protocol:207040
Population: Intent-to-Treat

Table 2.xx
Summary of Medical Device Incidents (Sensors)

		Arm 1 (N=xxx)	Arm 2 (N=xxx)	Arm 3 (N=xxx)	Arm 4 (N=xxx)	Arm 5 (N=xxx)	Total (N=xxx)
Relvar/Breo ELLIPTA Sensor	Number of incidents	xxx	xxx	xxx	xxx	xxx	xxx
	Subjects with at least one incident	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)
SABA MDI Sensor	Number of incidents	xxx	xxx	xxx	xxx	xxx	xxx
	Subjects with at least one incident	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)

Note: Devices incidents are classed as sensor malfunctions as noted in the eCRF.

EFF_T1
Protocol:207040
Population: Intent-to-Treat

Table 2.xx
Summary of Fractional Exhaled Nitric Oxide (FeNO)

Visit		Arm 1 (N=xxx)	Arm 2 (N=xxx)	Arm 3 (N=xxx)	Arm 4 (N=xxx)	Arm 5 (N=xxx)
Baseline [1]	n	xx	xx	xx	xx	xx
	Mean	xx.x	xx.x	xx.x	xx.x	xx.x
	SD	x.xx	x.xx	x.xx	x.xx	x.xx
	Median	xx.x	xx.x	xx.x	xx.x	xx.x
	Min.	xx	xx	xx	xx	xx
	Max.	xx	xx	xx	xx	xx
Visit 5 (Month 1)	n	xx	xx	xx	xx	xx
	Mean	xx.x	xx.x	xx.x	xx.x	xx.x
	SD	x.xx	x.xx	x.xx	x.xx	x.xx
	Median	xx.x	xx.x	xx.x	xx.x	xx.x
	Min.	xx	xx	xx	xx	xx
	Max.	xx	xx	xx	xx	xx
Change from Baseline at Visit 5	n	xx	xx	xx	xx	xx
	Mean	xx.x	xx.x	xx.x	xx.x	xx.x
	SD	x.xx	x.xx	x.xx	x.xx	x.xx
	Median	xx.x	xx.x	xx.x	xx.x	xx.x
	Min.	xx	xx	xx	xx	xx
	Max.	xx	xx	xx	xx	xx

[1] Baseline FeNO reading is taken from the Randomisation visit.
Programming note: repeat for Screening visit, Visit 10 (Month 6), Change from Baseline at Visit 10 (Month 6), 4, Early Withdrawal,

EFF_T23
Protocol:207040
Population: Intent-to-Treat

Table 2.xx
Summary of Change from Baseline (Randomisation) in Fractional Exhaled Nitric Oxide (FeNO) at Month 6 (Visit 10) by Percentage of ELLIPTA doses taken (daily adherence) between the beginning of Month 4 and the end of Month 6 Group

Adherence: <range of quartile %>

Visit		Arm 1 (N=xxx)	Arm 2 (N=xxx)	Arm 3 (N=xxx)	Arm 4 (N=xxx)	Arm 5 (N=xxx)	Total (N=xxx)
Baseline	n	xx	xx	xx	xx	xx	xx
	Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	SD	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx
	Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	Min.	xx	xx	xx	xx	xx	xx
	Max.	xx	xx	xx	xx	xx	xx
Visit 10 (Month 6)	n	xx	xx	xx	xx	xx	xx
	Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	SD	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx
	Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	Min.	xx	xx	xx	xx	xx	xx
	Max.	xx	xx	xx	xx	xx	xx
Change from Baseline at Visit 10	n	xx	xx	xx	xx	xx	xx
	Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	SD	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx
	Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	Min.	xx	xx	xx	xx	xx	xx
	Max.	xx	xx	xx	xx	xx	xx

EFF_T23

Protocol:207040
Population: Intent-to-Treat

Table 2.xx
Summary of Change from Baseline (Randomisation) in Peak Expiratory Flow (PEF) at Month 6 (Visit 10) by Percentage of ELLIPTA doses taken (daily adherence) between the beginning of Month 4 and the end of Month 6 Group

Adherence: <range of quartile %>

Visit		Arm 1 (N=xxx)	Arm 2 (N=xxx)	Arm 3 (N=xxx)	Arm 4 (N=xxx)	Arm 5 (N=xxx)	Total (N=xxx)
Baseline	n	xx	xx	xx	xx	xx	xx
	Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	SD	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx
	Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	Min.	xx	xx	xx	xx	xx	xx
	Max.	xx	xx	xx	xx	xx	xx
Visit 10 (Month 6)	n	xx	xx	xx	xx	xx	xx
	Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	SD	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx
	Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	Min.	xx	xx	xx	xx	xx	xx
	Max.	xx	xx	xx	xx	xx	xx
Change from Baseline at Visit 10	n	xx	xx	xx	xx	xx	xx
	Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	SD	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx
	Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	Min.	xx	xx	xx	xx	xx	xx
	Max.	xx	xx	xx	xx	xx	xx

EFF_T1
Protocol:207040

Population: Intent-to-Treat

Table 2.xx
Summary of Peak Expiratory Flow (PEF) (Litres/min)

Visit		Arm 1 (N=xxx)	Arm 2 (N=xxx)	Arm 3 (N=xxx)	Arm 4 (N=xxx)	Arm 5 (N=xxx)
Baseline [1]	n	xx	xx	xx	xx	xx
	Mean	xx.x	xx.x	xx.x	xx.x	xx.x
	SD	x.xx	x.xx	x.xx	x.xx	x.xx
	Median	xx.x	xx.x	xx.x	xx.x	xx.x
	Min.	xx	xx	xx	xx	xx
	Max.	xx	xx	xx	xx	xx
Visit 5 (Month 1)	n	xx	xx	xx	xx	xx
	Mean	xx.x	xx.x	xx.x	xx.x	xx.x
	SD	x.xx	x.xx	x.xx	x.xx	x.xx
	Median	xx.x	xx.x	xx.x	xx.x	xx.x
	Min.	xx	xx	xx	xx	xx
	Max.	xx	xx	xx	xx	xx
Change from Baseline at Visit 5	n	xx	xx	xx	xx	xx
	Mean	xx.x	xx.x	xx.x	xx.x	xx.x
	SD	x.xx	x.xx	x.xx	x.xx	x.xx
	Median	xx.x	xx.x	xx.x	xx.x	xx.x
	Min.	xx	xx	xx	xx	xx
	Max.	xx	xx	xx	xx	xx

[1] Baseline PEF reading is taken from the randomisation visit.

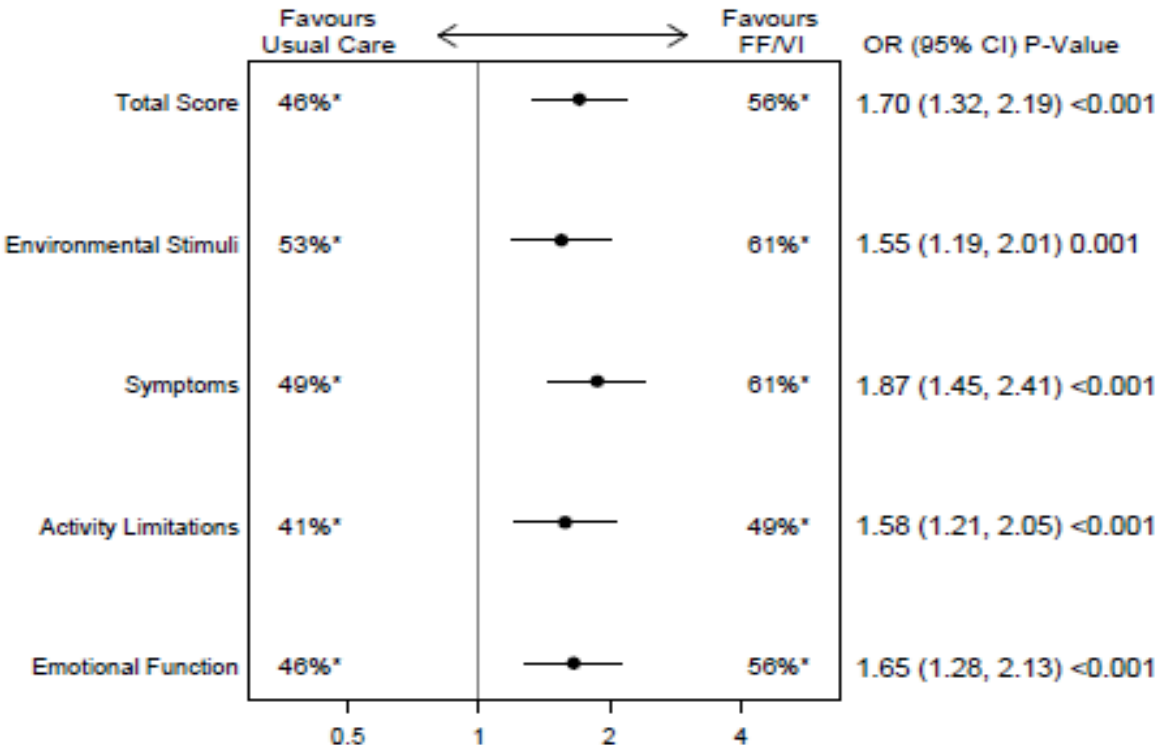
Programming note: repeat for Visit 10 (Month 6), Change from Baseline at Visit 10 (Month 6), 4, Early Withdrawal

EFFICACY FIGURES

Example: EFF_F1
Protocol: 207040
Population: Intent-to-Treat

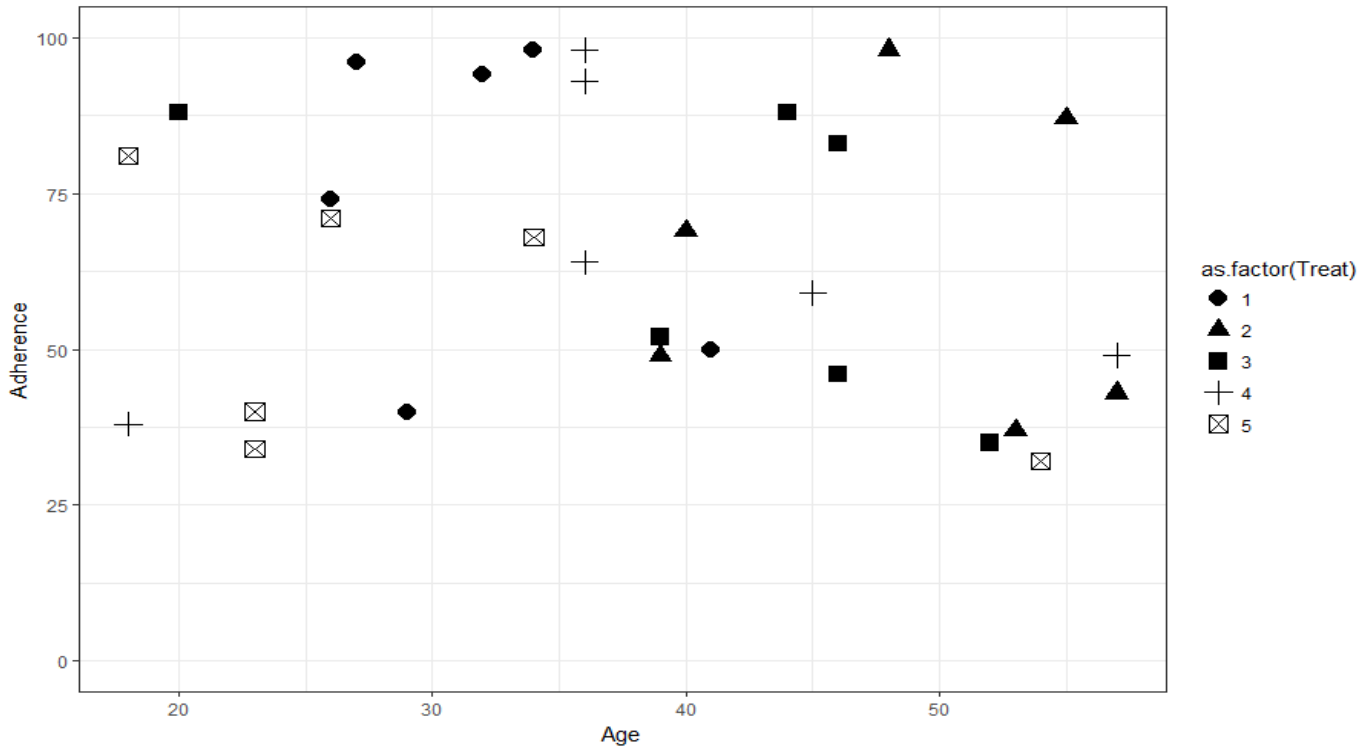
Figure 2.xx
Forest Plot for Odds Ratio of Either an ACT Total Score >= 20 and/ or Increase from Baseline of >= 3 in ACT Total Score at Visit 10 (Month 6)

Treatment Group: Arm 1



*=Proportion of responders, defined as ACT Total Score >= 20 and/ or Increase from Baseline of >= 3 in ACT Total Score at Visit 10 (Month 6)
Note: The analysis method was logistic regression adjusted for randomised treatment arm, baseline ACT total score, country, gender and age
Programming note: page 1 comparison between Arm 5 and Arm 1, following pages present the remaining Arm 5 v 2,3,4 treatment arm comparison
Example: EFF_F2
Protocol: 207040
Population: Intent-to-Treat

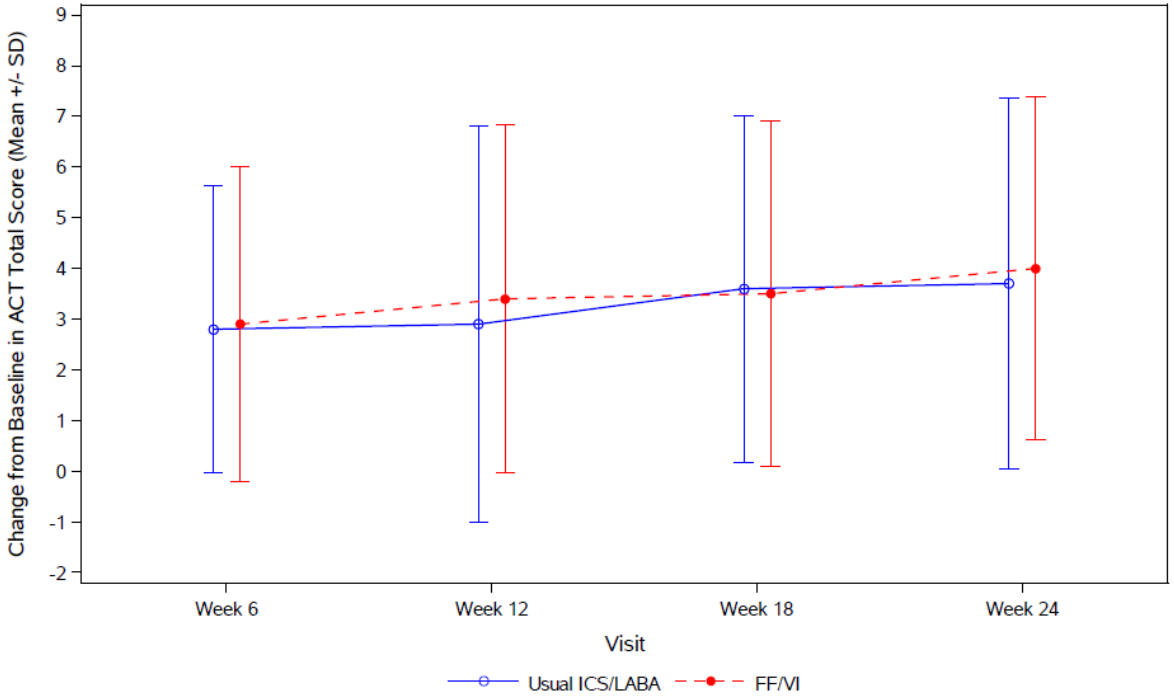
Figure 2.xx
Scatter Plot of Percentage of ELLIPTA doses taken (daily adherence) between the beginning of month 4 and the end of month 6 as determined by the maintenance sensor (Observed values) by Age



Programming Note: Requires the primary endpoint observed value, each treatment arm presented with a unique symbol/pattern. Be consistent with symbols/colours across all figures.

Example: EFF_F3
Protocol: 207040
Population: Intent-to-Treat

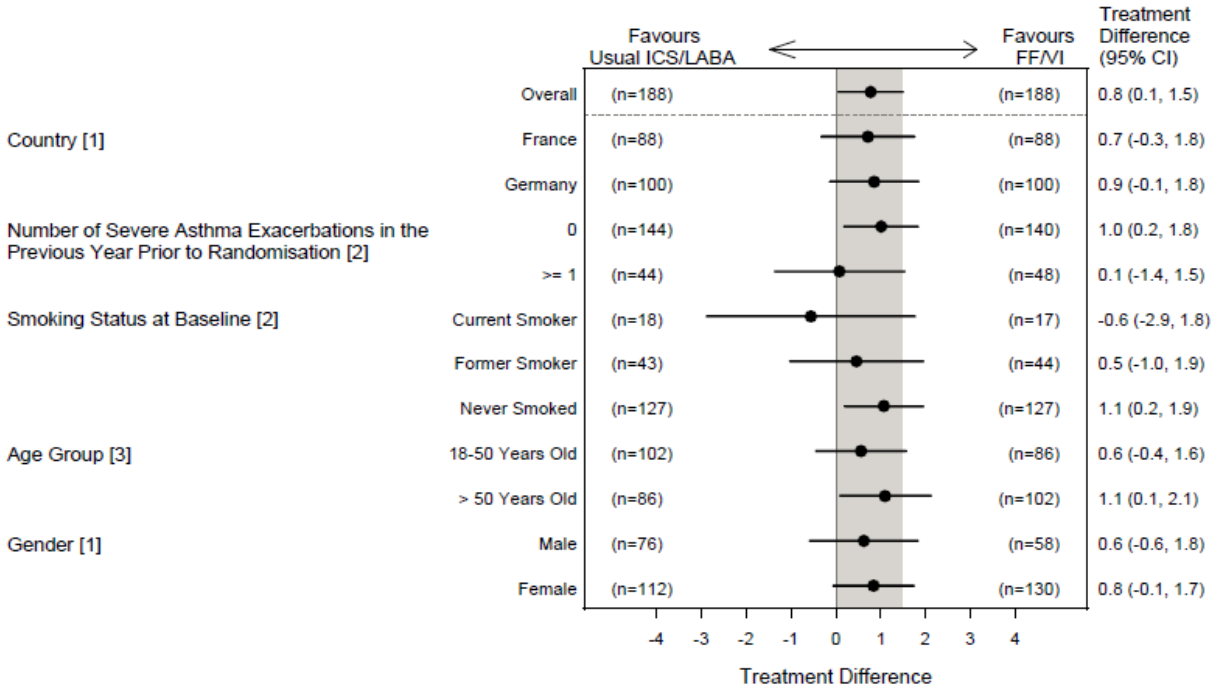
Figure 2.xx
Summary of Statistical Analysis for Change from Baseline (Randomisation) in ACT Total Score at Month 6



Programming Note: Present "Change from Baseline ACT Total Score" on y-axis and "Visit" on x-axis Baseline, Visit 5 (Month 1), Visit 10 (Month 6). Present mean ACT Total Score +- SD separately for treatment group at each visit, connecting the means with a solid line. Distinguish the treatment groups by different line types.

Example: EFF_F4
Protocol: 207040
Population: Intent-to-Treat

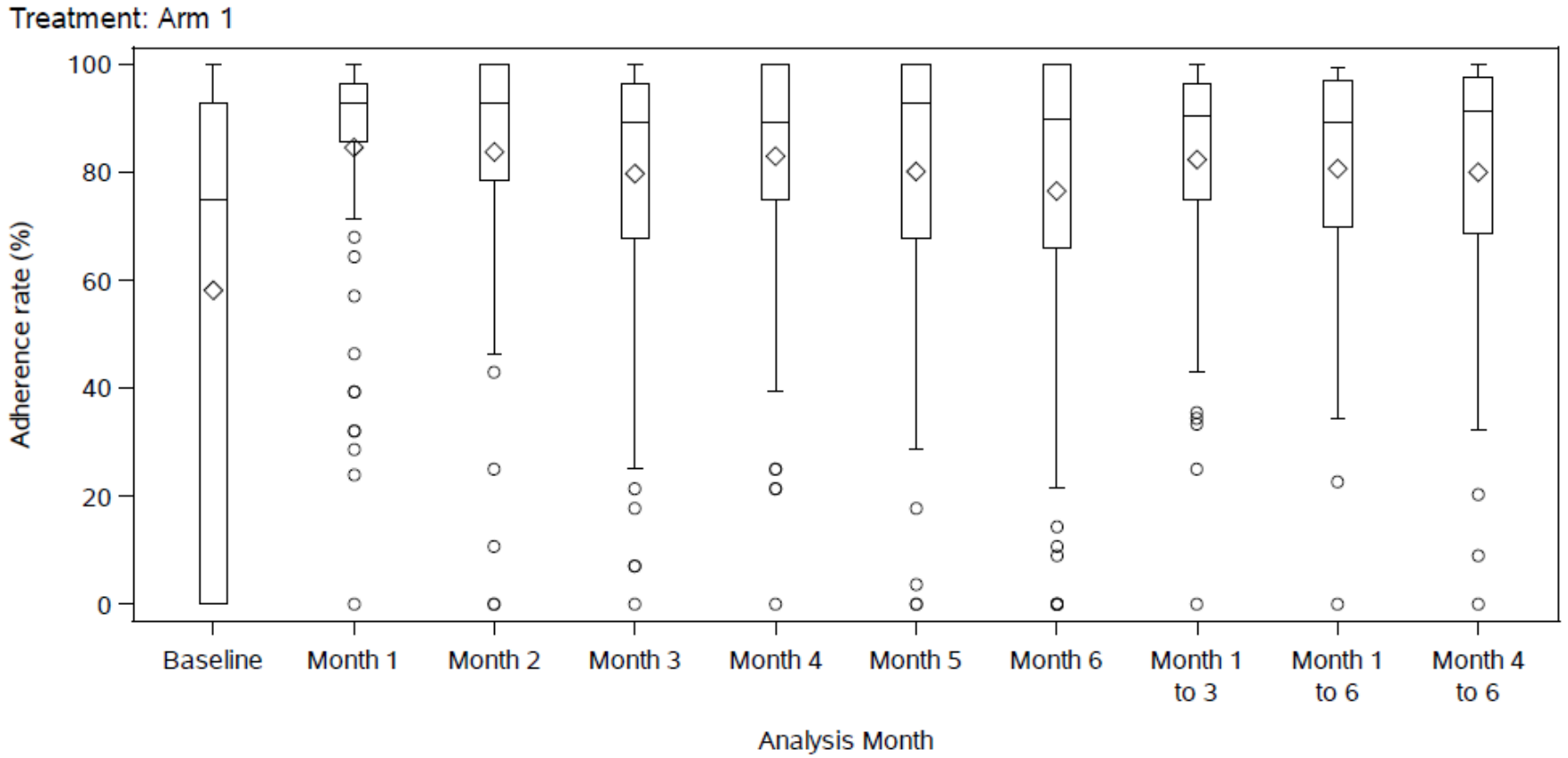
Figure 2.xx
Summary of Interaction Tests for Percentage of ELLIPTA doses taken (daily adherence) between the beginning of month 4 and the end of month 6 as determined by the maintenance sensor - – Comparisons Arm 1,2,3,4 v Arm 5



Note: The results displays are from an ANCOVA adjusted for randomised treatment arm, baseline adherence, duration of run-in (visits), country, gender
[1] age (years), covariate, and two-way interaction between randomised treatment arm and covariate
[2] covariate, two-way interaction between randomised treatment group and covariate.

Example: EFF_F5
Protocol: 207040
Population: Intent-to-Treat

Figure 2.xx
Box plot of Monthly Percentage of ELLIPTA doses taken (daily adherence) as determined by the maintenance sensor



Note: Baseline adherence is calculated using up to the last 28 days of daily adherence data during the run-in period.

SAFETY TABLES

Example: SAFE_T1 Page 1 of X
Protocol: 207040
Population: Intent-to-Treat

Table 3.1
Overview of On-Treatment and Post-Treatment Non-Serious AEs leading to Withdrawal, Non-Serious ADRs and SAEs

	Arm 1 (N=XXX)	Arm 2 (N=XXX)	Arm 3 (N=XXX)	Arm 4 (N=XXX))	Arm 5 (N=XXX)	Total (N=XXX)
Any Non-Serious AE	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)
Any Non-Serious ADR's	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)
Any On-Treatment Non-Serious ADRs	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)
Any Post-Treatment Non-Serious ADRs	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)
Any AEs leading to permanent discontinuation of study drug or withdrawal from study [1]	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)
Any SAE	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)
Any On-Treatment SAEs	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)
Any Post-Treatment SAEs	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)
Any On-Treatment Serious ADRs	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)
Any Post-Treatment Serious ADRs	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)
Any On-Treatment Fatal SAEs	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)
Any Post-Treatment Fatal SAEs	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)

Footnote: [1] Includes both on-treatment and post-treatment Non-Serious Adverse events leading to withdrawal, Non-serious ADRs and SAEs

SAFE_T2:
Protocol: 207040
Population: Intent-to-Treat

Table 3.xx
Top Ten Most Commonly Reported On-Treatment Adverse Events Per Treatment Group

Dictionary-Derived Term	Arm 1 (N=XXX)	Arm 2 (N=XXX)	Arm 3 (N=XXX)	Arm 4 (N=XXX)	Arm 5 (N=XXX)	Total (N=XXX)
Viral upper respiratory tract infection	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
Headache	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
Chronic obstructive pulmonary disease	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
Upper respiratory tract infection	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
Influenza	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
Pneumonia	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
Pharyngitis	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
Back pain	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
Hypertension	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
Bronchitis	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
Cough	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)

Note: The 10 most frequent preferred terms in Arm 1, Arm 2, Arm 3, Arm 4 and Arm 5.

SAFE_T2:
Protocol: 207040
Population: Intent-to-Treat

Table 3.xx
Top Ten Most Commonly Reported On-Treatment Adverse Drug Reactions Per Treatment Group

Dictionary-Derived Term	Arm 1 (N=XXX)	Arm 2 (N=XXX)	Arm 3 (N=XXX)	Arm 4 (N=XXX)	Arm 5 (N=XXX)	Total (N=XXX)
Viral upper respiratory tract infection	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
Headache	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
Chronic obstructive pulmonary disease	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
Upper respiratory tract infection	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
Influenza	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
Pneumonia	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
Pharyngitis	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
Back pain	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
Hypertension	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
Bronchitis	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)

Note: The 10 most frequent preferred terms in Arm 1, Arm 2, Arm 3, Arm 4 and Arm 4, and the 10 most frequent in Arm 5 are presented.

LISTINGS

POP_L1
Protocol: 207040
Population: Enrolled

Listing xx
Listing of Subjects Screened but Not in the Intent-to-Treat Population

Treatment	Site Id./ Unique Subject Id.	Disposition Status	Reason for Screen Failure/Run-in/Withdrawal
Arm 1	xxxxxx/ xxxxxx.xxxxxx.xxxxx	Early Withdrawal	xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx
	xxxxxx/ xxxxxx.xxxxxx.xxxxx	Early Withdraw	xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx
Arm 3	xxxxxx/ xxxxxx.xxxxxx.xxxxx	Early Withdrawal	xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx
	xxxxxx/ xxxxxx.xxxxxx.xxxxx	Early Withdraw	xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx
Non Treatment	xxxxxx/ xxxxxx.xxxxxx.xxxxx	Screen Failure	xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx
	xxxxxx/ xxxxxx.xxxxxx.xxxxx	Rin-in Failure	xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx

POP_L2
Protocol: 207040
Population: Intent-to-Treat

Listing xx
Listing of Subjects by Country

Country	Investigator Name	Subject	Treatment Arm
Netherlands	PPD		ARM1
			ARM3
			ARM4
United Kingdom			ARM2

POP_L3
Protocol: 207040
Population: Intent-to-Treat

Listing xx
Listing of Family History of Cardiovascular Risk Factors

Site Id./ Unique Subject Id.	ARM	Family History [1]
PPD	ARM1	Yes
		Unknown
	ARM3	Unknown
		Yes
	ARM4	Unknown

Footnote: [1] Family history of premature coronary artery disease in women < 65 years or men < 55 years in first degree relatives only (e.g., biological mother or father, biological brother or sister, biological son or daughter).

POP_L4
Protocol: 207040
Population: Intent-to-Treat

Listing xx
Listing of Asthma History

Treatment	Inv.	Subj.	Duration of Asthma		Number of Asthma Exacerbations in Last 12 Months	
			Years	Months	Type 1^	Type 2#
Arm 1	xxxxx	xxxx	xx	xx	xx	xx
		xxxx	xx	xx	xx	xx
		xxxx	xx	xx	xx	xx
		xxxx	xx	xx	xx	xx
	xxxxx	xxxx	xx	xx	xx	xx
		xxxx	xx	xx	xx	xx
		xxxx	xx	xx	xx	xx
		xxxx	xx	xx	xx	xx
Arm 2	xxxxx	xxxx	xx	xx	xx	xx
		xxxx	xx	xx	xx	xx
		xxxx	xx	xx	xx	xx
		xxxx	xx	xx	xx	xx
	xxxxx	xxxx	xx	xx	xx	xx
		xxxx	xx	xx	xx	xx
		xxxx	xx	xx	xx	xx
		xxxx	xx	xx	xx	xx

^Type 1: Required oral/systemic corticosteroids (not involving hospitalization)
#Type 2: Required hospitalization

POP_L5
Protocol:207040
Population: All Subjects Enrolled

Listing xx
Listing of Prescription Details

Site Id./ Unique Subject Id.	Actual number of prescriptions [1]	Number of prescriptions needing 100% compliance [2]
PPD	4	11
	8	5

[1] Actual number of asthma maintenance therapy prescriptions requested by subject or prescribed for subject.
[2] Number of asthma maintenance therapy prescriptions requested or prescribed that would be needed to be 100% compliant.

POP_L6
Protocol: 207040
Population: Intent-to-Treat

Listing xx
Listing of Preferred time of dosing

Site Id./ Unique Subject Id.	Treatment Arm	Preferred time	Incidence of Preferred time (%)
PPD	1	15:30	57.34%
	2	9:00	89.23%

Note: A subject is considered as having taken their dose at their preferred time if the actuation time from the Relvar/Breo ELLIPTA sensor is recorded ±1 hour of their preferred time as captured on the eCRF at screening

POP_L7
Protocol:207040
Population: Intent-to-Treat

Listing xx
Listing of HCP Dashboard Review

Site Id./ Unique Subject Id.	Treatment	Visit	Date of Dashboard data review	Was action taken	Action(s) Taken
PPD	Arm 4	Xxxxxxx	12DEC2008	N	Discuss adherence
	Arm 2	xxxxxxx	03FEB2009	Y	Discuss rescue medication

SAFE_L8
Protocol: 207040
Population: Intent-to-Treat

Listing xx
Listing of Treatment Compliance

Site Id./ Unique Subject Id.	Protocol prescribed dose	Start Date/ Study Day	Stop Date/ Study Day	Overall Compliance
PPD	200/25 mcg QD	PPD 1	PPD 1	71
	200/25 mcg QD	PPD 1	PPD 1	107

SAFE_L1
Protocol: 207040
Population: Intent-to-Treat

Listing xx
Listing of Adverse Event of Special Interest Group, Subgroup, Sub-SMQ and Preferred Term

AESI Group	AESI Subgroup	Sub-SMQ	Preferred Term
Adrenal suppression			ACTH stimulation test abnormal
			Addison's disease
			Adrenal androgen deficiency
			Adrenal atrophy
			Adrenal insufficiency

SAFE_L2
Protocol: 207040
Population: ITT

Listing xx
Listing of Relvar/Breo ELLIPTA Sensor Status

Site id/ Subj.	Treatment	Date of Sensor activation	Serial Number	Sensor return status	Sensor return date	Reasons for not returning the Sensor	Date of Sensor malfunction	Date of permanently stopping the use of Sensor
PPD								

SAFE_L3
Protocol: 207040
Population: Enrolled

Listing xx
Listing of Salbutamol MDI Sensor Status

Site id/ Subj.	Treatment	Date of Sensor activation	Serial Number	Sensor return status	Sensor return date	Reasons for not returning the Sensor	Date of Sensor malfunction	Date of permanently stopping the use of Sensor
PPD								

SAFE_L4
Protocol: 207040
Population: Intent-to-Treat

Listing xx
Listing of Sensor App Status

Site id./ Subj.	Arm	Date of permanent discontinuation/study day
PPD	Arm 1	PPD 23
	Arm 5	PPD 43

SAFE_L5
Protocol: 207040
Population: ITT

Listing xx
Listing of Device Malfunction

Site id./ Subj.	Arm	Date of malfunction	Malfunctioning device type	Reasons for device malfunction
PPD	Arm 2	07FEB2008	ELLIPTA	Dose counter is ambiguous
	Arm 4	12FEB2008	Rescue Medication	Inhaler is cracked or broken apart

EFF_L1
Protocol: 207040
Population: Intent-to-Treat

Listing xx
Listing of Relvar/Breo ELLIPTA Adherence – Observed Data

	Site id./ Subj.	Arm	Month	Day		Number of Days	Adherence (%)
PPD	Arm 2	Baseline		Adherence recorded	28	100%	
				Device incident	0		
				Post discontinuation of maintenance Sensor	0		
				Non-adherent	0		
		Month 1		Adherence recorded	20	71.42%	
				Device incident	0		
				Post discontinuation of maintenance Sensor	0		
		....		Non-adherent	8		
	Arm 4	Baseline		Adherence recorded	28	100%	
				Device incident	0		
				Post discontinuation of maintenance Sensor	0		
				Non-adherent	0		
		Month 1		Adherence recorded	18	.....	
				Device incident	1		
				Post discontinuation of maintenance Sensor	0		
		.....		Non-adherent	9		

Programming Note: Repeat for Month 2, 3, 4, 5 and 6

EFF_L2
Protocol: 207040
Population: Intent-to-Treat

Listing xx
Listing of Salbutamol MDI Rescue Free Days and Total Rescue Use – Observed Data

Site id./ Subj.	Arm	Month	Day	Number of Days	Rescue Free (%)	Total Rescue Use (Puffs)
PPD	Arm 1	Baseline	Rescue use recorded	9	67.86%	15
			Device incident	0		
			Post discontinuation of MDI rescue sensor	0		
			MDI rescue free	19		
		Month 1	Rescue use recorded	20	28.58%	42
			Device incident	0		
			Post discontinuation of MDI rescue sensor	0		
		....	MDI rescue free	8		
	Arm 3	Baseline	Rescue use recorded	0	100%	0
			Device incident	0		
			Post discontinuation of MDI rescue sensor	0		
			MDI rescue free	28		
		Month 1	Rescue use recorded	18	.....	29
			Device incident	1		
			Post discontinuation of MDI rescue sensor	0		
		.....	MDI rescue free	9		

Programming Note: Repeat for Month 2, 3, 4, 5 and 6

EFF_L3
Protocol: 207040
Population: ITT

Listing xx
Listing of Patient Reported Outcome Questionnaire Total Scores

Treatment: Arm 1

Inv./ Subj.	Visit/ Study Date/ Study Day	Total Score ACT	ASUI	MARS-A	PAM-13	SGRQ	BMQ
xxxxxx/ xxxxx	xxxxx DDMMMYYYY/ xx						

EFF_L4
Protocol: 207040
Population: Intent-to-Treat

Listing xx
Listing of Severe Asthma Exacerbations

Treatment/ Inv./ Subj.	Days Since 1st Dose of Onset	Date of Onset/ Resolution	Outcome	Withdrawn from Study Treatment?	Systemic/ Oral Corti-costeroids Taken?	Antibiotics Taken?	A medication Taken?	Hospitalized/ ER Visit/ Intubated?
xxxxxxx/ xxx/ xxxxx	xx	DDMMMYYYY/ DDMMMYYYY	xxxxxx	xxx	xxx	xxx	xxx	xxx/xxx/xxx
xxxxxxx/ xxx/ xxxxx	xx	DDMMMYYYY/ DDMMMYYYY	xxxxxx	xxx	xxx	xxx	xxx	xxx/xxx/xxx
xxxxxxx/ xxx/ xxxxx	xx	DDMMMYYYY/ DDMMMYYYY	xxxxxx	xxx	xxx	xxx	xxx	xxx/xxx/xxx
xxxxxxx/ xxx/ xxxxx	xx	DDMMMYYYY/ DDMMMYYYY	xxxxxx	xxx	xxx	xxx	xxx	xxx/xxx/xxx
	xx	DDMMMYYYY/ DDMMMYYYY	xxxxxx	xxx	xxx	xxx	xxx	xxx/xxx/xxx

EFF_L5
Protocol: 207040
Population: Intent-to-Treat

Listing xx
Listing of Unscheduled Asthma Related Healthcare Utilisation

Treatment: Placebo

Inv./ Subj.	Number of Telephone Calls	Number of Home Visits		Number of physician office/ practice visits	Number of urgent care/ outpatient visits	Number of emergency room visits	Number of Inpatient Hospitalisation Days	
		Day	Night				ICU	General Ward
xxxxxx/ xxxxxxx. xxxxxx	x	x	x	x	x	x	x	x

EFF_L11
Protocol: 207040
Population: Intent-to-Treat

Listing xx
Listing of Peak Expiratory Flow (PEF) and Fractional Exhaled Nitric Oxide (FeNO) Results

Site I.D/ Subj.	Treatment Arm	Visit	Date	PEF (unit)	FeNO (ppb)	FeNO Flow rate (mL/sec)
xxxx	xxxx	xxxxxxxxx	DDMMMYYYY	xxxxxxxxx	xxxxxxxxx	
		xxxxxxxxx	DDMMMYYYY	xxxxxxxxx	xxxxxxxxx	
		...				
	....					
....						

Programming Note: Include the FeNO flow rate (mL/sec)