TITLE PAGE

Protocol Title: 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.

Protocol Number: 207040/ Amendment 01

Short Title: A clinical study to evaluate the effect of the Connected Inhaler System (CIS) on adherence to maintenance therapy in poorly controlled asthmatic patients.

Compound Number: GW685698+GW642444 (GSK2285997)

Sponsor Name and Legal Registered Address:

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Regulatory Agency Identifying Number(s): EUDRACT: 2017-002266-45, IND 077855

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SPONSOR SIGNATORY:

PPD

10th Sept 2018.

Date

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Vice President, Respiratory Head Unit Physician

PPD

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

Document	**Date**
Amendment 01	10-SEP-2018
Original Protocol	22-JUN-2017

Amendment 01 10-SEP-2018

Overall Rationale for the Amendment:

Following scientific advice from regulatory agencies, a much faster study recruitment time than expected and a much lower than expected subject dropout rate, GSK have reassessed the rationale for the planned interim analysis and sample size re-estimation, which was planned for the study. The primary aim of this amendment is to remove the current requirement to perform the interim analysis and any subsequent need to include further subjects that followed that.

Also, the Benefit/Risk Assessment section has been amended to align with the updated EU-RMP.

Some other text changes to clarify protocol have been made as well as typographical corrections throughout.

Section # and Name	Description of Change	Brief Rationale
1. Synopsis	Deletion/amendment of text in these sections	Requirement for the interim analysis and sample size re-estimation to be removed from study protocol.
5.1 Overall Design		
5.2 Number of Subjects		
5.4. Scientific Rationale for Study Design		
7.5. Method of Treatment Assignment		
11.2.3. Sample Size Re-estimation		
11.4.4. Interim Analyses		
2.0. Schedule of Activities	SOA table updated to align with Section 9.2.1	Requirement to collect protocol defined safety events from start of run-in and once a subject has begun treatment with Relvar/Breo added to table and notes.

Section # and Name	Description of Change	Brief Rationale
3.3 Benefit/Risk Assessment	Removal of Potential Risks from this section to align with the latest RMP and updated Pneumonia risk with HZA115150 (SLS asthma) data	EU-RMP has been updated and version 10 approved in accordance with GVP module V, revision 2. Now aligns with the latest RMP and has been updated the Pneumonia risk with HZA115150 (SLS asthma) data.
1.0 Synopsis (*) and 4.0. Objectives and Endpoints	Deletion of Prescriptions Filled, from health care utilisation endpoints	This data will be reported as part of demography.
	*Addition of ACT 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)	To align ACT endpoint with other clinical studies.
	Correction to Asthma Symptom Utility Index (ASUI) endpoint	Changes to ASUI endpoint to correct measure and direction of improvement.
	Correction to BMQ endpoint	To include the multiple endpoints that the BMQ PRO has.
5.1 Overall Design	Clarification of Early Withdrawal	Clarify that patients who have discontinued the CIS but not Relvar/Breo ELLIPTA are encouraged to stay in the study.
7.9. Concomitant Therapy	Text amended	Clarify which asthma maintenance medication is collected in eCRF.
8.0. Discontinuation Criteria	Text amended.	To clarify which treatment (Relvar/Breo) withdrawal would lead to a subject's withdrawal from study.
9.1.3.6 Beliefs in Medicine Questionnaire (BMQ)	Text amended	Clarified that the BMQ also comprises a General Benefit scale.

Section # and Name	Description of Change	Brief Rationale
9.1.3.8. Exit Interviews	Text amended	To allow, for logistical reasons, the Exit Interview to be conducted, by phone, off -site within 14 days of V11.
9.2.6.1. Asthma Exacerbations	Text amended	To clarify definition for severe asthma exacerbation.
9.5. Biomarkers	Text amended	To clarify the period a subject must withhold rescue and ICS/LABA prior to FeNO and PEF assessments.
9.7. Prescription Record for Asthma Maintenance Medication	Text amended	To clarify which asthma maintenance medication Prescription Records are collected in the eCRF.
Minor corrections of typographical errors throughout.		

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1. SYNOPSIS

Protocol Title: 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

Short Title: A clinical study to evaluate the effect of the Connected Inhaler System (CIS) on adherence to maintenance therapy in poorly controlled asthmatic patients

Rationale: This study will be the first to evaluate the effect of the CIS on adherence to maintenance therapy (Relvar/Breo ELLIPTA) in uncontrolled asthmatic patients (Asthma Control Test [ACT] <20 at the screening visit and ACT <20 at a subsequent randomisation visit following run in)

The study has been designed to assess how the CIS impacts adherence, of asthmatic patients, to maintenance therapy, when both the subject and the healthcare professional (HCP) receive data from the sensor on the patient's Relvar/Breo ELLIPTA maintenance therapy.

In addition, the five treatment arms of the study will allow evaluation of different elements of the CIS including, having additional data provided from a sensor on rescue medication and also the effect of the patient alone seeing any data with no data shared to the HCP, or both the patient and HCP, seeing the data from the sensors Furthermore, this study will provide preliminary data evaluating the effect of the CIS on patient outcomes, including rescue medication use, patient reported outcomes and change in asthma control as assessed by the Asthma Control Test (ACT).

Objectives and Endpoints:

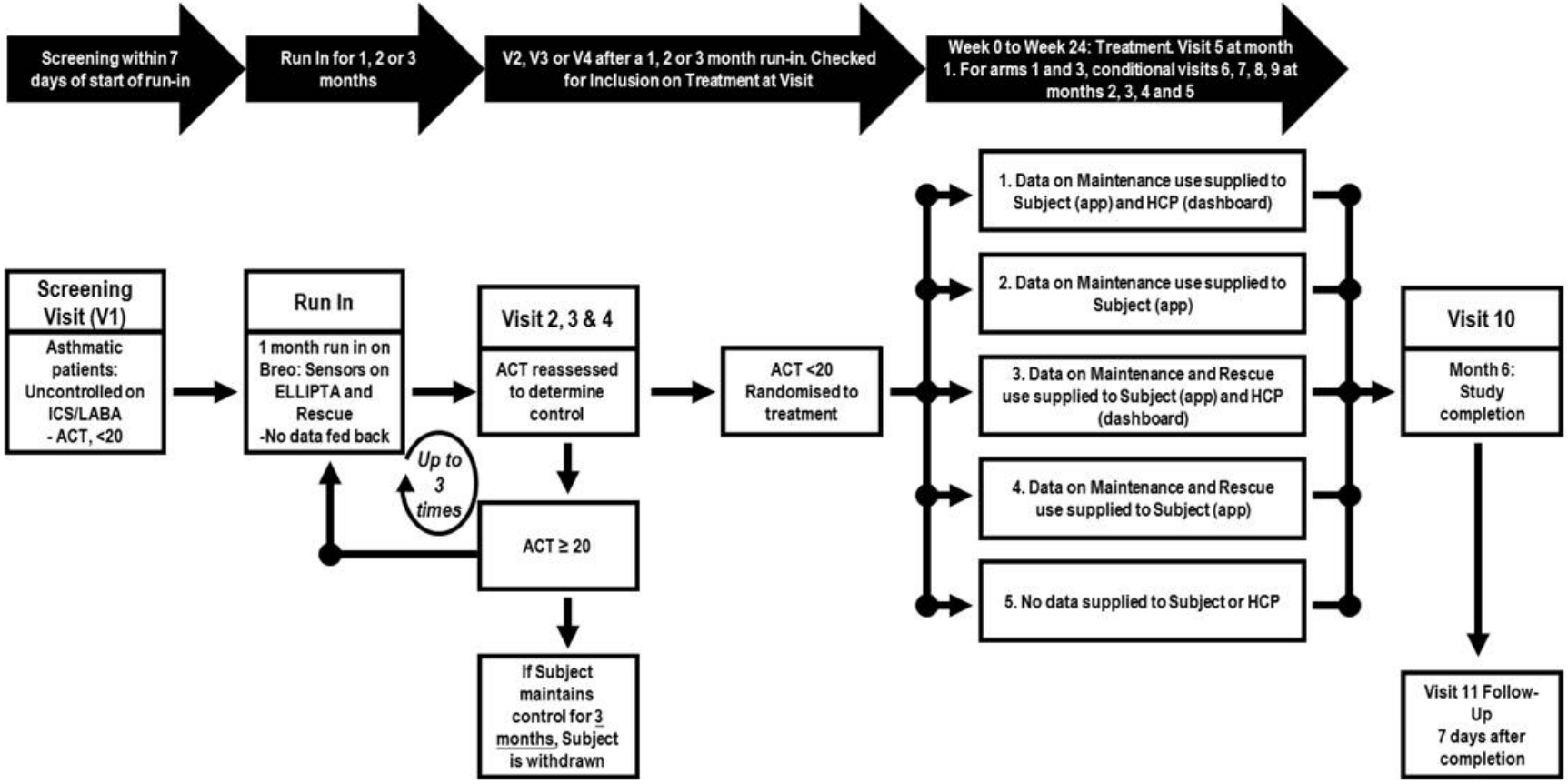
Objectives	Endpoints
Primary	
To compare the effect of 6 months use of the CIS on adherence to ELLIPTA maintenance therapy when both the subject and the HCP are supplied with data from the maintenance sensor versus no data supplied to the subject and HCP (Arm 1 vs Arm 5)	Percentage of ELLIPTA doses taken (daily adherence[1].) between the beginning of month 4 and the end of month 6 as determined by the maintenance sensor
Secondary	
To compare the effect of 6 months use of the CIS on adherence to ELLIPTA maintenance therapy for the following aspects of the CIS:	Percentage of ELLIPTA doses taken (daily adherence1.) between the beginning of month 4

Objectives	Endpoints
• Maintenance data only supplied to subjects versus no data supplied to the subject (Arm 2 vs Arm 5) • Rescue and Maintenance data supplied to subject and HCP versus no data supplied to the subject and HCP (Arm 3 vs Arm 5) • Rescue and Maintenance data only supplied to subject versus no data supplied to the subject (Arm 4 vs Arm 5)	and the end of month 6 as determined by the maintenance sensor
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 subject 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 subject'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 subject's asthma control	• Change from baseline in ACT total score at Month 6, measured at baseline (Visit 2, 3 or 4) and Month 6 (Visit10) • 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 or an increase from baseline of ≥ 3 in ACT total score at Month 6 (Visit 10)

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

Overall Design:

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.



Number of Subjects:

Approximately 600 subjects will be screened to achieve 432 randomised and a total of 380 subjects are anticipated to have data available for the primary analysis; an estimated total of 76 subjects per treatment group.

Treatment Groups and Duration:

All randomised subjects will receive Relvar/Breo ELLIPTA, at the dose allocated at the run in.

All subjects will have sensors attached to both their Relvar/Breo ELLIPTA and salbutamol Metered Dose Inhaler (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, (subject alone or subject and HCP), that defines the treatment arms.

The 5 treatments arms are as follow:

1. Data on Maintenance use supplied to Subject (app) and HCP (dashboard)
2. Data on Maintenance use supplied to Subject (app)
3. Data on Maintenance and Rescue use supplied to Subject (app) and HCP (dashboard)
4. Data on Maintenance and Rescue use supplied to Subject (app)
5. No data supplied to Subject or HCP

The treatment period for the study is 6 months. However, due to the flexible run in period a subject could be on the study for approximately 7, 8 or 9 months in total

2. SCHEDULE OF ACTIVITIES (SOA)

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 subject 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 subject and HCP/ designee prior to any other study assessments. May be completed at a separate visit to screening if required.
Subject 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**									Subject 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 subject 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**			
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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 subject is included. 2. The PRO's are only performed at the run-in visit (V2, V3 or V4) if a subject 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 subject 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**			
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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 subjects 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 subject is included. 2.PEF and FeNO is only performed at the Run-in visit if a subject 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**			Subjects 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 subjects 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**								Subjects are trained in fitting the sensors at screening. Following randomisation, subjects 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 subject 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**			
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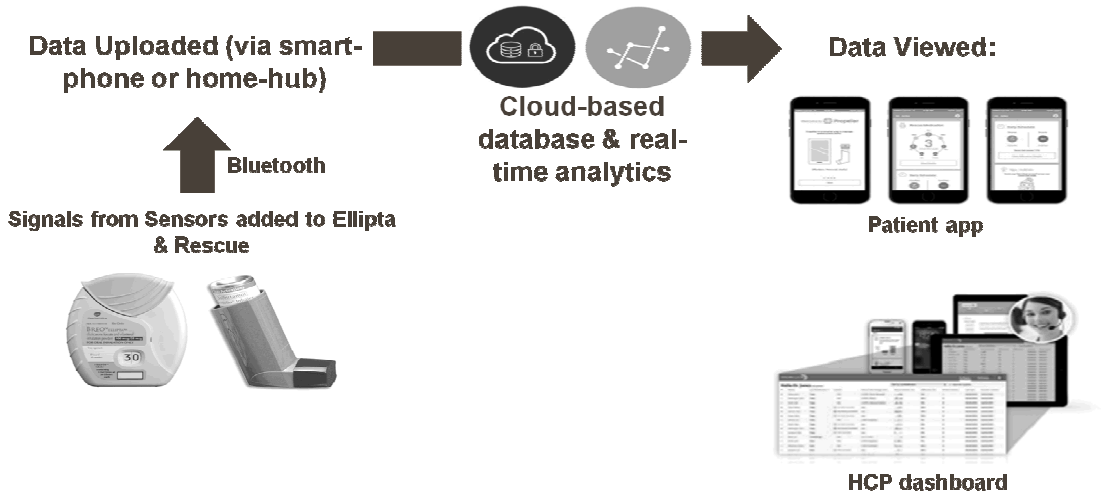
Visit Window (days)		**±2**	**±2**	**±2**	**±2**	**±7**	**±7**	**±7**	**±7**	**±7**		**±2**	
Conditional Visits			**X**	**X**		**X**	**X**	**X**	**X**				
Training in ELLIPTA & MDI correct use	**X**				**X**								Once included a subject should be trained in correct use of ELLIPTA and MDI devices
Correct 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.

3. INTRODUCTION

GSK has, in collaboration with Propeller Health, developed a sensor which clips on to the ELLIPTA dry powder inhaler (DPI), herein referred to as ELLIPTA. The sensor will measure when the ELLIPTA mouth piece cover is fully opened and closed and this data can be fed back, via an application (app) on a smart phone to the patient. This will inform a patient if/when a dose of Relvar/Breo has been actuated from the ELLIPTA. Other information, including: asthma management strategies, tracking of symptoms, asthma triggers, medication reminders and daily asthma forecasts involving weather and air quality data, will also be provided via the app. Information from a second sensor on a patient's rescue medication metered dose inhaler (MDI) could also provide feedback, via the app, to the patient on their salbutamol (albuterol) MDI use. The data from both Relvar/Breo ELLIPTA and salbutamol MDI can also be shared, via an online dashboard, with the patient's Health Care Professional (HCP), see Figure 1 and Propeller System Site Manual (PSSM). The sensors, app, dashboard and systems to provide data are subsequently described as the Connected Inhaler System (CIS).

Figure 1 Connected Inhaler System



3.1. Study Rationale

This study will be the first to evaluate the effect of the CIS on adherence to maintenance therapy (Relvar/Breo ELLIPTA) in uncontrolled asthmatic patients (Asthma Control Test [ACT] <20 at the screening visit and ACT <20 at a subsequent randomisation visit after run-in). The run-in exists to ensure a stable level of control prior to entry into the study, given the possible change in treatment and is described in detail in Section 5.1.

The study has been designed to assess how the CIS impacts adherence of asthmatic patients to maintenance therapy, when both the subject and the HCP receive data on adherence from the sensor on the patient's Relvar/Breo ELLIPTA maintenance therapy.

In addition, the five treatment arms of the study will allow evaluation of different elements of the CIS. These include; having additional data provided from a sensor on

rescue medication and the effect of the patient alone seeing any data with no data shared to the HCP, or both the patient and HCP seeing the data from the sensors. See Section 5, Section 7 and Table 1 for details on the 5 arms. Furthermore, this study will provide preliminary data evaluating the effect of the CIS on patient outcomes, including rescue medication use, change in ACT and patient reported outcomes (PROs).

3.2. Background

Asthma is a chronic inflammatory disease of the airways that results in hyperreactivity and clinically relevant episodes of wheezing, chest tightness and coughing. Although asthmatic symptoms can normally be controlled, by treatment, it remains a serious condition that is associated with a number of different impacts and co-morbidities such as; fatigue, activity impairment, psychological problems (anxiety, depression and stress), lung infections and delays in growth (paediatrics).

The underlying pathophysiology of asthma includes epithelial sloughing, smooth muscle contraction, bronchial hyperreactivity and airway inflammation [Koterba, 2012]. Depending on the asthmatic patient, these symptoms can become worse during the evening and/or with exercise [Martinez, 2007]. Asthma is believed to affect the lives of approximately 300 million people worldwide and this number is expected to rise to 400 million by 2025.

There are many reasons for poor adherence including, but not limited to, difficulties using inhalers, forgetfulness, misunderstanding of instructions, perceptions of the medicine and cost [GINA, 2017]. Also, as asthma is an inflammatory condition that is episodic in nature, patients can exhibit symptomatic adherence to maintenance therapies [Anarella, 2004].

Inadequate control of asthma symptoms continues to be a serious problem, and despite advancements in therapeutics for the treatment of asthma, adherence rates remain less than optimum [Anarella, 2004, Foster, 2014]. The significance of adherence to treatment regimens in the management of asthma is becoming ever more evident. A variety of studies have indicated that poor adherence to maintenance therapy is intimately associated with reduced quality of life and, increased; asthma symptoms, oral steroid usage, hospitalisation and mortality [Patel, 2013; Williams, 2011, Normansell, 2017]. Furthermore, reduced adherence to maintenance therapy can lead to an overuse of rescue medication, which has been linked to poorer health status [Patel, 2013].

Due to the chronic nature of the disease, low adherence rates are recognised as one of the main contributing factors to reduced control amongst asthmatic patients. Therefore, the requirement for routine and habitual use of maintenance therapy is paramount.

Currently, determination of inherent adherence rates are questionable due to their largely subjective (patient diaries), unreliable (prescription refills) and imprecise (dosage counters) data acquisition methodologies. Each of these methods can misrepresent what is occurring in the real world. Furthermore, clinicians' estimations of adherence rates can be inaccurate, patient self-reported adherence rates are notoriously overestimated and some electronic dose counters can also be problematic due to dose dumping [Bae, 2009;

Zeller, 2008]. Because of these uncertainties, there is an abundance of research being undertaken in the area of inhaler sensors for adherence. Novel solutions to some of the aforementioned problems are currently in development, such as; actuation switches (e.g. Smartinhaler and Propeller Health MDI sensor) for time stamping, heated thermistors (MDI log) for inhalation detection, microphones (INCA Device) for detecting peak inspiratory flow rates and actuations, accelerometers (Amiko and MDI Log) for time stamping and technique feedback, and light transmitters (SmartTrack and SmartTouch) for detection of canister depression and time stamping.

Dosing regimens (once daily vs. twice daily) have also unsurprisingly been found to have an effect on adherence to maintenance therapy. Fewer doses required on a daily basis as part of maintenance therapy, has been shown to increase adherence rates as well as creating a more routine and habitual dosing times [Coleman, 2012].

It has been shown that the addition of a sensor which has the ability to feedback information is associated with increased adherence rates in paediatric patients of between 30 and 50% [Chan, 2016; Foster, 2014]. Unfortunately, the population (paediatrics) and the inherent variability of the data make interpretation and extrapolation to other populations problematic. However, a 20-30% increase in adherence rates when using inhaled corticosteroids has been shown to lead to clinically relevant effects, such as, a reduction in exacerbations [Williams, 2011]. Whilst many studies have used sensors to measure adherence, relatively few studies have assessed the influence of sensors on adherence rates and even less information exists to demonstrate the link between adherence and clinically relevant outcomes or patient reported quality of life.

Adherence rate measurements should be unobtrusive, objective and accurate, in order to correctly identify innate patient adherence rates [Chan, 2015]. Accordingly, Propeller Health, in collaboration with GSK, has developed a sensor, which can clip onto any ELLIPTA DPI and can monitor the time and date that the ELLIPTA DPI cover is opened and closed. The sensor can be detached and transferred to subsequent inhalers by prescription. Propeller Health already produces a sensor that clips on to the top of a rescue MDI and records time and date of actuation. The data, from both of these sensors can then be fed back to the patient or patient and their HealthCare Professional (HCP) through the use of an app or dashboard. Patient/HCP interaction with the data through the app/dashboard may enable greater engagement between the patient and their HCP regarding their asthma. The app associated with the Propeller Health sensor also provides information on asthma management strategies, tracking of symptoms, asthma triggers, medication reminders and daily asthma forecasts involving weather and air quality data, in order to improve a patients' understanding of, and relationship with, their asthma.

It is believed that engaging a patient's interest in their asthma could improve their adherence to their maintenance therapy and ultimately improves their asthma outcomes as much of the research supports the importance of adherence rates to asthma control [Sapir, 2017]. Therefore, if through the use of the CIS, a patient can engage with their asthma, this may improve adherence and ultimately improve their level of asthma control. Furthermore, from an HCP perspective, having accurate adherence data would make discussions with their patients more objective and informed when considering appropriate asthma management strategies.

3.3. Benefit/Risk Assessment

3.3.1. Risk assessment for Relvar/Breo 100/25mcg and 200/25mcg

For Relvar/Breo ELLIPTA, the following risks and the corresponding mitigation strategies, as applicable to asthma patients, were taken from the summary of safety concerns in the European Union – Risk Management Plan (EU-RMP Version 10). For Relvar/Breo the rationale for the risk assessment was derived from the 2014-2016 Investigator Brochures, from an integrated analysis of key Relvar/Breo studies.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP) (fluticasone furoate [FF]/vilanterol [VI]])		
Pneumonia in patients with asthma	In an integrated analysis of 11 studies in asthma (7034 patients), the incidence of pneumonia (adjusted for exposure, due to low numbers and limited number of patients on placebo) seen with FF/VI 100/25 microgram strength (9.6/1000 patient years) was similar to placebo (8.0/1000 patient years). The incidence was slightly higher for FF/VI 200/25 microgram (18.4/1000 patient years). No risk factors were identified. In HZA115150 (SLS Asthma) the number of subjects who experienced a Pneumonia SAESI was low. In total, 23 subjects (1%) randomised to initiate treatment with FF/VI arm experienced 24 Pneumonia SAESIs, and 16 subjects (<1%) randomised to continue usual care experienced 18 Pneumonia SAESIs. The incidence rate of subjects experiencing a Pneumonia SAESI per 1000 subject-years at risk by randomised treatment arm, was 10.36 in the FF/VI arm and 7.14 in the usual care arm. The number of Pneumonia SAESIs per 1000 subject-years at risk by randomised treatment arm was 10.81 in the FF/VI arm and 8.03 in the usual care arm. The incidence ratio for Pneumonia SAESIs for subjects randomised to initiate treatment with FF/VI versus those randomised to continue usual care was 1.4 (95% CI: 0.8, 2.7). The upper limit of the 95% CI was	The risk of pneumonia in asthma patients is consistent with the risk of other ICS. Subjects are not at an increased risk in this study, since they enter the study on an existing ICS treatment. Subjects are alerted to the potential risk of pneumonia in the informed consent. Subjects with a concurrent respiratory disease are excluded from the study.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	higher than the pre-specified non-inferiority margin of 2; therefore, being randomised to initiate treatment with FF/VI was not shown to be non-inferior to being randomised to continue usual care with regards to the incidence of Pneumonia SAESIs.	
Serious cardiovascular events	In an analysis performed on the 18 key studies in subjects with asthma, eight serious cardiovascular events have been reported in patients exposed to FF/VI. Seven events in FF/VI 100/25 and one event in FF/VI 200/25. This represents an incidence less than 1% in the asthmatic patients exposed to FF/VI. [a] The events reported include atrial fibrillation, acute coronary syndrome, coronary artery disease, hypertension, myocardial ischemia, tachyarrhythmia and tachycardia. Therefore, fluticasone furoate/vilanterol should be used with caution in patients with severe cardiovascular disease or heart rhythm abnormalities, thyrotoxicosis, uncorrected hypokalaemia or patients predisposed to low levels of serum potassium.	Subjects with existing serious cardiovascular disease, thyrotoxicosis, uncorrected hypokalaemia or patients predisposed to low levels of serum potassium are excluded from the study. Investigators are made aware of the potential class effects of LABAs and are advised to exercise caution for subjects with existing serious cardiovascular disease (Section 6.3 [Warnings and Precautions] of the IB).
Decreased bone mineral density and associated fractures	Risk of fracture has been associated with oral corticosteroids. It is unclear if inhaled corticosteroids carry the same risk. Currently the risk of reduced bone mineral density has not been observed in the asthma population [Jones, 2002]. In addition specific assessments in adolescents with asthma have not demonstrated an	Subjects will be informed about the risk of decreased bone mineral density and bone fractures in the informed consent. Investigators are made aware of the potential for this ICS class effect. Subjects will be advised to seek medical treatment if any signs of decreased bone mineral density or fractures occur.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	effect on bone mineral density, when controlled for growth [König, 1993; Turpeinen, 2010]. In an analysis performed on the 11 key studies in subjects with asthma bone fractures were reported by <1% (7034 patients) of subjects who received FF/VI 100/25 and was usually associated with trauma	All subjects will already be prescribed ICS/LABA treatments for their asthma. Therefore, it is unlikely that such an effect will occur.
Corticosteroid associated eye disorders	This is considered a class effect of ICS. Preclinical studies showed FF at high dose comparable to other high dose corticosteroids. In study HZA106839 (FF/VI, FF and FP in subjects with asthma), formal ophthalmic assessments were conducted (including lens opacities classification system [LOCS] III evaluations for ocular opacities) throughout the study. This study showed no apparent effects on lens opacification, compared to baseline. During studies in both subjects with asthma and COPD, no associated affect on ocular disorders was observed.	Subjects will be informed about the risk of corticosteroid associated eye disorders in the informed consent. They will be advised to seek medical treatment if any signs of eye disorder occur. Investigators are made aware of the potential for this class effect in Section 5.3.3.7 (Ophthalmic Effects) of the IB. All subjects will already be prescribed ICS/LABA treatments for their asthma. Therefore, it is unlikely that such an effect will be experienced.
Paradoxical bronchospasm may occur with an immediate increase in wheezing after dosing.		First dose of Relvar/Breo will be administered at the clinical site under supervision Paradoxical bronchospasm should be treated immediately with a short-acting inhaled bronchodilator. Relvar/Breo ELLIPTA should be discontinued Immediately. The subject would be withdrawn from study.

a. RELVAR studies summarized include FFA109684, FFA109685, FFA109687, B2C109575, HZA106827, HZA106829, HZA113091, HZA113714, HZA113719, HZA116863, HZA106837, HZA106839, HZA106851, FFA112059, FFA114496, FFA115283, FFA115285, B2C112060.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of Relvar/Breo may be found in the Investigator's

Brochure, Development Safety Update Report or Summary of Product Characteristics Benefit Assessment.

As a result of switching from other prescribed ICS/LABA combination products and being randomised to a treatment arm in the study, subjects may switch from an inhaled therapy that is taken twice daily, to a once daily therapy (Relvar/Breo) the patients in this study may have better adherence and so possibly better asthma control. There is also a potential benefit from use of the CIS. This has the potential to increase their adherence through interaction with the data outputs and engagement with their asthma. Data with marketed products suggests that adherence improves with less frequent administration/simplification of therapy and therefore it is expected that a once-daily treatment could improve adherence, which may lead to improvements in disease control and reductions in healthcare resource utilisation costs [Foster, 2014, Price, 2010, Toy, 2011].

3.3.2. Overall Benefit: Risk Conclusion

GlaxoSmithKline (GSK) has assessed this study for any potential risks that a subject may experience. The investigational product (IP) FF/VI will be used as is detailed in the prescribing information and has an acceptable safety profile for clinical use and there are no significant associated risks. This conclusion is supported by the results of previously performed clinical studies with the products in healthy volunteers and subjects with Asthma and COPD and post-marketing experience (see local label).

There is a small risk of destabilising asthma when switching to Relvar/Breo. Patients will be provided with rescue medication and will be educated to recognise symptoms of asthma worsening and instructed to contact the HCP in this event.

Taking into account the measures taken to minimize risk to subjects participating in this study, the potential risks identified, associated with FF/VI are justified by the anticipated benefits that may be afforded to patients with asthma.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of Relvar/Breo ICS/LABA may be found in the IB, Summary of Product Characteristics and Subject Information Leaflet.

4. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
To compare the effect of 6 months use of the CIS on adherence to ELLIPTA maintenance therapy when both the subject and the HCP are supplied with data from the maintenance sensor versus no data supplied to the subject 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

Objectives	Endpoints
Secondary	
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 subjects versus no data supplied to the subject (Arm 2 vs Arm 5) • Rescue and Maintenance data supplied to subject and HCP versus no data supplied to the subject and HCP (Arm 3 vs Arm 5) • Rescue and Maintenance data only supplied to subject versus no data supplied to the subject (Arm 4 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
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 subject 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 subject'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 subject'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 (Visit10) • 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 or an increase from baseline of ≥ 3 in ACT total score at Month 6 (Visit 10)

Objectives	Endpoints
Exploratory and Other Objectives	
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 subject'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 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).	• Percentage of patients meeting a responder threshold of ≥ 0.09 points improvement (increase) from baseline (Randomisation) for the 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 (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

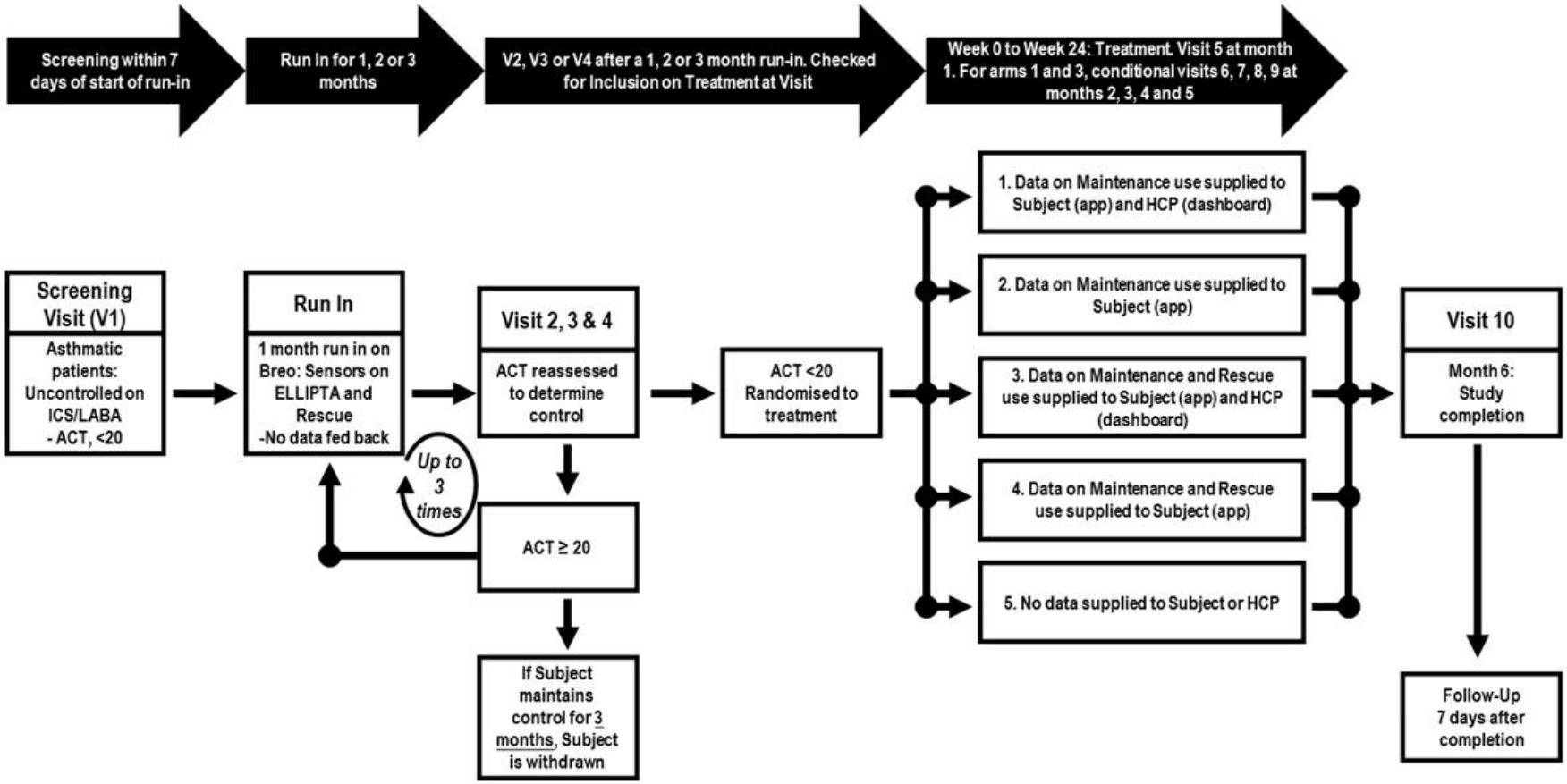
Objectives	Endpoints
	○ General Overuse score ○ Specific Necessity score ○ Specific Concern score
To assess the reliability and usability of the CIS	• Incidence of Medical Device Incidents between the beginning of Month 1 and the end of Month 6.
To explore impact of adherence on the biomarker Fractional exhaled Nitric Oxide (FeNO)	FeNO at Screening (Visit 1), Randomisation (Visit 2,3 or 4), 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 subjects	• Exit Questionnaires at Month 6 (Visit 10) • Exit Interviews for a sub set of subjects 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 subjects 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 subject taking one dose of Relvar/Breo ELLIPTA, within a 24 hour period, starting at 12.00am each day.

5. STUDY DESIGN

5.1. Overall Design

Figure 2 : Study Schematic



This is an open-label, randomised, multi-centre, parallel group study consisting of 5 treatment arms, in asthmatic patients currently on a fixed dose ICS/LABA maintenance therapy.

The procedures to be performed at each visit are shown in Section 2. The study and visits are described here.

At all visits will require subjects to withhold a daily dose of maintenance therapy and rescue medication for 6 hours; as some assessments will require this restriction for validity of the assessment (PEF and FeNO) and also so correct use can be demonstrated with that days Relvar/Breo ELLIPTA dose at any required visit.

The treatment period for the study is 6 months. However, due to the flexible run in period a subject could be on the study for approximately 7, 8 or 9 months in total

Screening Visit (V1)

Subjects who have provided their informed consent will be screened at Visit 1 (V1) for inclusion on the study. Subjects who meet all the inclusion criteria, including an ACT of <20, will enter the flexible run-in period. Screening and starting the flexible run-in can occur at the same visit, however for logistical reasons the flexible run-in can start at a separate visit, which must be within 7 days of the screening visit and the subject's inclusion on the study. Should a subject not meet the inclusion/exclusion criteria, they will be registered as a screen failure.

Flexible Run-in

Following inclusion at screening all subjects will receive Relvar/Breo ELLIPTA DPI maintenance therapy and salbutamol MDI rescue medication and be instructed to take these as prescribed.

Instruction on correct use of the Relvar/Breo ELLIPTA DPI and salbutamol MDI will be provided, particularly in the case of subjects previously using other devices, and/or using medication requiring twice-daily dosing.

Both the Relvar/Breo ELLIPTA and salbutamol MDI medication used by all subjects included on the study will have a sensor fitted and switched on at the clinic visit. However, during this run-in period, there will be no information provided to the subjects or HCPs on their adherence to Relvar/Breo ELLIPTA or on their use of salbutamol MDI. Subjects will also be instructed in fitting the sensors onto both the ELLIPTA and MDI.

The run-in period can last for 1, 2 or 3 months, dependent on a subjects ACT at end of each month of the run-in period.

Conditional Visits 2, 3 and 4 (V2, V3 and V4)

At the end of each month of the flexible run-in period, ACT will be re-assessed at the clinical centre. If at the first monthly visit of the flexible run-in the subject's ACT is <20 (uncontrolled) then the subject will be randomised to study treatment and subsequent run-

in visits are not required. Subjects with an ACT of ≥20 at V2 or V3 repeat the month run-in period. However, subjects who have an ACT ≥20 at all 3 visits, during the flexible run-in, will not be randomised and will be registered as a run-in failure.

Randomization/treatment: Conditional Visits 2, 3 and 4 (V2, V3 and V4)

Subjects who meet the randomisation inclusion criteria will be randomised to one of five CIS treatment arms at this visit (V2, V3 or V4). All treatment arms continue with Relvar/Breo ELLIPTA (ICS/LABA) maintenance therapy and Salbutamol MDI rescue therapy as in the run-in period and both inhalers continue having a sensor fitted. The treatment arms are defined by whether the data, from Relvar/Breo ELLIPTA (maintenance) or Relvar/Breo ELLIPTA (maintenance) and salbutamol MDI (rescue), is fed back to the subject or subject and HCP, or not at all. The 5 treatments arms are as follows:

1. Data on Maintenance use supplied to Subject (app) and HCP (dashboard)
2. Data on Maintenance use supplied to Subject (app)
3. Data on Maintenance and Rescue use supplied to Subject (app) and HCP (dashboard)
4. Data on Maintenance and Rescue use supplied to Subject (app)
5. No data supplied to Subject or HCP

Following randomisation, subjects in arms 1, 2, 3 and 4, will receive training on how to download and use the smart phone app, including how to connect and register the sensors via Bluetooth to their smart phone and to the app. Subjects in arm 5 who receive no data will be provided with a home hub so that their data will be uploaded during study, though they and their HCP will not see that data. Technical and operational details around registering sensors, connecting sensors to smart phone or a home hub and other details of app connectivity and function will be provided/referenced in the Study Reference Manual (SRM).

Visit 5 (V5)

Following randomisation, subjects will be asked to return to the site, after one month, at V5. At this visit the HCP will ensure that all subjects are able to use the provided inhalers correctly (correct use). For Arms 1, 2, 3 and 4 the site should ensure the sensors are attached correctly to the inhalers, are connected to the smart-phone via bluetooth and the HCP should ensure that subjects have been able to use the app. For subjects on Arm 5, the HCP will need to ensure that sensors are correctly attached to the inhalers.

At this visit, for subjects on Arms 1 and 3 the HCP will also, be able to review the subject's adherence to treatment from month 1, and for Arm 3 also review the subject's rescue medication use. The HCP can as needed use the data (Arms 1 and 3) to discuss with these subjects their adherence and if needed the importance of taking their medication as it is prescribed. In reviewing the data the HCP should consider how they would respond if this data was available as part of normal standard of care. For Arm 3 the HCP can also review the subject's rescue medication use and again should consider how they would respond if this data was available as part of normal standard care. The

outcome of the HCP data review will be recorded in the electronic Case Report Form (eCRF).

Conditional Visits 6, 7, 8 and 9 (V6, V7, V8, V9)

For subjects included on treatment arms 1 and 3, the HCP will review a subject's sensor data via the dashboard, as a minimum every 4 weeks. However, the data can be assessed more often as needed. After assessment of the data, the HCP will be able to, at their own discretion, act on this data by calling/emailing or inviting the subject to the clinic to discuss their asthma further, or they can decide to take no action. When reviewing the data the HCP should consider how they would respond if this data was available as part of normal standard of care. The action(s) and any outcomes taken in response to these conditional visits, initiated by the HCP, will be recorded in the eCRF and in the subject's medical record, including if no action was taken. If the HCP reviews the data at a time other than for the conditional visit and schedules a visit for the subject, this will be recorded in the eCRF as an unscheduled visit. Furthermore, subjects in all arms will be educated to recognise symptoms of asthma worsening and instructed to contact the HCP in this event. These events will also be recorded in the eCRF as unscheduled visits.

Visit 10 (V10)

All Subjects will return to site for final study assessments at the end of the 6 month treatment period.

Visit 11 (V11 Follow Up)

A follow-up visit will take place one week (±2 days) after V10 and may be conducted as either a clinical visit or a phone call for final safety check.

A subject will be considered to have completed the study when they have completed all phases of the study including screening, flexible run-in, the randomized treatment phase, and safety follow-up.

Dispensing Visits

All Subjects will be asked to return to the pharmacy or an independent nurse/designee at the study centre if a pharmacy is not available for these dispensing visits. They will need to bring their used Relvar/Breo ELLIPTA and/or salbutamol MDI and clip-on sensors in order to pick up their next Relvar/Breo ELLIPTA and/or salbutamol MDI as required during the course of the study. During these dispensing visits, the sensor will be attached to the new devices and switched on at the site. There will be no assessments performed, these visits are only for dispensing of study drug, as well as to ensure that subjects are able to transfer and pair the sensors. Subjects should return the previous Relvar/Breo ELLIPTA and any salbutamol MDI that need replacing at these visits.

As a minimum, the following will need to be captured: the date of visit, medication dispensed to the subject and also medication returned by the subject, including remaining doses on the ELLIPTA dose counter. This data should be recorded for entry into the eCRF.

Early Withdrawal Visit (EW)

Subjects who have permanently discontinued from the CIS, but continue Relvar/Breo study treatment and have not withdrawn consent are encouraged to continue in the study and complete all remaining protocol specified clinic visits. If a subject is withdrawn then they should complete the assessments as per Section 2. Reasons for withdrawal are provided in Section 8.2.

5.2. Number of Subjects

Approximately 600 subjects will be screened to achieve 432 randomised and 380 subjects are anticipated to have data available for the primary analysis for an estimated total of 76 subjects per treatment group.

5.3. Subject and Study Completion

A subject is considered to have completed the study if he/she has completed the last scheduled procedure shown in Section 2, including the follow up visit.

The end of the study is defined as the date that the last subject completes the last scheduled procedure shown in the Section 2.

5.4. Scientific Rationale for Study Design

This study will be an open label study, as it is not possible to blind the treatment arms to which sensors (maintenance or rescue) are providing feedback to the patient via the app, and also, whether or not the patients' HCP has access to this data via the dashboard.

A true control arm (no sensors on ELLIPTA or MDI) cannot be incorporated into the design. All subjects need to have a sensor on their maintenance and rescue medication in order to consistently measure their adherence to maintenance and level of rescue medication use; as other methods of measuring adherence and rescue medication use (paper or electronic diaries and prescription refills) have inherent problems. Therefore, arm 5 is considered the best attempt at a control arm as neither subjects nor HCP will receive any data from either the ELLIPTA or rescue medication sensors and so could be considered the closest possible match to normal current practise.

Any asthmatic patient who is currently uncontrolled (ACT<20) on their current ICS/LABA medication may be recruited and will, as needed, switch to Relvar/Breo ELLIPTA, if not already prescribed that. Due to this possible change in maintenance medication, a flexible run-in period has been incorporated into the study design, to enable assessment of any impact associated with the change of drug/dosing frequency, or simply being on the study, before being randomised to treatment on the study.

The 5 treatment arms of the study will allow future development of the CIS and provide directional data on which aspects of the CIS have an impact on adherence, in particular,

the impact of HCP being able to review adherence data and the impact of data being provided from both maintenance and rescue medications on adherence.

5.5. Dose Justification

Relvar/Breo ELLIPTA and Salbutamol MDI will be prescribed as per label. The dosage of Relvar/Breo prescribed to a subject at the beginning of the study will depend on the dosage of their current ICS/LABA treatment and therefore, whether they will receive either 100/25 mcg or 200/25 mcg Relvar/Breo ELLIPTA. Changing between doses is permitted during the study treatment period if deemed necessary by the investigator.

6. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted.

6.1. Inclusion Criteria

AGE
1. Subjects aged 18 years or older, at the time of signing the informed consent.
TYPE OF SUBJECT AND DIAGNOSIS
2. Subjects with documented physician diagnosis of asthma as their primary respiratory disease. 3. Asthma Control Test (ACT) score <20 at screening visit 4. Non-smokers (never smoked or not smoking for >6 months with <10 pack years history (Pack years = [cigarettes per day smoked/20] x number of years smoked)
SEX
5. Male or Female subjects: A female subject is eligible to participate if she is not pregnant (see Appendix 4), not breastfeeding, and at least one of the following conditions applies: (i) Not a woman of childbearing potential (WOCBP) as defined in Appendix 4. OR (ii) A WOCBP who agrees to follow the contraceptive guidance in Appendix 4 during the treatment period and for at least 5 days] after the last dose of study treatment.

INFORMED CONSENT
6. Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the consent form and in this protocol. 7. Subject understands and is willing, able, and likely to comply with study procedures and restrictions. 8. Subject must be able to read in a language supported by the smart phone app in their region
CURRENT ASTHMA THERAPY
9. Subject must have been on maintenance therapy (Fixed dose combination ICS/LABA) for 3 months, cannot have changed dose in the month prior to screening and be able to change to an equivalent dose of Relvar/Breo for the duration of the study. Other background asthma medication such as anti-leukotrienes and oral corticosteroids are permitted provided the dose has been stable for 1 month prior to screening. 10. Subject must be able to change to Salbutamol/Albuterol MDI rescue for the duration of the study and judged capable of withholding albuterol/salbutamol for at least 6 hours prior to study visits.
DIGITAL CRITERIA
11. Subject must have their own Android or IOS smart phone and a data package suitable for the installation and running of the app and sending and receiving data. Data used by the CIS is approximately 1MB per month as a maximum; this is less data than a 1 minute video streamed from YouTube (2MB)). 12. Subjects must be willing and able to download the app on their personal smart phone and keep it turned on for the duration of the study. This will also require Bluetooth to be turned on for duration of the study. Subjects will also have to turn on mobile data for the app for the duration of study; unless travelling and when extra data roaming costs could be incurred.

6.2. Exclusion Criteria

A subject will not be eligible for inclusion in this study if any of the following criteria apply:

RELEVANT HABITS
1. Subjects with a known or suspected alcohol or drug abuse which in the opinion of the investigator could interfere with the subject's proper completion of the protocol requirement
CONTRAINDICATIONS
2. History of life threatening asthma: Defined for this protocol as an asthma episode that required intubation and/or was associated with hypercapnea, respiratory arrest or hypoxic seizures within the last 6 months 3. A lower respiratory tract infection within 7 days of the screening visit. 4. Concurrent diagnosis of COPD or other respiratory disorders including active tuberculosis, lung cancer, bronchiectasis, sarcoidosis, lung fibrosis, pulmonary hypertension, interstitial lung diseases or other active pulmonary diseases. 5. History of hypersensitivity/intolerance to any components of the study inhalers (e.g., lactose, magnesium stearate). In addition, subjects with a history of severe milk protein allergy that, in the opinion of the study physician, contraindicates participation will also be excluded. 6. Historical or current evidence of clinically significant or rapidly progressing or unstable cardiovascular, neurological, cardiovascular, neurological, renal, hepatic, immunological, endocrine (including uncontrolled diabetes or thyroid disease) or hematological abnormalities that are uncontrolled. Significant is defined as any disease that, in the opinion of the investigator, would put the safety of the subject at risk through participation, or which would affect the analysis if the disease/condition exacerbated during the study.
DIAGNOSTIC ASSESSMENTS AND OTHER CRITERIA
7. Patient who have ever received treatment with biological based therapy e.g. omalizumab, mepolizumab, for asthma 8. Subjects who have received an investigational drug and/or medical device within 30 days of entry into this study (Screening), or within five drug half-lives of the investigational drug, whichever is longer 9. A subject will not be eligible for this study if he/she is an immediate family member of the participating investigator, sub-investigator, study coordinator, employee of the participating investigator, or any family member of a Propeller Health employee

Inclusion Criteria for Randomisation

ACT Control at V2, or V3 or V4 of run-in period
1. Asthma Control Test (ACT) score <20 at randomisation visit (V2)

6.3. Lifestyle Restrictions

There are no lifestyle restrictions.

6.4. Screen, Run-in and Randomisation Failures

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently entered the run-in period.

A subject who completes V1 assessments and is dispensed the study medication for the run-in period is considered to have entered the run-in period.

A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse events (SAEs) will be collected in the eCRF.

Run-in failures are defined as subjects who consent to participate in the clinical study, enter the run-in period but are not subsequently randomised and do not have any randomisation visit (V2, V3, or V4) procedures other than ACT assessment. Information including demography, run-in failure details, eligibility criteria, and any serious adverse events (SAEs) will be collected in the eCRF.

Randomisation failures are those subjects that complete at least one Randomization procedure other than ACT but are not subsequently randomised and do not enter the study treatment period.

Any subject who completes the run-in period and then meets the randomization criteria and is dispensed the study treatment at V2 is considered to have entered the treatment period.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened, at the discretion of the investigator and should be assigned with a new subject number.

7. TREATMENTS

Study treatment is defined as any investigational treatment(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study subject according to the study protocol.

7.1. Treatments Administered

All subjects will 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. Guidance on which Relvar/Breo dose is appropriate, dependent on current therapy is included in Section 7.2.

Salbutamol MDI rescue medication will be prescribed to subjects to use as needed throughout the study for relief of asthma symptoms as per usual practice.

Study Treatment Name:	RELVAR/BREO ELLIPTA	Salbutamol MDI
Dosage formulation:	ELLIPTA DPI – 30 doses per device	Metered Dose Inhaler – 200 doses per device
Unit dose strength(s)/Dosage level(s):	100/25 mcg per actuation and 200/25 mcg per actuation	100 mcg salbutamol per actuation
Route of Administration	Inhaled	Inhaled
Dosing instructions:	One inhalation once daily	PRN
Packaging and Labelling	Study Treatment will be provided in a container. Each container will be labelled as required per country requirement.	Treatment will be provided locally. and will be labelled as per country requirements.
Manufacturer	GlaxoSmithKline (GSK)	

All subjects 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 (subject alone or subject and HCP) that defines the treatment arms. See Table 1 for a description of what data is fed back to who for each treatment arm. Further information /reference material for the CIS is provided in the SRM.

Table 1 Treatment Arms

	Relvar/Breo Sensor Data Available to		Salbutamol MDI Sensor Data Available to	
Treatment Arm	**Subject**	**HCP**	**Subject**	**HCP**
1	X	X		
2	X			
3	X	X	X	X
4	X		X	
5				

7.2. Relvar/Breo Dose Guidance:

FF/VI 100mcg/25mcg dose is comparable to fluticasone propionate/salmeterol low and medium doses. See SRM for further guidance for dose conversion for other corticosteroids.

Further information detailing equivalence of Relvar/Breo to other ICS/LABA combination treatment, for subjects who are switched, will be included in the SRM.

7.3. Medical Devices

The clip on sensors and associated app for subjects' Smartphone are produced by Propeller Health and are being provided by GSK for use in this study. These devices, which are fitted on to the Relvar/Breo ELLIPTA DPI and albuterol/salbutamol MDI to electronically record actuation data and associated app and HCP dashboard to provides that data, both have US FDA 510(K) clearance to market (Class II device) and European Union (EU) European Conformity (CE) marking (Class I device).

Instructions for medical device use are provided in the SRM, PSSM and in the pack insert for each device.

7.4. Dose Modification

During the treatment period, investigators may modify the dose of a given subject during the study. Subjects in turn may change their dose from 100/25mcg FF/VI to 200/25mcg FF/VI and vice-versa if deemed absolutely necessary by the investigator.

7.5. Method of Treatment Assignment

Assignment of Subject Number

A unique Subject Number will be assigned to any subject who has signed the informed consent at V1. The unique Subject Number will be used to identify individual subjects during the course of the study.

Assignment of Randomisation Number

At V2, V3 or V4 (Run-in visits), subjects meeting the eligibility criteria will be assigned to study treatment using an interactive web response system (IWRS) that will be used by HCP or designee to register the subject, randomise the subject and provide treatment assignment information. Details on how to use RAMOS NG, the IWRS, to register and randomise subjects is provided in the RAMOS NG IWRS manual and SRM.

Once a randomisation number has been assigned to a subject, it cannot be reassigned to any other subject in the study.

Subjects will be assigned to study treatment in accordance with the randomisation schedule. The randomisation code will be generated by GSK using a validated computerised system. A subject will be randomised using RAMOS NG. The study will use central-based randomisation system to allocate treatments.

Subjects will be randomized 1:1:1:1:1 to one of the five treatments arms for the duration of the treatment period. See Section 5 for description and numbering of arms.

Each investigator will be provided with sufficient study supplies to respond directly to subject requests for study treatment as required. Additional supplies will be supplied as needed to the sites. Details of how to use the IWRS system (RAMOS NG) to randomise subjects and manage study treatment supplies (including dispensing) is provided in the RAMOS NG IWRS manual and SRM.

7.6. Blinding

The study is open label, neither the subject, HCP, site staff, or sponsor is blinded to treatment assignment.

7.7. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.
2. Only subjects enrolled in the study may receive study treatment and only authorised site staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorised site staff.

3. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (i.e. receipt, reconciliation, and final disposition records).
4. Further guidance and information for the final disposition of unused study treatment are provided in the SRM.

Under normal conditions of handling and administration, study treatment is not expected to pose significant safety risks to site staff.

A Material Safety Data Sheet (MSDS)/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from GSK.

7.8. Treatment Compliance

The primary measure of treatment compliance for both Relvar/Breo ELLIPTA and Salbutamol MDI will be captured by the respective sensor for those treatments. However, the date of prescription and date of return of the inhaler, as well as start and finished dose count on each Relvar/Breo ELLIPTA, will be recorded in source documents at the dispensing visit and also transferred to the eCRF.

7.9. Concomitant Therapy

All medications for asthma, excluding biological therapy and for other disorders that are not contra indicated in asthma, or prohibited in this study, may be continued throughout the study.

Please consult the prescribing information for the full list of medications which need to be used with caution:

Beta-blockers: Use with caution. May block bronchodilatory effects of beta-agonists and produce severe bronchospasm.

Diuretics: Use with caution. Electrocardiographic changes and/or hypokalemia associated with non-potassium-sparing diuretics may worsen with concomitant beta-agonists.

Non-study asthma medications: A detailed history of previous 3 months and up to 12 months prior to inclusion, as available, for prescriptions for maintenance medications (ICS/LABA combination) will be captured in the subjects eCRF and also any other ongoing asthma medications at inclusion.

Any medication or vaccine of relevance to the study or prescribed for safety events, including exacerbations experienced during the study, that the subject is receiving at the time of enrolment or receives during the study must be recorded in the eCRF in addition to medical records. As minimum the following will be needed:

- reason for use
- dates of administration including start and end dates

- dosage information including dose and frequency

Over-the-counter medicines, vitamins, and/or herbal supplements are not required to be captured.

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

7.10. Prohibited Concomitant Medication

Subjects must abstain from taking the following medications from 5 days prior to the first dose of study medication until completion of the follow-up visit.

- Strong cytochrome P450 3A4 inhibitors (e.g., ketoconazole)
- Monoamine oxidase inhibitors and tricyclic antidepressants:
- Subjects must never have been treated with a biological therapy for asthma e.g. omalizumab, mepolizumab.

Patients using Relvar/Breo ELLIPTA should not use another medicine containing a LABA (e.g., salmeterol, formoterol fumarate, arformoterol tartrate, indacaterol) for any reason.

Do not use in combination with an additional medicine containing a LABA because of risk of overdose.

For full list of cautions for use and medicine interactions please consult the prescribing information and/or consult the study Medical Monitor if in doubt.

7.11. Treatment after the End of the Study

There is no plan to continue to provide treatment following the end of the study. The investigator is responsible for ensuring that consideration has been given to the post-study care of the subject's medical condition, whether or not GSK is providing specific post-study treatment.

Medications initiated after completion of the assessments at V10 or the EW visit will not be recorded in the eCRF unless taken to treat an AE or asthma exacerbation. subjects who have completed the EW visit are allowed to use any medications prescribed by the Investigator or primary care physician.

8. DISCONTINUATION CRITERIA

Subjects that permanently stop study treatment (any aspect of the CIS) are encouraged to remain in the study. Subjects have the right to discontinue study treatment before the end of the study. A subject may also be asked to discontinue study treatment at the investigator's discretion.

Subjects who withdraw from study treatment prematurely (for any reason) should, where possible, continue to be followed-up as per protocol until the completion of the Safety Follow-up assessments. If patients want to discontinue use of the CIS but will continue taking the Relvar/Breo ELLIPTA DPI then they will be given the option to continue to remain in study if they continue using the clip-on sensor for ELLIPTA. If this is not possible, the Investigator must encourage the subject to participate in as much of the study as they are willing (or able) to. For those subjects who do not want to use the sensor during the study, their health outcome information will be collected along with any additional adherence data. Likewise, subjects who change their dose of Relvar/Breo (FF/VI) at the discretion of the investigator during the study will be given the option to remain on the study, all information will continue to be collected for the duration of the study. However, subjects who permanently discontinue from Relvar/Breo ELLIPTA should be withdrawn from the study.

A subject may be withdrawn from study treatment at any time. A reason for premature discontinuation of study treatment must be captured in the eCRF.

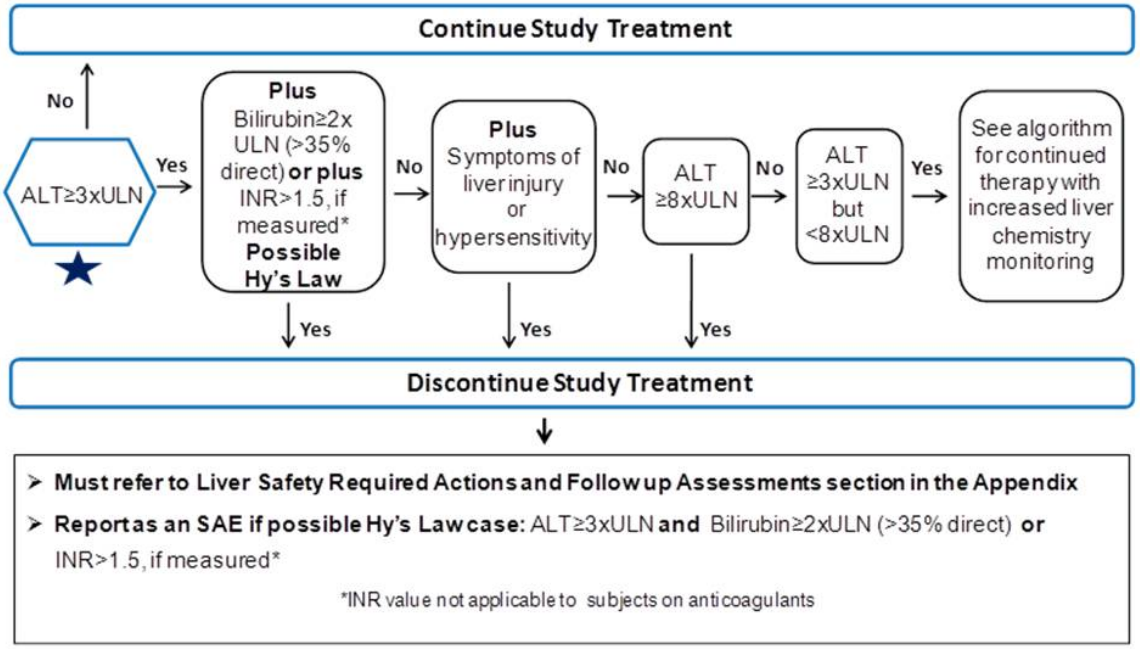
8.1. Discontinuation of Study Treatment

8.1.1. Liver Chemistry Stopping Criteria

There are no scheduled blood tests in this study. If however, the subject has a routine blood test during the study and the results suggest abnormal liver function, then the liver stopping criteria will apply.

Liver chemistry stopping and increased monitoring criteria have been designed to assure subject safety and evaluate liver event etiology (in alignment with the FDA premarketing clinical liver safety guidance). These protocol guidelines are in alignment with FDA premarketing clinical liver safety guidance: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf.

Discontinuation of study treatment for abnormal liver tests should be considered by the investigator when a subject meets one of the conditions outlined in the algorithm, see Appendix 5, or if the investigator believes that it is in the best interest of the subject.



8.1.2. QTc Stopping Criteria

ECGs are not planned at Screening or during this study. However, if during the study a subject has an ECG performed the following stopping criteria apply and treatment should be withdrawn:

A subject who meets the bulleted criteria below will be withdrawn from the study:

- QTcF>500 msec or uncorrected QT>600 msec
- Change from V1 baseline: QTcF> 60msec

For patients with underlying **bundle branch block**, follow the discontinuation criteria listed below:

Discontinuation QTc with Bundle Branch Block	
< 450 msec	> 500 msec
450 – 480 msec	≥ 530 msec [Note: QTc(F)>500 msec for Korean subjects]

8.2. Withdrawal from the Study

- A subject may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioural, compliance to protocol or administrative reasons.

- Subjects should be reminded at each visit that if they do choose to withdraw themselves then, they should contact the Investigator or Study staff as soon as possible and arrange an EW visit.
- Female subject will be withdrawn if they produce a positive pregnancy test whilst on the study.
- If the subject withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

Refer to the Section 2 for data to be collected at the time of EW from the study

8.3. Lost to Follow Up

A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.
- Before a subject is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.
- Should the subject continue to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

9. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarised in Section 2.

Protocol waivers or exemptions are not allowed

Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the subject should continue or discontinue study treatment.

Adherence to the study design requirements, including those specified in the Section 2, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the subject's routine clinical management (e.g., blood count) and obtained before signing of the informed consent form (ICF) may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and was performed within the time frame defined in the Section 2.

9.1. Efficacy Assessments

9.1.1. Primary, Secondary and Other Adherence Measures

The Primary, Secondary and Other adherence endpoint (adherence to maintenance medication) data is collected by the Clip-on Sensor for ELLIPTA and records the time and date when the ELLIPTA cover is opened and closed.

The sensor will be attached to subjects ELLIPTA Relvar/Breo treatment from start of run-in until V10. References and material for fitting the sensors, downloading the app and other aspects of using the CIS are included in the SRM.

9.1.2. Secondary Efficacy Endpoints

9.1.2.1. Asthma Control Test

This assessment is described in Section 9.1.3.1 and will be collected electronically at the site at the timepoints detailed in Section 2. This will be carried out via use of the electronic Patient Reported Outcome (ePRO) device.

9.1.2.2. Rescue Medication Use

Rescue Medication use endpoint data is collected by the Clip on Sensor for salbutamol MDI and records time and date when the MDI is actuated.

The sensor will be attached to the subject's salbutamol MDI treatment from start of run-in until V10. Details for fitting the sensor and other aspects of using the CIS are included in the SRM.

9.1.3. Questionnaires and Interviews

It is preferred that the questionnaires are administered at the same time of day at each visit and that this time of day is the same as when they were originally administered (as is feasible/appropriate), in order to avoid potential bias due to the time of day when responding. The subjects should not be told the results of any diagnostic tests prior to completing the questionnaires and the questionnaires should be completed before any procedures are performed on the subject to avoid influencing the subject's response. Adequate time in a quiet, comfortable location must be allowed to complete all items on the questionnaires and if necessary, the subject must be encouraged to complete any questionnaires or missing items fully. Full guidance for obtaining good quality data from patient-completed questionnaires is included in the SRM.

All the questionnaires will be completed on an ePRO device at the clinical study site and at the time detailed in the Section 2. **Further instructions for completing the questionnaires can be found in the SRM.**

9.1.3.1. 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) with a range of 5 to 25. By answering all 5 questions a subject with asthma can obtain a score that may range between 5 and 25, with higher scores indicating better control. An ACT score of 5 to 19 suggests that the subject's asthma is unlikely to be well controlled. A score of 20 to 25 suggests that the subject's asthma is likely to be well controlled. The total score is calculated as the sum of the scores from all 5 questions [Nathan, 2004]. The minimally important difference (MID) for ACT is 3 [Schatz, 2009].

Subjects will complete the ACT at times shown in the Section 2 using the electronic version on the ePRO device at the clinical site.

The ACT has been developed as a measure of subjects' asthma control that can be quickly and easily completed in clinical practice and by telephone. The questions are designed to be self-completed by the subject.

Please refer to the SRM for further details.

9.1.3.2. 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 will be completed on an ePRO device at the clinical study site and at the times detailed in the Section 2.

Please refer to the SRM for further details.

9.1.3.3. St Georges Respiratory Questionnaire (SGRQ)

The St. George's Respiratory Questionnaire is a well established instrument, comprising 50 questions 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 subject with a recall over the past 4 weeks [Jones, 1992]

SGRQ will be completed on an ePRO device at the clinical study site and at the times detailed in the Section 2.

Please refer to the SRM for further details.

9.1.3.4. Patient Activation Measure (PAM)

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 questionnaire will be completed at the times shown in the Section 2.

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].

PAM will be completed by subjects on an ePRO device at the clinical study site and at the times detailed in the Section 2.

Please refer to the SRM for further details.

9.1.3.5. Medication Adherence Report Scale for Asthma (MARS-A), 10-item questionnaire

Reported adherence to medication will be assessed with the Medication Adherence Report Scale for Asthma (MARS-A) questionnaire at times shown in the Schedule of Activities (SoA).

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 has no specified timeframe on which responses should be based but generally refer to the present moment. MARS-A will be completed on an ePRO device at the clinical study site and at the times detailed in the Section 2.

Please refer to the SRM for further details.

9.1.3.6. 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 rated on a 5-point Likert scale [Horne, 2002].

The BMQ General comprises a General Benefit scale, General Harm scale and a General Overuse scale assessing beliefs about pharmaceuticals as a class of treatment. The General Harm scale assesses beliefs about the intrinsic nature of medicines and the degree to which they are perceived as harmful and should be avoided if possible. The General Overuse scale represents beliefs about the use of medicines and whether they are

overprescribed by clinicians. The BMQ Specific (Asthma) comprises two scales: one assessing patients' beliefs about the necessity of preventer medication for maintaining present and future health (Necessity scale), and the other assessing their concerns about the potential adverse consequences of using it (Concerns scale). Four items were added for use in patients with asthma.

BMQ will be completed on an ePRO device at the clinical study site and at the times detailed in the Section 2.

Please refer to the SRM for further details.

9.1.3.7. Exit Questionnaire

All subjects will complete a questionnaire at the end of the final study visit (V10) to assess the CIS. This questionnaire is designed to understand the subject's perceptions of the CIS. It is self-completed on the ePRO device by subjects. It includes questions relating to the concepts below:

- Overall satisfaction with CIS
- Parts of the CIS that were most /least helpful
- Level of engagement with the CIS
- Challenges/difficulties with using CIS
- Subject perception of the impact of the CIS on asthma
- Subject perception of future use of a similar system
- Impact of CIS on physician interaction

9.1.3.8. Exit Interviews

Exit interviews will be conducted for subjects at selected sites at the visit after they have completed their course of study medication (V11). Exit interviews are qualitative interviews conducted with study subjects to capture a subject's experience on changes in asthma and perceptions of the CIS.

Interview questions are designed to fully assess a subject's experience in a structured format by a trained interviewer. Subject feedback will audio-taped for subsequent transcription and qualitative analysis.

These exit interviews will be conducted by external vendors after subjects have completed V11. For logistical reasons, this phone call need not occur at the clinical site and can be completed within 14 days of V11. The analysis and report of the exit interview will be managed by a separate RAP.

9.2. Serious Adverse Events (SAE), Non-Serious Adverse Events that leads to withdrawal and Non Serious Adverse Drug Reactions (ADR)

The Investigator or site staff will be responsible for detecting, documenting and reporting events that meet the definition of a, non-serious adverse events that leads to withdrawal, non-serious adverse drug reaction (ADR) or SAE. The definition of an ADR is any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, for which there is a reasonable possibility that the untoward occurrence is *causally related* to the medicinal product. ADRs are a subset of AEs for a given medicinal product.

Potential SAEs and associated non serious ADRs may be identified from a subject's primary HCP report or a subject's health records. The HCP will have the ultimate responsibility for determining causality and seriousness.

In some countries extra safety information may be requested as required by local Regulatory Agencies and information providing detail of these extra safety events and how these should be reported are included in Appendix 7.

In this study, only information regarding non- serious adverse drug reactions (ADRs), AEs leading to withdrawal and serious adverse events (SAEs) will be detected, documented and reported. However, the definition of an AE is critical for the definition of non-serious ADRs and SAEs.

The definitions of an AE or SAE can be found in Appendix 3

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious or that caused the subject to discontinue the study (see Section 8.1).

9.2.1. Time Period and Frequency for Collecting AE, ADR and SAE Information

- Any SAEs assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time a subject consents to participate in the study up to and including any follow-up contact.
- AEs leading to withdrawals and ADRs will be collected from the start of Study Treatment until the follow-up contact at the timepoints specified in SoA Section 2
- Medical occurrences that begin prior to the start of study treatment but after obtaining informed consent may be recorded on the Medical History/Current Medical Conditions section of the eCRF.
- All SAEs will be recorded and reported to the sponsor or designee within 24 hours, as indicated in Appendix 3 The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

- Investigators are not obligated to actively seek AEs or SAEs in former study subjects. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify the sponsor.
- The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

9.2.2. Method of Detecting AEs, ADRs and SAEs

Care will be taken not to introduce bias when detecting AE and/or SAE. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrence.

The Investigator or site staff will be responsible for detecting, documenting and reporting events that meet the definition of a non-serious adverse drug reaction (ADR), AE (leading to withdrawal) or SAE.

Potential SAEs, AE (leading to withdrawal) and associated non serious ADRs may be identified from patient's medical records. The Investigator will have the ultimate responsibility for determining causality and seriousness.

In this study, only information regarding non- serious adverse drug reactions (ADRs), AE leading to withdrawal and serious adverse events (SAEs) will be detected, documented and reported.

9.2.3. Follow-up of AEs, ADRs and SAEs

After the initial AE that led to withdrawal/non-serious ADR/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs, will be followed until the event is resolved, stabilized, otherwise explained, or the subject is lost to follow-up (as defined in Section 8.3). Further information on follow-up procedures is given in Appendix 3.

9.2.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a study treatment under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.

- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information e.g., summary or listing of SAE) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

In some countries extra safety information may be requested as required by local Regulatory Agencies and information for this and how these should be reported are included in Appendix 7.

9.2.5. Cardiovascular and Death Events

For any cardiovascular events as detailed in Appendix 3 and all deaths, whether or not they are considered SAEs, specific Cardiovascular (CV) and Death sections of the CRF will be required to be completed. These sections include questions regarding cardiovascular (including sudden cardiac death) and non-cardiovascular death.

The CV CRFs are presented as queries in response to reporting of certain CV Medical Dictionary of Regulatory Activities (MedDRA) terms. The CV information should be recorded in the specific cardiovascular section of the CRF within one week of receipt of a CV Event data query prompting its completion.

The Death CRF is provided immediately after the occurrence or outcome of death is reported. Initial and follow-up reports regarding death must be completed within one week of when the death is reported.

9.2.6. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as SAEs

The following disease related events (DREs) are common in subjects with asthma and can be serious/life threatening:

9.2.6.1. Asthma Exacerbations

For the purposes of this study, severe asthma exacerbations will be collected and recorded on the asthma exacerbation eCRF page from the start of treatment until follow up/or the EW visit for those subjects that withdraw from participation in the study.

A severe asthma exacerbation is defined as deterioration of asthma requiring the use/additional use of systemic corticosteroids (tablets, suspension, or injection), or antibiotics and inpatient hospitalisation, or emergency department visit due to asthma that required systemic corticosteroids or antibiotics. Further clarification will be present in the SRM.

Asthma exacerbations should not be recorded as an AE unless they meet the definition of an SAE.

These events will be recorded on the DRE page in the subject's eCRF within 24 hours of the physician becoming aware. The time period for collection of exacerbation information in the eCRF will be from the time that the ICF is signed until the Exit visit or EW.

For consistency, exacerbations separated by less than 7 days will be treated as a continuation of the same exacerbation.

9.2.7. Pregnancy

Details of all pregnancies in female subjects will be collected after the start of study treatment and until at least 5 terminal half-lives after the last dose.

If a pregnancy is reported, the investigator should inform GSK within 2 weeks of learning of the pregnancy and should follow the procedures outlined in Appendix 4.

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAE.

9.2.8. Medical Device Incidents (Including Malfunctions)

Procedures for Documenting Medical Device Incidents are provided in Appendix 6.

9.3. Treatment of Overdose

For this study, any dose of Relvar/Breo ELLIPTA greater than the prescribed dose within a 24-hour time period will be considered an overdose.

GSK is not recommending specific treatment guidelines for overdose and toxicity management. The investigator is advised to refer to the relevant document(s) for detailed information regarding warnings, precautions, contraindications, adverse events, and other significant data pertaining to the study drug being used in this study. Such documents may include, but not be limited to, the IB or equivalent document provided by GSK.

In the event of an overdose, the HCP/treating physician should:

1. Contact the Medical Monitor immediately.
2. Document the quantity of the excess dose as well as the duration of the overdosing in the CRF.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the subject.

9.4. Screening and Safety Assessments

Planned time points for all screening and safety assessments are provided in Section 2.

9.4.1. Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the Skin, Cardiovascular, Respiratory, Gastrointestinal and Neurological systems. Height and weight will also be measured and recorded.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

The physical exam is to inform on inclusion and only needs to be recorded in the subject's source/medical notes. Physical exams will be performed at the time points specified in the Section 2.

9.4.2. Vital Signs

Vital signs (systolic and diastolic blood pressure and pulse rate) will be performed at the screening visit only as part of physical exam. The measurement will be taken after 5 minutes rest in a semi-supine position. One reading of blood pressure and pulse will be taken.

The vital signs are to inform on inclusion and only needs to be recorded in the subject's source/medical notes.

9.4.3. Clinical Safety Laboratory Assessments

Urine pregnancy tests are performed at timelines detailed in Section 2. The tests will be provided locally. The results of the tests should be recorded in the subject's medical records only.

If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in subject management or are considered clinically significant by the investigator (e.g., SAE or AE), then the results must be recorded in the eCRF.

9.5. Biomarkers

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

9.5.1. FeNO in breath

FeNO will be measured using a handheld electronic device. Measurements will be obtained in accordance with the American Thoracic Society (ATS)/European Respiratory Society (ERS) Recommendations for Standardized Procedures for the Online and Offline Measurement of Exhaled Lower Respiratory Nitric Oxide and Nasal Nitric Oxide [Silkoff, 2005]. All sites will use standardized equipment provided by a central vendor. For each observation, at least 2 measurements will be obtained to establish reproducibility (up to 8 measurements can be performed). FeNO measurements will be

interpreted in accordance with the Official ATS Clinical Practice Guideline: Interpretation of Exhaled Nitric Oxide Levels (FeNO) for Clinical Applications [Dweik, 2011]. FeNO observations must be completed before PEF assessments. Peak Expiratory Flow (PEF)

PEF will be performed using a Mini Wright Peak Flow Meter provided by GSK. Details of how this procedure is performed is detailed in the SRM.

PEF will be taken in triplicate at timelines detailed in the Section 2. All 3 measures should be recorded in the subject's record and transferred to the eCRF.

9.5.2. Peak Expiratory Flow (PEF)

PEF will be performed using a Mini Wright Peak Flow Meter provided by GSK. Details of how this procedure is performed is detailed in the SRM.

PEF will be taken in triplicate at timelines detailed in the Section 2. All 3 measures should be recorded in the subjects record and transferred to the eCRF.

9.6. Prescription Record for Asthma Maintenance Medication

The following will be collected in the eCRF and confirmed by a subject's medical records, or the prescribing physician. Prescriptions for a subject's asthma maintenance therapy (ICS/LABA combinations) for a minimum of 3 months and up to 12 months prior to inclusion, as available.

9.7. Medical Resource Utilisation and Health Economics

Medical resource utilisation associated with medical encounters, will be collected in the eCRF by the investigator and study-site personnel for all subjects throughout the study.

These events should be recorded and reviewed by the HCP or designee with the subject at all study visits and where available confirmed with a subject's medical records.

Protocol-mandated procedures, tests, and encounters are excluded, though visits relating to HCP review of the CIS dashboard will be captured.

The data collected may be used to conduct exploratory health care resource utilization (HCRU) and economic analyses and will include:

- 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
- Number of prescriptions filled/requested for maintenance medication in the 12 months prior to inclusion.
- Annualised rate of severe exacerbations

- Number of unscheduled visits to primary care related to Asthma

10. DATA MANAGEMENT

- For this study, subject data will be entered into a GSK defined eCRF, transmitted electronically to GSK or designee and combined with data provided from other sources in a validated data system.
- Management of clinical data will be performed in accordance with applicable GSK standards and data cleaning procedures to ensure the integrity of the data, e.g., removing errors and inconsistencies in the data.
- Adverse events and concomitant medication terms will be coded using MedDRA (Medical Dictionary for Regulatory Activities) and an internal validated medication dictionary, GSKDrug.
- eCRFs (including queries and audit trails) will be retained by GSK, and copies will be sent to the investigator to maintain as the investigator copy. Subject initials will not be collected or transmitted to GSK according to GSK policy.

11. STATISTICAL CONSIDERATIONS

11.1. Hypothesis

The main purpose of the study is to compare the effect of 6 months use with the CIS on adherence to ELLIPTA maintenance therapy with adherence to ELLIPTA maintenance therapy without CIS use (sensor alone), in subjects with poorly controlled asthma. 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 and 95% confidence intervals. 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, and arms with rescue medication use feedback versus none, 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, in order to obtain estimated mean treatment differences and 95% confidence intervals. This will be a descriptive comparison and no formal inference is planned.

11.2. Sample Size Determination

11.2.1. Sample Size Assumptions

The fixed sample size calculation is based on the primary endpoint, percentage of ELLIPTA doses taken (daily adherence) between Months 4 and 6 as determined by the maintenance sensor and has approximately 90% power to detect an absolute difference of 15% in the primary comparison. The treatment difference is based on the limited published data [Charles, 2007, van Boven, 2016]. This assumes a conservative standard deviation of 28% (based on a previous study [Charles, 2007]) and significance declared at the two-sided 5% level.

Approximately 432 patients will be randomised in order to obtain at least 380 subjects (i.e. 76 subjects per arm) with available data over the last three months of the treatment period, in anticipation of a 12% drop-out within the first three months. Subjects will be randomised to one of five treatment arms with a ratio of 1:1:1:1:1.

Using the above assumptions the smallest observed effect predicted to result in a statistically significant difference between treatment groups is 9% (minimum detectable difference).

11.2.2. Sample Size Sensitivity

Due to limited historical data within GSK, an external party was hired to conduct a literature review. Based on results from the literature review only one paper in an asthmatic adult population provided adherence rates and variability estimates that could be used as assumptions for power calculations [Charles, 2007].

The study presented sample size assumptions for the treatment difference in mean daily % adherence of 10% and a standard deviation of the data of 18% [s1]. The reported raw means (standard deviation) of mean daily % adherence were 88% (16%) and 66% (27%) in the intervention and control groups, respectively. Due to uncertainty in data variability a wide range of values were explored. Table 2 below presents the power achieved with

the proposed sample size of 76 completers per arm should the assumptions of standard deviation of the data change.

Table 2 Standard Deviation Affect on Power from the Fixed Sample Size

Standard Deviation (%)	Power for Primary Comparison
22	99
24	97
26	94
28	90
30	86
32	81
34	77

11.3. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All subjects who sign the ICF
Total Population	The Total Population will comprise all subjects screened and for whom a record exists on the study database and will be used for the tabulation and listing of reasons for withdrawal before randomisation.
Intent-to-treat	The Intent–to–Treat (ITT) population is defined as all subjects who have been randomised and exposed to at least one dose of treatment. The ITT population will be used for all endpoint analyses and Outcomes will be reported according to the randomised treatment allocation.

11.4. Statistical Analyses

Where possible, data from subjects who withdraw prematurely from the study treatment or the study will be included in any relevant analyses. Specific details for inclusion will be detailed in the Reporting and Analysis Plan (RAP).

The covariates to be considered in the efficacy analyses include age, sex, region and the baseline values, if relevant. Other covariates, if appropriate, may be considered. Specific details will be provided in the RAP.

11.4.1. Adherence Analyses

Endpoint	Statistical Analysis Methods
Primary	The primary analysis will estimate the treatment effect of 6 months use of the ELLIPTA maintenance therapy with CIS when both the subject and the HCP are supplied with data from the maintenance sensor versus no data supplied to the subject and HCP (Arm 1 vs Arm 5) for the primary endpoint 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. The analysis will be performed on the ITT population. The analysis will be performed on the percentage adherence between Months 4 and 6 measured using an Analysis of Covariance (ANCOVA) model allowing for effects due to randomised treatment, baseline adherence, duration (days) in run-in, region, sex, 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. Any subjects with missing intermittent adherence data will be imputed to as non-adherent i.e. 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. Subjects who prematurely discontinue from study will have their post-withdrawal daily adherence data imputed using data from the control arm using an appropriate method of imputation, such as the jump to reference method. This method of assessing the primary endpoint corresponds to a de-facto treatment policy estimand which reflects the anticipated behaviour that subjects will continue to take an asthma combination therapy without the CIS intervention. Missing data due to a medical device incident such as device failure, technical failure of the e-sensor, or data transmission failure will be assumed to be missing at random (MAR). For each subject the percentage adherence measure will be calculated under the assumption that any missing data is MAR, from the proportion of the number of days a subject is adherent divided by the number of days data provided for the last 3 months treatment period. 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 p-value. Summary statistics (mean, standard deviation, median, minimum, maximum) of the primary endpoint will be provided. Where possible, adherence data collected from subjects who withdraw prematurely from study treatment will be included in the analysis. Sensitivity analyses of the primary adherence endpoint will be performed on the ITT population and an assessment of the impact of the missing data will be carried out using multiple imputation methods under different assumptions for missing data for withdrawn subjects. Details will be provided in the RAP.

Endpoint	**Statistical Analysis Methods**
Secondary	The following secondary analyses 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 subjects versus no data supplied to the subject (Arm 2 vs Arm 5) • Rescue and Maintenance data supplied to subject and HCP versus no data supplied to the subject and HCP (Arm 3 vs Arm 5) • Rescue and Maintenance data only supplied to subject versus no data supplied to the subject (Arm 4 vs Arm 5) for the following secondary endpoints: • 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, • Percentage of ELLIPTA doses taken (daily adherence) 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 The analysis will be performed using an ANCOVA model allowing for effects due to randomised treatment effect, baseline adherence, duration (days) in run-in, region, sex, 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. Any subjects with missing intermittent adherence data will be imputed to as non-adherent i.e. 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. Where possible, adherence data collected from subjects who withdraw prematurely from study treatment will be included in the analysis. Subjects who prematurely discontinue from study will be handled as per the primary endpoint analysis. 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. Summary statistics (mean, standard deviation, median, minimum, maximum) of the secondary endpoint will be provided. If a subject has changed dose during the study, sensitivity analyses on the secondary endpoint(s) regarding ACT will be performed where these subjects are removed from the analysed population. Further details will be provided in the RAP.
Exploratory	Will be described in the RAP.

11.4.2. Safety Analyses

All safety analyses will be performed on the ITT Population.

Endpoint	Statistical Analysis Methods
Safety	SAEs, AEs leading to withdrawal and non-serious ADRs will be collected. Safety endpoints will include: • Incidence and type of serious adverse events • Incidence and type of adverse drug reactions • Incidence and type of non-serious adverse events leading to study withdrawal • Incidence of subjects experiencing a severe exacerbation The incidence of any given adverse event (SAE or ADR) for each treatment group is defined as the proportion of subjects in that group who have experienced at least one such adverse event during the study period. The number and percentage of subjects with SAEs, non-serious ADRs and AEs leading to study withdrawal will be summarised by preferred term. The number and percentage of subjects experiencing severe exacerbations over treatment period and the follow-up period will be summarised for each treatment group alongside the primary causes of the exacerbation.

11.4.3. Other Analyses

All other exploratory endpoints, except for qualitative data from exit interviews and questionnaires, will be detailed in the RAP.

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).

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13. APPENDICES

13.1. Appendix 1: Abbreviations and Trademarks

ACT	Asthma Control Test
ADR	Adverse Drug Reaction
AE	Adverse Event
ALT	Alanine amino transferase
ANCOVA	Analysis of Covariance
ASE	All Subjects Enrolled
ASUI	Asthma Symptom Utility Index
ATS	American Thoracic Society
BMQ	Beliefs in Medicine Questionnaire
CE	Europen Conformity
CFR	Code of Federal Regulations
CI	Confidence Interval
CIOMS	Council for International Organizations of Medical Sciences
CIS	Connected Inhaler System
CONSORT	Consolidated Standards of Reporting Trials
COPD	Chronic Obstructive Pulmonary Disease
CP	Conditional Power
CRF	Case Report Form
CSR	Clinical Study Report
CV	Cardiovascular
DPI	Dry Powder Inhaler
DRE	Disease Related Event
ER	Emergency Room
ERS	European Respiratory Society
EW	Early Withdrawal
EU-RMP	European Union – Risk Management Plan
FDA	Food And Drug Administration
FeNO	Fractional exhaled Nitric Oxide
FF	Fluticasone Furoate
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GSK	GlaxoSmithKline
HCP	Healthcare Professional
HCRU	Health Care Resource Utilization
HIPAA	Health Insurance Portability and Accountability Act
HPA	Hypothalamic-pituitary adrenal axis
HRT	Hormonal Replacement Therapy
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference On Harmonisation
ICS	Inhaled Corticosteroids
IEC	Independent Ethics Committees

IP	Investigational Product
IRB	Institutional Review Boards
ITT	Intent-to-Treat
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
IWRS	Interactive Web Response System
LABA	Long-Acting Beta2-Agonist
LOCS	Lens Opacities Classification System
MAR	Missing At Random
MARS-A	Medication Adherence Report Scale for Asthma
MDI	Metered Dose Inhaler
MedRA	Medical Dictionary of Regulatory Activities
MHPD	Marketed Health Products Directorate
MID	Minimally Important Difference
MSDS	Material Safety Data Sheet
PAM	Patient Activation Measure
PEF	Peak Expiratory Flow
PIL	Patient Instruction Leaflet
PRO	Patient Reported Outcomes
RAP	Reporting Analysis Plan
SAE	Serious Adverse Event
SGRQ	St Georges Respiratory Questionnaire
SoA	Schedule of Activities
SRM	Study Reference Manual
SUSAR	Suspected Unexpected Serious Adverse Reactions
UFIE	Unusual Failure in Efficacy
VI	Vilantrol
WOCP	Woman Of Childbearing Potential

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13.2. Appendix 2: Study Governance Considerations

Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with:
    - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
    - Applicable ICH Good Clinical Practice (GCP) Guidelines
    - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IEC/IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects.
- The investigator will be responsible for the following:
    - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC
    - Notifying the IRB/IEC of SAE or other significant safety findings as required by IRB/IEC procedures
    - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the subject or his/her legally authorized representative and answer all questions regarding the study.

- Subjects must be informed that their participation is voluntary. Subjects or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the subject was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Subjects must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the subject or the subject's legally authorized representative.
- Subjects who are rescreened are required to sign a new ICF.

Data Protection

- Subjects will be assigned a unique identifier by the sponsor. Any subject records or datasets that are transferred to the sponsor will contain the identifier only; subject names or any information which would make the participant identifiable will not be transferred.
- The subject must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the subject.
- The subject must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Dissemination of Clinical Study Data

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.

GSK will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate.

The procedures and timing for public disclosure of the results summary and for development of a manuscript for publication will be in accordance with GSK Policy.

Data Quality Assurance

- All subject data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 25 years from the issue of the final Clinical Study Report (CSR)/ equivalent summary unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

Source Documents

- Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Study and Site Closure

GSK or its designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of GSK. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines

Inadequate recruitment of subjects by the investigator

Discontinuation of further study treatment development

13.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

AE Definition
An AE is any untoward medical occurrence in a clinical study subject, temporally associated with the use of a study treatment, whether or not considered related to the study treatment. NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study treatment.

Events <u>Meeting</u> the AE Definition
Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease). Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study. Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE. The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE. Also, "lack of efficacy" or "failure of expected pharmacological action" constitutes an AE or SAE.

Events <u>NOT</u> Meeting the AE Definition
Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject’s condition.

The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition.

Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.

Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

A SAE is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AE. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in persistent disability/incapacity

The term disability means a substantial disruption of a person's ability to conduct normal life functions.

This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect
f. Other situations: Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Definition of Cardiovascular Events

Cardiovascular Events (CV) Definition:
Investigators will be required to fill out the specific CV event page of the CRF for the following AEs and SAEs: Myocardial infarction/unstable angina Congestive heart failure Arrhythmias Valvulopathy Pulmonary hypertension Cerebrovascular events/stroke and transient ischemic attack Peripheral arterial thromboembolism Deep venous thrombosis/pulmonary embolism • Revascularization

Recording AE and SAE

AE and SAE Recording
When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) related to the event. The investigator will then record all relevant AE/SAE information in the CRF. It is **not** acceptable for the investigator to send photocopies of the subject's medical records to GSK in lieu of completion of the GSK /AE/SAE CRF page. There may be instances when copies of medical records for certain cases are requested by

GSK. In this case, all subject identifiers, with the exception of the subject number, will be redacted on the copies of the medical records before submission to GSK.

The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

Mild: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.

Moderate: An event that causes sufficiently discomfort and interferes with normal everyday activities.

Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AE and SAE can be assessed as severe.

> An event is defined as ‘serious’ when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

The investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE.

A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

The investigator will use clinical judgment to determine the relationship.

Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.

The investigator will also consult the Investigator’s Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.

For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to** GSK**.**

The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by GSK to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

If a subject dies during participation in the study or during a recognized follow-up period, the investigator will provide GSK with a copy of any post-mortem findings including histopathology

New or updated information will be recorded in the originally completed CRF.

The investigator will submit any updated SAE data to GSK within 24 hours of receipt of the information.

Reporting of SAE to GSK

SAE Reporting to GSK via Electronic Data Collection Tool

The primary mechanism for reporting SAE to GSK will be the electronic data collection tool.

If the electronic system is unavailable for more than 24 hours, then the site will use the paper SAE data collection tool (see next section).

The site will enter the SAE data into the electronic system as soon as it becomes available.

The investigator or medically-qualified sub-investigator must show evidence within the eCRF (e.g., check review box, signature, etc.) of review and verification of the relationship of each SAE to IP/study participation (causality) within 72 hours of SAE entry into the eCRF.

After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.

If a site receives a report of a new SAE from a study subject or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the /medical monitor/SAE coordinator by telephone.

Contacts for SAE reporting can be found in the SRM.

SAE Reporting to GSK via Paper CRF

Scanned transmission of the SAE paper, by email of CRF is the preferred method to transmit this information to the **medical monitor or the SAE coordinator**.

In rare circumstances and in the absence of email, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service. Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames. Contacts for SAE reporting can be found in the SRM

13.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below)

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with ONE of the following:

- Documented hysterectomy
- Documented bilateral salpingectomy
- Documented bilateral oophorectomy

Note: Documentation can come from the site personnel's: review of subject's medical records, medical examination, or medical history interview.

3. Postmenopausal female

- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
- Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance

Female subjects

Female subjects of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in Table 3.

Table 3 Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User Dependent [a] *Failure rate of <1% per year when used consistently and correctly.*
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] • oral • intravaginal • transdermal
Progestogen-only hormonal contraception associated with inhibition of ovulation[b] • injectable
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation[b] • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • bilateral tubal occlusion
Vasectomized partner *(A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.)*
Sexual abstinence (*Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject.)*

NOTES:

a. Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for subjects in clinical studies.

b. Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraceptive method. In this case two highly effective methods of contraception should be utilized during the treatment period and for at least 5 days after the last dose of study treatment

Pregnancy Testing

WOCBP should only be included after a negative highly sensitive urine test

Additional pregnancy testing should be performed during the treatment period as decribed in the SOA and a time (>5 days) corresponding to time needed to eliminate study treatment after the last dose of study treatment and as required locally

Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected

Pregnancy testing, with a sensitivity of [5, 10, 25] mIU/mL will be performed using the test kit provided locally or by the sponsor and in accordance with instructions provided in its package insert

Collection of Pregnancy Information

Female Subjects who become pregnant

Investigator will collect pregnancy information on any female subject, who becomes pregnant while participating in this study.

Information will be recorded on the appropriate form and submitted to GSK within 2 weeks of learning of a subject's pregnancy.

Subject will be followed to determine the outcome of the pregnancy. The investigator will collect follow up information on subject and neonate, which will be forwarded to GSK Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.

Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.

A spontaneous abortion is always considered to be an SAE and will be reported as such.

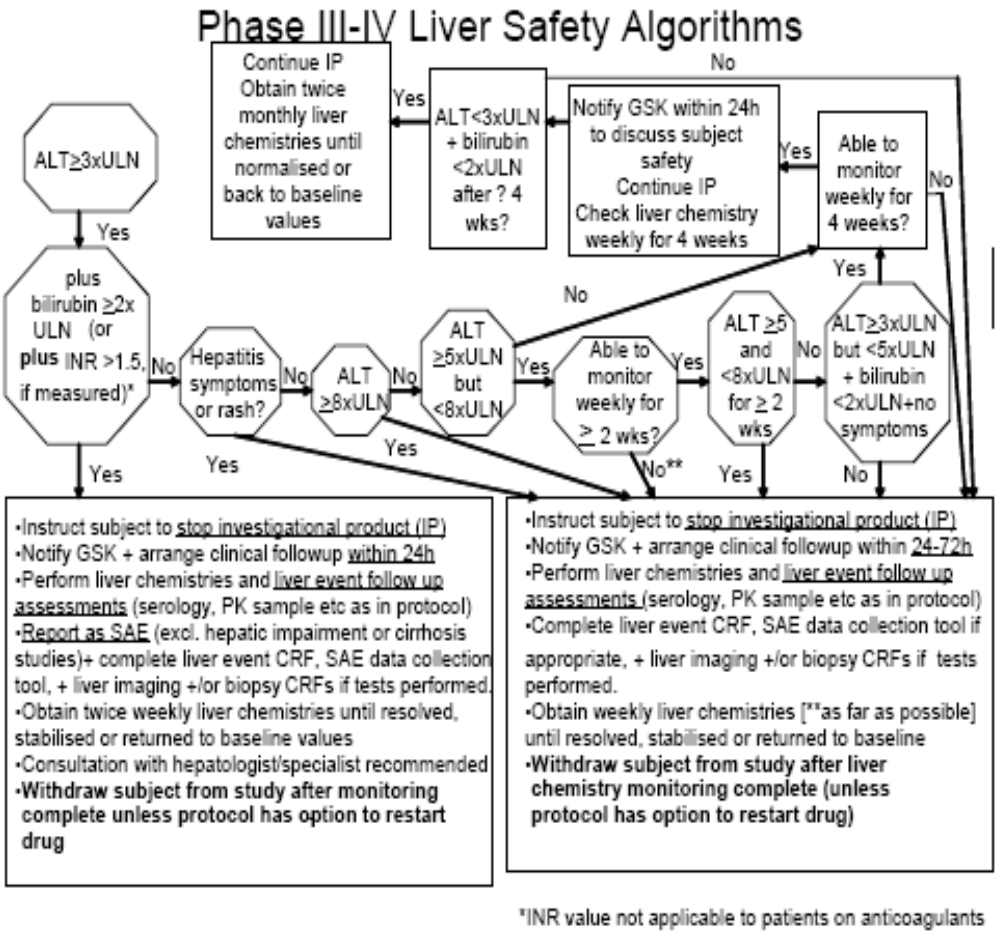
Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the investigator, will be reported to GSK as described in Appendix 3. While the investigator is not obligated to actively seek this information in former study subjects, he or she may learn of an SAE through spontaneous reporting.

Any female subject who becomes pregnant while participating

will discontinue study treatment or be withdrawn from the study

13.5. Appendix 5: Liver Safety: Required Actions, Follow-up Assessments

Phase III-IV liver chemistry stopping criteria and required follow up assessments



Liver Chemistry Stopping Criteria	
ALT-absolute	ALT ≥ 8xULN
ALT Increase	ALT ≥ 5xULN but <8xULN persists for ≥2 weeks ALT ≥ 3xULN but <5xULN persists for ≥4 weeks
Bilirubin[1, 2]	ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin)
INR[2]	ALT ≥ 3xULN **and** INR>1.5, if INR measured
Cannot Monitor	ALT ≥ 5xULN but <8xULN and cannot be monitored weekly for ≥2 weeks ALT ≥ 3xULN but <5xULN and cannot be monitored weekly for ≥4 weeks
Symptomatic[3]	ALT ≥ 3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity

Required Actions and Follow up Assessments	
Actions	**Follow Up Assessments**
• Immediately discontinue study treatment • Report the event to GSK **within 24 hours** • Complete the liver event CRF and complete an SAE data collection tool if the event also meets the criteria for an SAE[2] • Perform liver event follow up assessments • Monitor the subject until liver chemistries resolve, stabilize, or return to within baseline (see **MONITORING** below) • **Do not restart/rechallenge** subject with study treatment • Permanently discontinue study treatment and continue subject in the study for any protocol specified follow up assessments **MONITORING:** **<u>For bilirubin or INR criteria:</u>** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24 hrs**	• Viral hepatitis serology[4] • Obtain INR and recheck with each liver chemistry assessment until the transaminases values show downward trend • Only in those with underlying chronic Hepatitis B at study entry (identified by positive Hepatitis B surface antigen) quantitative Hepatitis B DNA and Hepatitis delta antibody[5]. • Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH). • Fractionate bilirubin, if total bilirubin≥2xULN • Obtain complete blood count with differential to assess eosinophilia • Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form • Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal

• Monitor subjects twice weekly until liver chemistries resolve, stabilize or return to within baseline • A specialist or hepatology consultation is recommended **For All other criteria:** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24-72 hrs** • Monitor subjects weekly until liver chemistries resolve, stabilize or return to within baseline	remedies, other over the counter medications. • Record alcohol use on the liver event alcohol intake case report form (CRF) page **For bilirubin or INR criteria:** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG) or gamma globulins. • Serum acetaminophen adduct high performance liquid chromatography (HPLC) assay (quantifies potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week [James, 2009]). • Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy CRF forms.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that subject if alanine aminotransferase (ALT) ≥ 3xULN **and** bilirubin ≥ 2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin) or ALT ≥ 3xULN **and** INR>1.5, if INR measured which may indicate severe liver injury (possible 'Hy's Law'), **must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**; INR measurement is not required and the threshold value stated will not apply to subjects receiving anticoagulants
3. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia)
4. Includes: Hepatitis A IgM antibody; Hepatitis B surface antigen (HbsAg) and Hepatitis B Core Antibody (IgM); Hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody
5. If Hepatitis delta antibody assay cannot be performed,, it can be replaced with a PCR of Hepatitis D RNA virus (where needed) [Le Gal, 2005] .

13.6. Appendix 6: Medical Device Incidents: Definition and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definition and Documentation of Medical Device Incidents

Definitions of a Medical Device Incident

The detection and documentation procedures described in this protocol apply to all GSK medical devices provided for use in the study (see Section 7.3 for the list of GSK medical devices).

Medical Device Incident Definition
A medical device incident is any malfunction or deterioration in the characteristics and/or performance of a device as well as any inadequacy in the labeling or the instructions for use which, directly or indirectly, might lead to or might have led to the death of a subject/user/other person or to a serious deterioration in his/her state of health.
Not all incidents lead to death or serious deterioration in health. The nonoccurrence of such a result might have been due to other fortunate circumstances or to the intervention of health care personnel.

It is sufficient that:

- An **incident** associated with a device happened and
- The **incident** was such that, if it occurred again, might lead to death or a serious deterioration in health.

A serious deterioration in state of health can include any of the following:

- Life-threatening illness
- Permanent impairment of body function or permanent damage to body structure
- Condition necessitating medical or surgical intervention to prevent one of the above
- Fetal distress, fetal death, or any congenital abnormality or birth defects

Examples of incidents
A subject, user, caregiver, or healthcare professional is injured as a result of a medical device failure or its misuse. A subject's study treatment is interrupted or compromised by a medical device failure. A misdiagnosis due to medical device failure leads to inappropriate treatment. A subject's health deteriorates due to medical device failure.

Documenting Medical Device Incidents

Medical Device Incident Documenting
Any medical device incident occurring during the study will be documented in the subject's medical records, in accordance with the investigator's normal clinical practice, and on the appropriate form. For incidents fulfilling the definition of an AE or an SAE, the appropriate AE/SAE CRF page will be completed as described in Appendix 3 The form will be completed as thoroughly as possible and signed by the investigator before transmittal to the GSK. It is very important that the investigator provides his/her assessment of causality (relationship to the medical device provided by GSK) at the time of the initial report and describes any corrective or remedial actions taken to prevent recurrence of the incident. A remedial action is any action other than routine maintenance or servicing of a medical device where such action is necessary to prevent recurrence of an incident. This includes any amendment to the device design to prevent recurrence.

13.7. Appendix 7: Country-specific requirements

13.7.1. Additional Adverse Event (AE) Reporting: Country-specific requirements for Canadian investigators:

The purpose of this information is to comply with Health Canada guidelines. They state that all events associated with lack of efficacy of marketed investigational products must be documented and reported.

Health Canada requires pharmaceutical manufacturers to expeditiously report domestic cases of unusual failure in efficacy (UFIE) for new drugs to the Marketed Health Products Directorate (MHPD) within 15 days of first notification. This regulation applies to marketed drugs, and used as directed per the Canadian prescribing information, including those drugs used in Phase IV (non CTA filed) clinical trials.

Adverse event (AE): Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding) symptom or disease (new or exacerbated) temporally associated with the use of a Medicinal Product. For a marketed Medicinal Product, this can also include failure to produce expected benefits (i.e. lack of efficacy, with or without an adverse event),

In order for GSK to comply this Canadian regulatory requirement, Canadian investigators are required to collect, record and report lack of efficacy events as per Table 4.

Table 4 Collection and Reporting of Adverse Events and Lack of Efficacy

Adverse Event criteria	Electronic case record form (eCRF) only	Paper form only	Electronic case record form (eCRF) + Paper form
Non serious	Non drug related lack of efficacy reports with associated signs or symptoms or clinical sequelae	Drug related lack of efficacy reports without associated signs or symptoms or clinical sequelae.	Drug related lack of efficacy with associated signs or symptoms or clinical sequelae
Serious	Non drug related lack of efficacy reports with associated signs or symptoms or clinical sequelae	Drug related lack of efficacy reports without associated signs or symptoms or clinical sequelae.	Drug related lack of efficacy reports with associated signs or symptoms or clinical sequelae

The investigator will then record all relevant information regarding an AE/SAE in the electronic CRF “and/or paper form as applicable

For lack of efficacy reports the paper form will be used to submit to GSK as per Table 4.

All paper forms are required to be faxed to GSK Canada’s Drug Safety department at PPD **within 24 hrs of first awareness**.

13.8. Appendix 8: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

TITLE PAGE

Protocol Title: 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.

Protocol Number: 207040

Short Title: A clinical study to evaluate the effect of the Connected Inhaler System (CIS) on adherence to maintenance therapy in poorly controlled asthmatic patients.

Compound Number: GW685698+GW642444 (GSK2285997)

Sponsor Name and Legal Registered Address:

GlaxoSmithKline Research & Development Limited
980 Great West Road
Brentford
Middlesex, TW8 9GS
UK

Medical Monitor Name and Contact Information can be found in the Study Reference Manual

Regulatory Agency Identifying Number(s): EUDRACT: 2017-002266-45, IND 077855

Approval Date: 22-JUN-2017

SPONSOR SIGNATORY:

PPD

22nd June 2017

Date

Steven Pascoe, MD

Vice President, Respiratory Head Unit Physician

PPD

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1. SYNOPSIS

Protocol Title: 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

Short Title: A clinical study to evaluate the effect of the Connected Inhaler System (CIS) on adherence to maintenance therapy in poorly controlled asthmatic patients

Rationale: This study will be the first to evaluate the effect of the CIS on adherence to maintenance therapy (Relvar/Breo ELLIPTA) in uncontrolled asthmatic patients (Asthma Control Test [ACT] <20 at the screening visit and ACT <20 at a subsequent randomisation visit following run in)

The study has been designed to assess how the CIS impacts adherence, of asthmatic patients, to maintenance therapy, when both the subject and the healthcare professional (HCP) receive data from the sensor on the patient's Relvar/Breo ELLIPTA maintenance therapy.

In addition, the five treatment arms of the study will allow evaluation of different elements of the CIS including, having additional data provided from a sensor on rescue medication and also the effect of the patient alone seeing any data with no data shared to the HCP, or both the patient and HCP, seeing the data from the sensors Furthermore, this study will provide preliminary data evaluating the effect of the CIS on patient outcomes, including rescue medication use, patient reported outcomes and change in asthma control as as assessed by the Asthma Control Test (ACT).

Objectives and Endpoints:

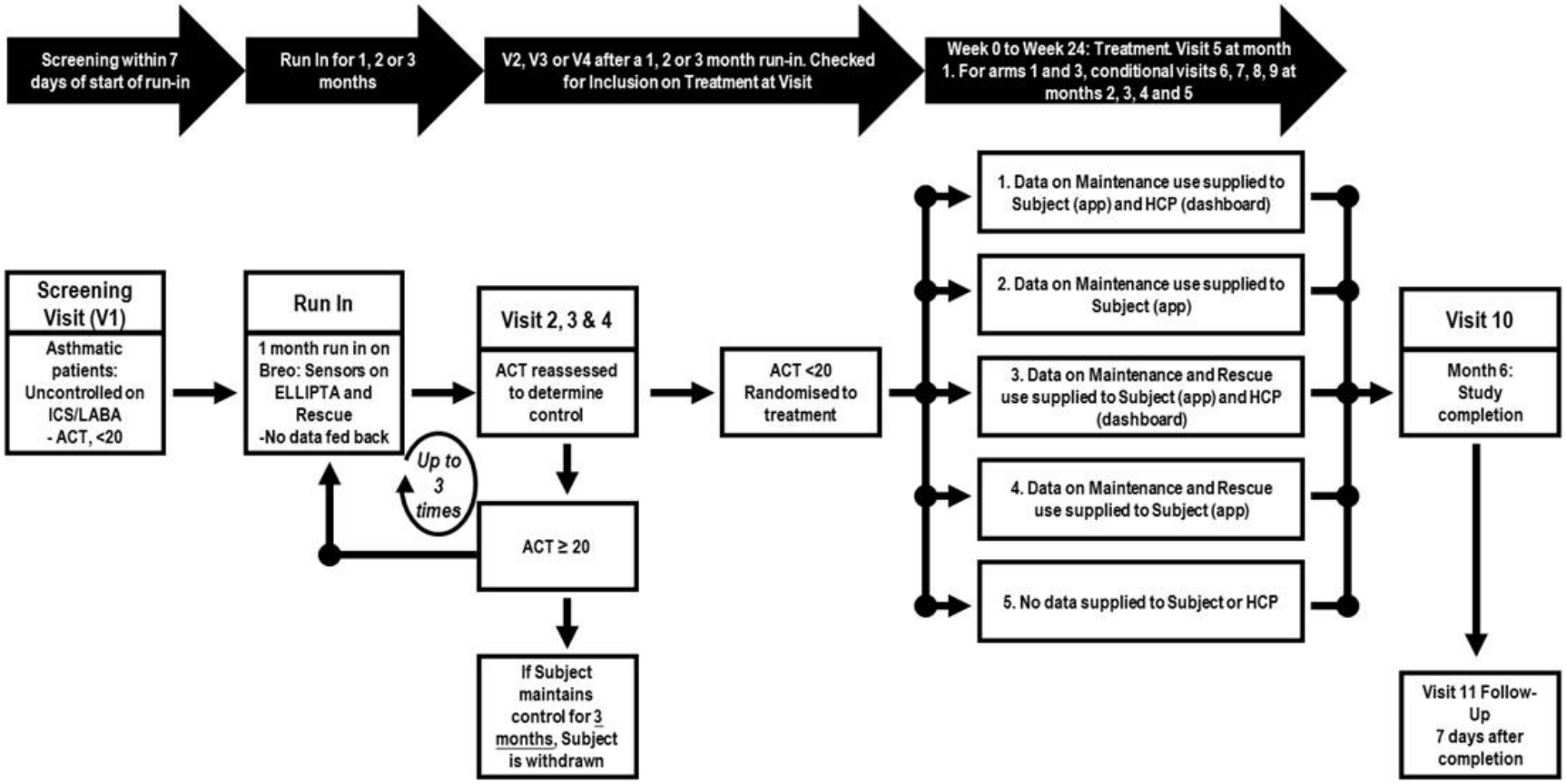
Objectives	Endpoints
Primary	
To compare the effect of 6 months use of the CIS on adherence to ELLIPTA maintenance therapy when both the subject and the HCP are supplied with data from the maintenance sensor versus no data supplied to the subject and HCP (Arm 1 vs Arm 5)	Percentage of ELLIPTA doses taken (daily adherence[1].) between the beginning of month 4 and the end of month 6 as determined by the maintenance sensor

Secondary	
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 subjects versus no data supplied to the subject (Arm 2 vs Arm 5) • Rescue and Maintenance data supplied to subject and HCP versus no data supplied to the subject and HCP (Arm 3 vs Arm 5) • Rescue and Maintenance data only supplied to subject versus no data supplied to the subject (Arm 4 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
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 subject 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 subject'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 subject's asthma control	• Change from baseline in ACT total score at Month 6, measured at baseline (Visit 2, 3 or 4) and Month 6 (Visit10) • 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)

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

Overall Design:

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.



Number of Subjects:

Approximately 600 subjects will be screened to achieve 432 randomised and a total of 380 subjects are anticipated to have data available for the primary analysis; an estimated total of 76 subjects per treatment group.

An unblinded sample size re-estimation will take place, once 50% of the planned number of subjects have completed Visit 10. An adjustment of the sample size, for arms 1 and 5, is conditional on the primary endpoint analysis results observed. However, no more than a further 42 subjects will be randomised in to each of arms 1 and 5 to provide an anticipated maximum of approximately 114 (76+38) subjects in each of those 2 arms and so an estimated total number of 456 subjects in all arms.

Treatment Groups and Duration:

All randomised subjects will receive Relvar/Breo ELLIPTA, at the dose allocated at the run in.

All subjects will have sensors attached to both their Relvar/Breo ELLIPTA and salbutamol Metered Dose Inhaler (MDI). It is the type of data provided by the CIS (either Relvar/Breo ELLIPTA alone or Relvar/Breo ELLIPTAand salbutamol MDI) , as well as who sees that data, (subject alone or subject and HCP), that defines the treatment arms.

The 5 treatments arms are as follow:

1. Data on Maintenance use supplied to Subject (app) and HCP (dashboard)
2. Data on Maintenance use supplied to Subject (app)
3. Data on Maintenance and Rescue use supplied to Subject (app) and HCP (dashboard)
4. Data on Maintenance and Rescue use supplied to Subject (app)
5. No data supplied to Subject or HCP

The treatment period for the study is 6 months. However, due to the flexible run in period a subject could be on the study for approximately 7, 8 or 9 months in total

2. SCHEDULE OF ACTIVITIES (SOA)

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 subject 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 subject and HCP/ designee prior to any other study assessments. May be completed at a separate visit to screening if required.
Subject 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**									Subject 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 subject 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**											Non-serious adverse events that leads to dose modification, drug discontinuation, or withdrawal from the trial
Non-serious Adverse Drug Reactions		**X**											
Exacerbations		**X**											Severe Exacerbation are to be reviewed and recorded
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 subject is included. 2. The PRO's are only performed at the run-in visit (V2, V3 or V4) if a subject 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**		

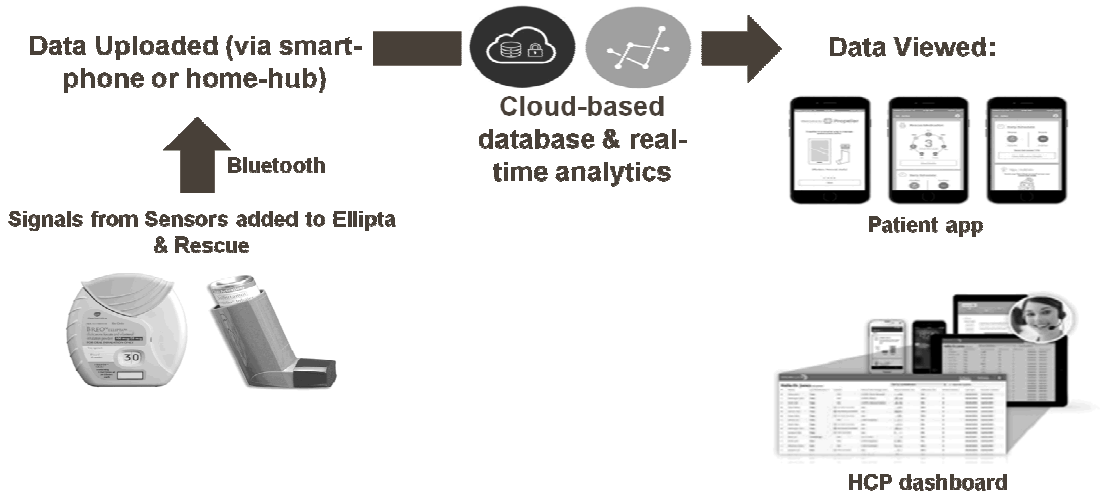
Procedures	Screen	Run-In			Treatment Period						EW	Follow -up	Notes
Visit/Contact	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**		**V11**	**Conditional Visits**::V3& V4 are only required if a subject is not included at prior run in visit. V6, V7, V8 & V9 are only required for 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 subjects 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 subject is included. 2.PEF and FeNO is only performed at the Run in visit if a subject 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**			Subjects 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 subjects 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**								Subjects are trained in fitting the sensors at screening. Following randomisation, subjects 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 subject 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 subject 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.

3. INTRODUCTION

GSK has, in collaboration with Propeller Health, developed a sensor which clips on to the ELLIPTA dry powder inhaler (DPI), herein referred to as ELLIPTA. The sensor will measure when the ELLIPTA mouth piece cover is fully opened and closed and this data can be fed back, via an application (app) on a smart phone to the patient. This will inform a patient if/when a dose of Relvar/Breo has been actuated from the ELLIPTA. Other information, including: asthma management strategies, tracking of symptoms, asthma triggers, medication reminders and daily asthma forecasts involving weather and air quality data, will also be provided via the app. Information from a second sensor on a patient's rescue medication metered dose inhaler (MDI) could also provide feedback, via the app, to the patient on their salbutamol (albuterol) MDI use. The data from both Relvar/Breo ELLIPTA and salbutamol MDI can also be shared, via an online dashboard, with the patient's Health Care Professional (HCP), see Figure 1 and Propeller System Site Manual (PSSM). The sensors, app, dashboard and systems to provide data are subsequently described as the Connected Inhaler System (CIS).

Figure 1 Connected Inhaler System



3.1. Study Rationale

This study will be the first to evaluate the effect of the CIS on adherence to maintenance therapy (Relvar/Breo ELLIPTA) in uncontrolled asthmatic patients (Asthma Control Test [ACT] <20 at the screening visit and ACT <20 at a subsequent randomisation visit after run-in). The run-in exists to ensure a stable level of control prior to entry into the study, given the possible change in treatment and is described in detail in Section 5.1.

The study has been designed to assess how the CIS impacts adherence of asthmatic patients to maintenance therapy, when both the subject and the HCP receive data on adherence from the sensor on the patient's Relvar/Breo ELLIPTA maintenance therapy.

In addition, the five treatment arms of the study will allow evaluation of different elements of the CIS. These include; having additional data provided from a sensor on

rescue medication and the effect of the patient alone seeing any data with no data shared to the HCP, or both the patient and HCP seeing the data from the sensors. See Section 5, Section 7 and Table 1 for details on the 5 arms. Furthermore, this study will provide preliminary data evaluating the effect of the CIS on patient outcomes, including rescue medication use, change in ACT and patient reported outcomes (PROs).

3.2. Background

Asthma is a chronic inflammatory disease of the airways that results in hyperreactivity and clinically relevant episodes of wheezing, chest tightness and coughing. Although asthmatic symptoms can normally be controlled, by treatment, it remains a serious condition that is associated with a number of different impacts and co-morbidities such as; fatigue, activity impairment, psychological problems (anxiety, depression and stress), lung infections and delays in growth (paediatrics).

The underlying pathophysiology of asthma includes epithelial sloughing, smooth muscle contraction, bronchial hyperreactivity and airway inflammation [Koterba, 2012]. Depending on the asthmatic patient, these symptoms can become worse during the evening and/or with exercise [Martinez, 2007]. Asthma is believed to affect the lives of approximately 300 million people worldwide and this number is expected to rise to 400 million by 2025.

There are many reasons for poor adherence including, but not limited to, difficulties using inhalers, forgetfulness, misunderstanding of instructions, perceptions of the medicine and cost [GINA, 2017]. Also, as asthma is an inflammatory condition that is episodic in nature, patients can exhibit symptomatic adherence to maintenance therapies [Anarella, 2004].

Inadequate control of asthma symptoms continues to be a serious problem, and despite advancements in therapeutics for the treatment of asthma, adherence rates remain less than optimum [Anarella, 2004, Foster, 2014]. The significance of adherence to treatment regimens in the management of asthma is becoming ever more evident. A variety of studies have indicated that poor adherence to maintenance therapy is intimately associated with reduced quality of life and, increased; asthma symptoms, oral steroid usage, hospitalisation and mortality [Patel, 2013; Williams, 2011, Normansell, 2017]. Furthermore, reduced adherence to maintenance therapy can lead to an overuse of rescue medication, which has been linked to poorer health status [Patel,2013].

Due to the chronic nature of the disease, low adherence rates are recognised as one of the main contributing factors to reduced control amongst asthmatic patients. Therefore, the requirement for routine and habitual use of maintenance therapy is paramount.

Currently, determination of inherent adherence rates are questionable due to their largely subjective (patient diaries), unreliable (prescription refills) and imprecise (dosage counters) data acquisition methodologies. Each of these methods can misrepresent what is occurring in the real world. Furthermore, clinicians' estimations of adherence rates can be inaccurate, patient self-reported adherence rates are notoriously overestimated and some electronic dose counters can also be problematic due to dose dumping [Bae, 2009;

Zeller, 2008]. Because of these uncertainties, there is an abundance of research being undertaken in the area of inhaler sensors for adherence. Novel solutions to some of the aforementioned problems are currently in development, such as; actuation switches (e.g. Smartinhaler and Propeller Health MDI sensor) for time stamping, heated thermistors (MDI log) for inhalation detection, microphones (INCA Device) for detecting peak inspiratory flow rates and actuations, accelerometers (Amiko and MDI Log) for time stamping and technique feedback, and light transmitters (SmartTrack and SmartTouch) for detection of canister depression and time stamping.

Dosing regimens (once daily vs. twice daily) have also unsurprisingly been found to have an effect on adherence to maintenance therapy. Fewer doses required on a daily basis as part of maintenance therapy, has been shown to increase adherence rates as well as creating a more routine and habitual dosing times [Coleman, 2012].

It has been shown that the addition of a sensor which has the ability to feedback information is associated with increased adherence rates in paediatric patients of between 30 and 50% [Chan, 2016; Foster, 2014]. Unfortunately, the population (paediatrics) and the inherent variability of the data make interpretation and extrapolation to other populations problematic. However, a 20-30% increase in adherence rates when using inhaled corticosteroids has been shown to lead to clinically relevant effects, such as, a reduction in exacerbations [Williams, 2011]. Whilst many studies have used sensors to measure adherence, relatively few studies have assessed the influence of sensors on adherence rates and even less information exists to demonstrate the link between adherence and clinically relevant outcomes or patient reported quality of life.

Adherence rate measurements should be unobtrusive, objective and accurate, in order to correctly identify innate patient adherence rates [Chan, 2015]. Accordingly, Propeller Health, in collaboration with GSK, has developed a sensor, which can clip onto any ELLIPTA DPI and can monitor the time and date that the ELLIPTA DPI cover is opened and closed. The sensor can be detached and transferred to subsequent inhalers by prescription. Propeller Health already produces a sensor that clips on to the top of a rescue MDI and records time and date of actuation. The data, from both of these sensors can then be fed back to the patient or patient and their HealthCare Professional (HCP) through the use of an app or dashboard. Patient/HCP interaction with the data through the app/dashboard may enable greater engagement between the patient and their HCP regarding their asthma. The app associated with the Propellor Health sensor also provides information on asthma management strategies, tracking of symptoms, asthma triggers, medication reminders and daily asthma forecasts involving weather and air quality data, in order to improve a patients' understanding of, and relationship with, their asthma.

It is believed that engaging a patient's interest in their asthma could improve their adherence to their maintenance therapy and ultimately improves their asthma outcomes as much of the research supports the importance of adherence rates to asthma control [Sapir, 2017]. Therefore, if through the use of the CIS, a patient can engage with their asthma, this may improve adherence and ultimately improve their level of asthma control. Furthermore, from an HCP perspective, having accurate adherence data would make discussions with their patients more objective and informed when considering appropriate asthma management strategies.

3.3. Benefit/Risk Assessment

3.3.1. Risk assessment for Relvar/Breo 100/25mcg and 200/25mcg

For Relvar/Breo ELLIPTA, the following risks and the corresponding mitigation strategies, as applicable to asthma patients, were taken from the summary of safety concerns in the European Union – Risk Management Plan (EU-RMP). For Relvar/Breo the rationale for the risk assessment was derived from the 2014-2016 Investigator Brochures, from an integrated analysis of key Relvar/Breo studies.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP) (fluticasone furoate [FF]/vilanterol [VI]])		
Pneumonia in patients with asthma	The incidence (adjusted for exposure) seen with FF/VI 100/25 microgram strength (9.6/1000 patient years) was similar to placebo (8.0/1000 patient years). The incidence was slightly higher for FF/VI 200/25 microgram (18.4/1000 patient years). No risk factors were identified.	The risk of pneumonia in asthma patients is consistent with the risk of other ICS. Subjects are not at an increased risk in this study, since they enter the study on an existing ICS treatment. Subjects are alerted to the potential risk of pneumonia in the informed consent. Subjects with a concurrent respiratory disease are excluded from the study.
Asthma related intubations and deaths	This is a class effect of Long-Acting Beta2-Agonist (LABA) in asthma. This has not been observed for FF/VI. A Food And Drug Administration (FDA) meta-analysis of LABA vs. no LABA (60,954 patients in 110 trials) by age group on a composite endpoint of asthma-related deaths, intubations, and hospitalizations (asthma composite index) showed a statistically significant difference among age groups. The composite event incidence difference for all ages was 6.3 events per 1000 patient-years (95% CI: 2.2-10.3) with LABAs compared with no LABA use. Among the 15,192 patients with concurrent ICS use, the incidence difference was 0.4 events per 1000 patient-years (95%	Subjects with a history of life-threatening asthma are excluded from the study.

	CI: -3.8 to 4.6). The authors noted a trend of greater excess risk with LABA among the younger age groups [McMahon, 2011]. Three large studies (two in adults, one in children) with ICS/LABA compounds have shown no increased risk of serious asthma related events compared with ICS alone (Stempel, 2016a; Stempel et al, 2016b, Peters et al, 2016).	
Serious cardiovascular events	In an analysis performed on the 18 key studies in subjects with asthma, eight serious cardiovascular events have been reported in patients exposed to FF/VI. Seven events in FF/VI 100/25 and one event in FF/VI 200/25. This represents an incidence less than 1% in the asthmatic patients exposed to FF/VI. [a] The events reported include atrial fibrillation, acute coronary syndrome, coronary artery disease, hypertension, myocardial ischemia, tachyarrhythmia and tachycardia. Therefore fluticasone furoate/vilanterol should be used with caution in patients with severe cardiovascular disease or heart rhythm abnormalities, thyrotoxicosis, uncorrected hypokalaemia or patients predisposed to low levels of serum potassium.	Subjects with existing serious cardiovascular disease, thyrotoxicosis, uncorrected hypokalaemia or patients predisposed to low levels of serum potassium are excluded from the study. Investigators are made aware of the potential class effects of LABAs and are advised to exercise caution for subjects with existing serious cardiovascular disease (Section 6.3 [Warnings and Precautions] of the IB).
Hypersensitivity	No FF/VI drug related hypersensitivity was noted in clinical trials. Spontaneous reports of hypersensitivity reactions have been reported in post-marketing data for FF/VI. A possible causal association cannot be ruled out	Subjects will be informed about the risk of hypersensitivity in the informed consent. They will be advised to seek medical treatment if any signs of hypersensitivity occur. Subjects with milk protein allergy or known hypersensitivity to FF, VI, the classes ICS or beta-

	based on the temporal association between drug administration and hypersensitivity events including anaphylactic reaction, angioedema, urticaria, pruritis and rash.	agonist or any ingredient of the Investigational Product (IP) preparation will be excluded from participating in the study.
Decreased bone mineral density and associated fractures	Risk of fracture has been associated with oral corticosteroids. It is unclear if inhaled corticosteroids carry the same risk. Currently the risk of reduced bone mineral density has not been observed in the asthma population [Jones, 2002]. In addition specific assessments in adolescents with asthma have not demonstrated an effect on bone mineral density, when controlled for growth [König, 1993; Turpeinen, 2010]. In an analysis performed on the 11 key studies in subjects with asthma bone fractures were reported by <1% (7034 patients) of subjects who received FF/VI 100/25 and was usually associated with trauma	Subjects will be informed about the risk of decreased bone mineral density and bone fractures in the informed consent. Investigators are made aware of the potential for this ICS class effect. Subjects will be advised to seek medical treatment if any signs of decreased bone mineral density or fractures occur. All subjects will already be prescribed ICS/LABA treatments for their asthma. Therefore, it is unlikely that such an effect will occur.
Adrenal Suppression	This is considered a class effect of ICS. Preclinical studies showed that FF effects are comparable with other corticosteroids. No studies have shown a clinically relevant effect of FF/VI on the hypothalamic-pituitary adrenal axis (HPA) at the 100/25 strength. This includes a formal HPA study (HZA106851), using 24-hour serum cortisol measurements, and multiple studies with chronic obstructive pulmonary disease (COPD) and asthma subjects which monitored urinary cortisol.	Subjects will be informed about the risk of adrenal suppression in the informed consent. Investigators are made aware of the potential for this class effect in Section 6.3 (Warnings and Precautions) of the Investigators Brochure (IB). If systematic symptoms appear, investigators should implement an appropriate treatment while observing the subject's' asthma symptoms. All subjects will already be prescribed ICS/LABA treatments for their asthma. Therefore, it is unlikely that such an effect will be experienced.
Corticosteroid associated eye	This is considered a class effect of ICS. Preclinical studies showed FF	Subjects will be informed about the risk of corticosteroid

disorders	at high dose comparable to other high dose corticosteroids. In study HZA106839 (FF/VI, FF and FP in subjects with asthma), formal ophthalmic assessments were conducted (including lens opacities classification system [LOCS] III evaluations for ocular opacities) throughout the study. This study showed no apparent effects on lens opacification, compared to baseline. During studies in both subjects with asthma and COPD, no associated affect on ocular disorders was observed.	associated eye disorders in the informed consent. They will be advised to seek medical treatment if any signs of eye disorder occur. Investigators are made aware of the potential for this class effect in Section 5.3.3.7 (Ophthalmic Effects) of the IB. All subjects will already be prescribed ICS/LABA treatments for their asthma. Therefore, it is unlikely that such an effect will be experienced.
Paradoxical bronchospasm may occur with an immediate increase in wheezing after dosing.		First dose of Relvar/Breo will be administered at the clinical site under supervision Paradoxical bronchospasm should be treated immediately with a short-acting inhaled bronchodilator. Relvar/Breo ELLIPTA should be discontinued Immediately. The subject would be withdrawn from study.

a. RELVAR studies summarized include FFA109684, FFA109685, FFA109687, B2C109575, HZA106827, HZA106829, HZA113091, HZA113714, HZA113719, HZA116863, HZA106837, HZA106839, HZA106851, FFA112059, FFA114496, FFA115283, FFA115285, B2C112060.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of Relvar/Breo may be found in the Investigator's Brochure, Development Safety Update Report or Summary of Product Characteristics.Benefit Assessment.

As a result of switching from other prescribed ICS/LABA combination products and being randomised to a treatment arm in the study, subjects may switch from an inhaled therapy that is taken twice daily, to a once daily therapy (Relvar/Breo) the patients in this study may have better adherence and so possibly better asthma control. There is also a potential benefit from use of the CIS. This has the potential to increase their adherence through interaction with the data ouputs and engagement with their asthma. Data with marketed products suggests that adherence improves with less frequent administration/simplification of therapy and therefore it is expected that a once-daily treatment could improve adherence, which may lead to improvements in disease control and reductions in healthcare resource utilisation costs [Foster, 2014, Price, 2010, Toy, 2011].

3.3.2. Overall Benefit:Risk Conclusion

GlaxoSmithKline (GSK) has assessed this study for any potential risks that a subject may experience. The investigational product (IP) FF/VI will be used as is detailed in the prescribing information and has an acceptable safety profile for clinical use and there are no significant associated risks. This conclusion is supported by the results of previously performed clinical studies with the products in healthy volunteers and subjects with Asthma and COPD and post-marketing experience (see local label).

There is a small risk of destabilising asthma when switching to Relvar/Breo. Patients will be provided with rescue medication and will be educated to recognise symptoms of asthma worsening and instructed to contact the HCP in this event.

Taking into account the measures taken to minimize risk to subjects participating in this study, the potential risks identified, associated with FF/VI are justified by the anticipated benefits that may be afforded to patients with asthma.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of Relvar/Breo ICS/LABA may be found in the IB, Summary of Product Characteristics and Subject Information Leaflet.

4. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
To compare the effect of 6 months use of the CIS on adherence to ELLIPTA maintenance therapy when both the subject and the HCP are supplied with data from the maintenance sensor versus no data supplied to the subject 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	
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 subjects versus no data supplied to the subject (Arm 2 vs Arm 5) • Rescue and Maintenance data supplied to subject and HCP versus no data supplied to the subject and HCP (Arm 3 vs Arm 5) • Rescue and Maintenance data only supplied to subject versus no data supplied to the subject (Arm 4 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
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 subject 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 subject'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 subject'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 (Visit10) • 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)

Exploratory and Other Objectives	
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 subject'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 • Number of prescriptions filled/requested for maintenance medication in the 12 months prior to inclusion. • 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 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).	• Percentage of patients meeting a responder threshold of ≥ 0.9 points improvement (decrease) from baseline (Randomisation) for the 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 (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) in BMQ total score at

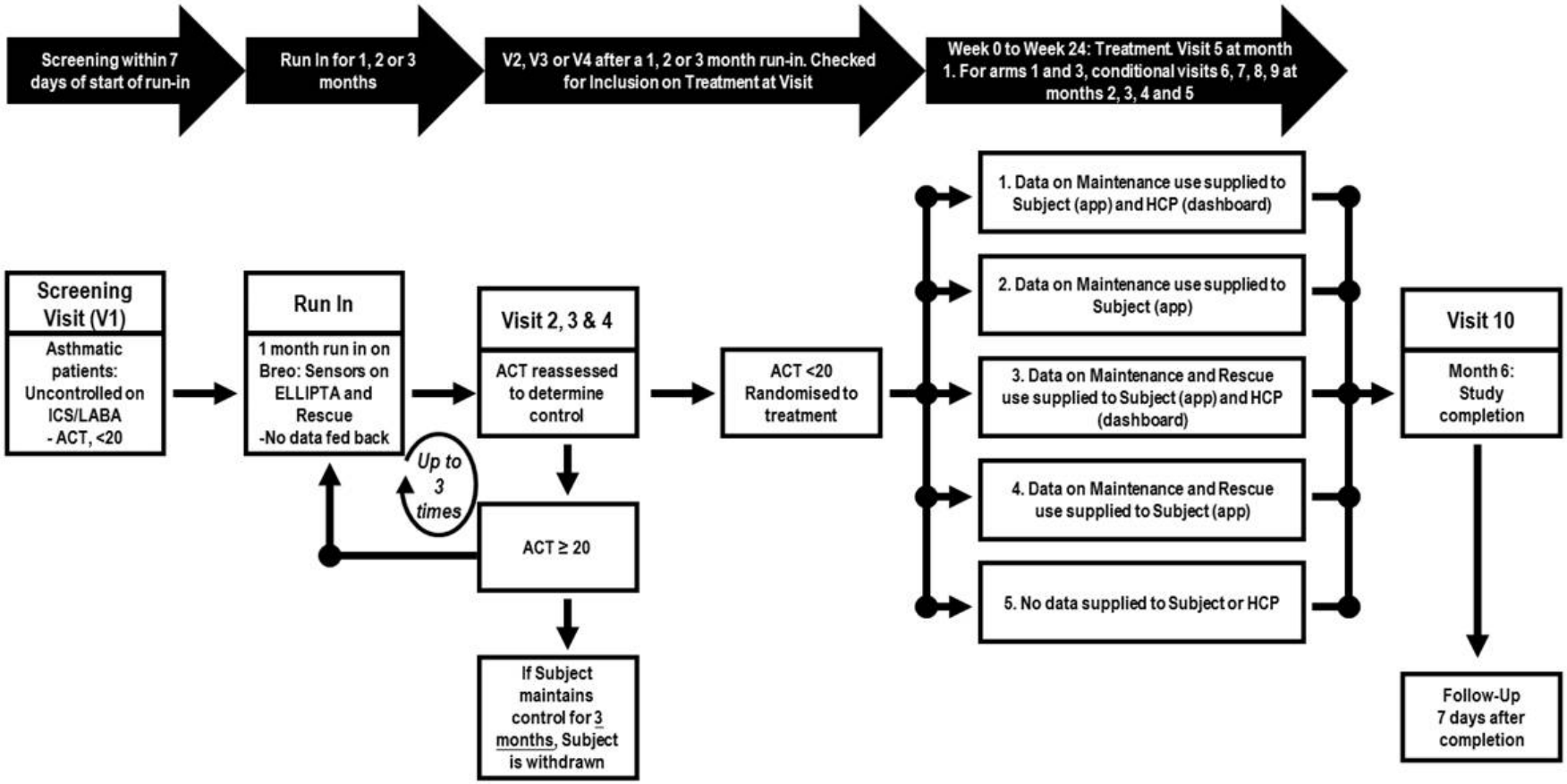
	Month 6
To assess the reliability and usability of the CIS	• Incidence of Medical Device Incidents between the beginning of Month 1 and the end of Month 6.
To explore impact of adherence on the biomarker Fractionated exhaled Nitric Oxide (FeNO)	FeNo at Screening (Visit 1), Randomisation (Visit 2,3 or 4), Month 1 (Visit 5) and Month 6 (Visit 10).
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 subjects	• Exit Questionnaires at Month 6 (Visit 10) • Exit Interviews for a sub set of subjects 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 subjects 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 subject taking one dose of Relvar/Breo ELLIPTA, within a 24 hour period, starting at 12.00am each day.

5. STUDY DESIGN

5.1. Overall Design

Figure 2 : Study Schematic



This is an open-label, randomised, multi-centre, parallel group study consisting of 5 treatment arms, in asthmatic patients currently on a fixed dose ICS/LABA maintenance therapy.

The procedures to be performed at each visit are shown in Section 2.The study and visits are described here.

At all visits will require subjects to withhold a daily dose of maintenance therapy and rescue medication for 6 hours; as some assessments will require ths restriction for validity of the assessment (PEF and FeNO) and also so correct use can be demonstrated with that days Relvar/Breo ELLIPTA dose at any required visit.

The treatment period for the study is 6 months. However, due to the flexible run in period a subject could be on the study for approximately 7, 8 or 9 months in total

Screening Visit (V1)

Subjects who have provided their informed consent will be screened at Visit 1 (V1) for inclusion on the study. Subjects who meet all the inclusion criteria, including an ACT of <20, will enter the flexible run-in period. Screening and starting the flexible run-in can occur at the same visit, however for logistical reasons the flexible run-in can start at a separate visit, which must be within 7 days of the screening visit and the subject's inclusion on the study. Should a subject not meet the the inclusion/exclusion criteria, they will be registered as a screen failure.

Flexible Run-in

Following inclusion at screening all subjects will receive Relvar/Breo ELLIPTA DPI maintenance therapy and salbutamol MDI rescue medication and be instructed to take these as prescribed.

Instruction on correct use of the Relvar/Breo ELLIPTA DPI and salbutamol MDI will be provided, particularly in the case of subjects previously using other devices, and/or using medication requiring twice-daily dosing.

Both the Relvar/Breo ELLIPTA and salbutamol MDI medication used by all subjects included on the study will have a sensor fitted and switched on at the clinic visit. However, during this run-in period, there will be no information provided to the subjects or HCPs on their adherence to Relvar/Breo ELLIPTA or on their use of salbutamol MDI. Subjects will also be instructed in fitting the sensors onto both the ELLIPTA and MDI.

The run-in period can last for 1, 2 or 3 months, dependent on a subjects ACT at end of each month of the run-in period.

Conditional Visits 2, 3 and 4 (V2, V3 and V4)

At the end of each month of the flexible run-in period, ACT will be re-assessed at the clinical centre. If at the first monthly visit of the flexible run-in the subject's ACT is <20 (uncontrolled) then the subject will be randomised to study treatment and subsequent run-

in visits are not required. Subjects with an ACT of ≥20 at V2 or V3 repeat the month run-in period. However, subjects who have an ACT ≥20 at all 3 visits, during the flexible run-in, will not be randomised and will be registered as a run-in failure.

Randomization/treatment: Conditional Visits 2, 3 and 4 (V2, V3 and V4)

Subjects who meet the randomisation inclusion criteria will be randomised to one of five CIS treatment arms at this visit (V2, V3 or V4). All treatment arms continue with Relvar/Breo ELLIPTA (ICS/LABA) maintenance therapy and Salbutamol MDI rescue therapy as in the run-in period and both inhalers continue having a sensor fitted. The treatment arms are defined by whether the data, from Relvar/Breo ELLIPTA (maintenance) or Relvar/Breo ELLIPTA (maintenance) and salbutamol MDI (rescue), is fed back to the subject or subject and HCP, or not at all. The 5 treatments arms are as follows:

1. Data on Maintenance use supplied to Subject (app) and HCP (dashboard)
2. Data on Maintenance use supplied to Subject (app)
3. Data on Maintenance and Rescue use supplied to Subject (app) and HCP (dashboard)
4. Data on Maintenance and Rescue use supplied to Subject (app)
5. No data supplied to Subject or HCP

Following randomisation, subjects in arms 1, 2, 3 and 4, will receive training on how to download and use the smart phone app, including how to connect and register the sensors via Bluetooth to their smart phone and to the app. Subjects in arm 5 who receive no data will be provided with a home hub so that their data will be uploaded during study, though they and their HCP will not see that data. Technical and operational details around registering sensors, connecting sensors to smart phone or a home hub and other details of app connectivity and function will be provided/referenced in the Study Reference Manual (SRM).

Visit 5 (V5)

Following randomisation, subjects will be asked to return to the site, after one month, at V5. At this visit the HCP will ensure that all subjects are able to use the provided inhalers correctly (correct use). For Arms 1, 2, 3 and 4 the site should ensure the sensors are attached correctly to the inhalers, are connected to the smart-phone via bluetooth and the HCP should ensure that subjects have been able to use the app. For subjects on Arm 5, the HCP will need to ensure that sensors are correctly attached to the inhalers.

At this visit, for subjects on Arms 1 and 3 the HCP will also, be able to review the subject's adherence to treatment from month 1, and for Arm 3 also review the subject's rescue medication use. The HCP can as needed use the data (Arms 1 and 3) to discuss with these subjects their adherence and if needed the importance of taking their medication as it is prescribed. In reviewing the data the HCP should consider how they would respond if this data was available as part of normal standard of care. For Arm 3 the HCP can also review the subject's rescue medication use and again should consider how they would respond if this data was available as part of normal standard care. The

outcome of the HCP data review will be recorded in the electronic Case Report Form (eCRF).

Conditional Visits 6, 7, 8 and 9 (V6, V7, V8, V9)

For subjects included on treatment arms 1 and 3, the HCP will review a subject's sensor data via the dashboard,as a minimum every 4 weeks. However, the data can be assessed more often as needed. After assessment of the data, the HCP will be able to, at their own discretion, act on this data by calling/emailing or inviting the subject to the clinic to discuss their asthma further, or they can decide to take no action. When reviewing the data the HCP should consider how they would respond if this data was available as part of normal standard of care. The action(s) and any outcomes taken in response to these conditional visits, initiated by the HCP, will be recorded in the eCRF and in the subject's medical record, including if no action was taken. If the HCP reviews the data at a time other than for the conditional visit and schedules a visit for the subject, this will be recorded in the eCRF as an unscheduled visit. Furthermore,subjects in all arms will be educated to recognise symptoms of asthma worsening and instructed to contact the HCP in this event. These events will also be recorded in the eCRF as unscheduled visits.

Visit 10 (V10)

All Subjects will return to site for final study assessments at the end of the 6 month treatment period.

Visit 11 (V11 Follow Up)

A follow-up visit will take place one week (±2 days) after V10 and may be conducted as either a clinical visit or a phone call for final safety check.

A subject will be considered to have completed the study when they have completed all phases of the study including screening, flexible run-in, the randomized treatment phase, and safety follow-up.

Dispensing Visits

All Subjects will be asked to return to the pharmacy or an independent nurse/designee at the study centre if a pharmacy is not available for these dispensing visits. They will need to bring their used Relvar/Breo ELLIPTA and/or salbutamol MDI and clip-on sensors in order to pick up their next Relvar/Breo ELLIPTA and/or salbutamol MDI as required during the course of the study. During these dispensing visits, the sensor will be attached to the new devices and switched on at the site. There will be no assessments performed, these visits are only for dispensing of study drug, as well as to ensure that subjects are able to transfer and pair the sensors. Subjects should return the previous Relvar/Breo ELLIPTA and any salbutamol MDI that need replacing at these visits.

As a minimum, the following will need to be captured: the date of visit, medication dispensed to the subject and also medication returned by the subject, including remaining doses on the ELLIPTA dose counter. This data should be recorded for entry into the eCRF.

Early Withdrawal Visit (EW)

Subjects who have permanently discontinued study treatment and have not withdrawn consent are encouraged to continue in the study and complete all remaining protocol specified clinic visits If a subject is withdrawn then they should complete the assessments as per Section 2. Reasons for withdrawal are provided in Section 8.2.

5.2. Number of Subjects

Approximately 600 subjects will be screened to achieve 432 randomised and 380 subjects are anticipated to have data available for the primary analysis for an estimated total of 76 subjects per treatment group.

An unblinded sample size re-estimation will take place, once 50% of the planned number of subjects have completed V10. An adjustment of the sample size, for arms 1 and 5, is conditional on the primary endpoint analysis results observed. However, no more than a further 42 subjects will be randomised in to each of arms 1 and 5 to provide a maximum of approximately 114 (76+38) subjects with data available for the primary analysis in each of those 2 arms and so a total number of 456 subjects in all arms are expected.

5.3. Subject and Study Completion

A subject is considered to have completed the study if he/she has completed the last scheduled procedure shown in Section 2, including the follow up visit.

The end of the study is defined as the date that the last subject completes the last scheduled procedure shown in the Section 2.

5.4. Scientific Rationale for Study Design

This study will be an open label study, as it is not possible to blind the treatment arms to which sensors (maintenance or rescue) are providing feedback to the patient via the app, and also, whether or not the patients' HCP has access to this data via the dashboard.

A true control arm (no sensors on ELLIPTA or MDI) cannot be incorporated into the design. All subjects need to have a sensor on their maintenance and rescue medication in order to consistently measure their adherence to maintenance and level of rescue medication use; as other methods of measuring adherence and rescue medication use (paper or electronic diaries and prescription refills) have inherent problems. Therefore, arm 5 is considered the best attempt at a control arm as neither subjects nor HCP will receive any data from either the ELLIPTA or rescue medication sensors and so could be considered the closest possible match to normal current practise.

Any asthmatic patient who is currently uncontrolled (ACT<20) on their current ICS/LABA medication may be recruited and will, as needed, switch to Relvar/Breo ELLIPTA, if not already prescribed that. Due to this possible change in maintenance medication, a flexible run-in period has been incorporated into the study design, to enable assessment of any impact associated with the change of drug/dosing frequency, or simply being on the study, before being randomised to treatment on the study.

The 5 treatment arms of the study will allow future development of the CIS and provide directional data on which aspects of the CIS have an impact on adherence, in particular, the impact of HCP being able to review adherence data and the impact of data being provided from both maintenance and rescue medications on adherence.

Due to the novelty of CIS and the limited literature to guide this study in terms of statistical assumptions, an unblinded sample size re-estimation will take place once 50% of the planned number of evaluable subjects have completed. Further information on this process is provided in Section 11.

5.5. Dose Justification

Relvar/Breo ELLIPTA and Salbutamol MDI will be prescribed as per label. The dosage of Relvar/Breo prescribed to a subject at the beginning of the study will depend on the dosage of their current ICS/LABA treatment and therefore,whether they will receive either 100/25 mcg or 200/25 mcg Relvar/Breo ELLIPTA. Changing between doses is permitted during the study treatment period if deemed necessary by the investigator.

6. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted.

6.1. Inclusion Criteria

AGE
1. Subjects aged 18 years or older, at the time of signing the informed consent.
TYPE OF SUBJECT AND DIAGNOSIS
2. Subjects with documented physician diagnosis of asthma as their primary respiratory disease. 3. Asthma Control Test (ACT) score <20 at screening visit 4. Non-smokers (never smoked or not smoking for >6 months with <10 pack years history (Pack years = [cigarettes per day smoked/20] x number of years smoked)
SEX
5. Male or Female subjects: A female subject is eligible to participate if she is not pregnant (see Appendix 5), not breastfeeding, and at least one of the following conditions applies: (i) Not a woman of childbearing potential (WOCBP) as defined in Appendix 5. OR (ii) A WOCBP who agrees to follow the contraceptive guidance in Appendix 5 during the treatment period and for at least 5 days] after the last dose of study treatment.

INFORMED CONSENT
6. Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the consent form and in this protocol. 7. Subject understands and is willing, able, and likely to comply with study procedures and restrictions. 8. Subject must be able to read in a language supported by the smart phone app in their region
CURRENT ASTHMA THERAPY
9. Subject must have been on maintenance therapy (Fixed dose combination ICS/LABA) for 3 months, cannot have changed dose in the month prior to screening and be able to change to an equivalent dose of Relvar/Breo for the duration of the study. Other background asthma medication such as anti-leukotrienes and oral corticosteroids are permitted provided the dose has been stable for 1 month prior to screening. 10. Subject must be able to change to Salbutamol/Albuterol MDI rescue for the duration of the study and judged capable of withholding albuterol/salbutamol for at least 6 hours prior to study visits.
DIGITAL CRITERIA
11. Subject must have their own Android or IOS smart phone and a data package suitable for the installation and running of the app and sending and receiving data. Data used by the CIS is approximately 1MB per month as a maximum; this is less data than a 1 minute video streamed from YouTube (2MB)). 12. Subjects must be willing and able to download the app on their personal smart phone and keep it turned on for the duration of the study. This will also require Bluetooth to be turned on for duration of the study. Subjects will also have to turn on mobile data for the app for the duration of study; unless travelling and when extra data roaming costs could be incurred.

6.2. Exclusion Criteria

A subject will not be eligible for inclusion in this study if any of the following criteria apply:

RELEVANT HABITS
1. Subjects with a known or suspected alcohol or drug abuse which in the opinion of the investigator could interfere with the subject's proper completion of the protocol requirement
CONTRAINDICATIONS
2. History of life threatening asthma: Defined for this protocol as an asthma episode that required intubation and/or was associated with hypercapnea, respiratory arrest or hypoxic seizures within the last 6 months 3. A lower respiratory tract infection within 7 days of the screening visit. 4. Concurrent diagnosis of COPD or other respiratory disorders including active tuberculosis, lung cancer, bronchiectasis, sarcoidosis, lung fibrosis, pulmonary hypertension, interstitial lung diseases or other active pulmonary diseases. 5. History of hypersensitivity/intolerance to any components of the study inhalers (e.g., lactose, magnesium stearate). In addition, subjects with a history of severe milk protein allergy that, in the opinion of the study physician, contraindicates participation will also be excluded. 6. Historical or current evidence of clinically significant or rapidly progressing or unstable cardiovascular, neurological, cardiovascular, neurological, renal, hepatic, immunological, endocrine (including uncontrolled diabetes or thyroid disease) or hematological abnormalities that are uncontrolled. Significant is defined as any disease that, in the opinion of the investigator, would put the safety of the subject at risk through participation, or which would affect the analysis if the disease/condition exacerbated during the study.
DIAGNOSTIC ASSESSMENTS AND OTHER CRITERIA
7. Patient who have ever received treatment with biological based therapy e.g. omalizumab, mepolizumab, for asthma 8. Subjects who have received an investigational drug and/or medical device within 30 days of entry into this study (Screening), or within five drug half-lives of the investigational drug, whichever is longer 9. A subject will not be eligible for this study if he/she is an immediate family member of the participating investigator, sub-investigator, study coordinator, employee of the participating investigator, or any family member of a Propeller Health employee

Inclusion Criteria for Randomisation

ACT Control at V2, or V3 or V4 of run-in period
1. Asthma Control Test (ACT) score <20 at randomisation visit (V2)

6.3. Lifestyle Restrictions

There are no lifestyle restrictions.

6.4. Screen, Run-in and Randomisation Failures

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently entered into the run-in period.

A subject who completes V1 assessments and is dispensed the study medication for the run-in period is considered to have entered the run-in period.

A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse events (SAEs) will be collected in the eCRF.

Run-in failuresare defined as subjects who consent to participate in the clinical study, enter the run-in period but are not subsequently randomised and do not have any randomisation visit (V2, V3, or V4) procedures other than ACT assessment. Information including demography, run-in failure details, eligibility criteria, and any serious adverse events (SAEs) will be collected in the eCRF.

Randomisation failures are those subjects that complete at least one Randomization procedure other than ACT but are not subsequently randomised and do not enter the study treatment period.

Any subject who completes the run-in period and then meets the randomization criteria and is dispensed the study treatment at V2 is considered to have entered the treatment period.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened, at the discretion of the investigator and should be assigned with a new subject number.

7. TREATMENTS

Study treatment is defined as any investigational treatment(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study subject according to the study protocol.

7.1. Treatments Administered

All subjects will 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. Guidance on which Relvar/Breo dose is appropriate, dependent on current therapy is included in Section 7.2.

Salbutamol MDI rescue medication will be prescribed to subjects to use as needed throughout the study for relief of asthma symptoms as per usual practice.

Study Treatment Name:	**RELVAR/BREO ELLIPTA**	**Salbutamol MDI**
Dosage formulation:	ELLIPTA DPI – 30 doses per device	Metered Dose Inhaler – 200 doses per device
Unit dose strength(s)/Dosage level(s):	100/25 mcg per actuation and 200/25 mcg per actuation	100 mcg salbutamol per actuation
Route of Administration	Inhaled	Inhaled
Dosing instructions:	One inhalation once daily	PRN
Packaging and Labelling	Study Treatment will be provided in a container. Each container will be labelled as required per country requirement.	Treatment will be provided locally. and will be labelled as per country requirements.
Manufacturer	GlaxoSmithKline (GSK)	

All subjects 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 ELLIPTAand salbutamol MDI) , as well as who sees that data (subject alone or subject and HCP) that defines the treatment arms. See Table 1 for a description of what data is fed back to who for each treatment arm. Further information /reference material for the CIS is provided in the SRM.

Table 1 Treatment Arms

	Relvar/Breo Sensor Data Available to		Salbutamol MDI Sensor DataAvailable to	
Treatment Arm	**Subject**	**HCP**	**Subject**	**HCP**
1	X	X		
2	X			
3	X	X	X	X
4	X		X	
5				

7.2. Relvar/Breo Dose Guidance:

FF/VI 100mcg/25mcg dose is comparable to fluticasone propionate/salmeterol low and medium doses. See SRM for further guidance for dose conversion for other corticosteroids.

Further information detailing equivalence of Relvar/Breo to other ICS/LABA combination treatment, for subjects who are switched, will be included in the SRM.

7.3. Medical Devices

The clip on sensors and associated app for subjects' Smartphone are produced by Propeller Health and are being provided by GSK for use in this study. These devices, which are fitted on to the Relvar/Breo ELLIPTA DPI and albuterol/salbutamol MDI to electronically record actuation data and associated app and HCP dashboard to provides that data, both have US FDA 510(K) clearance to market (Class II device) and European Union (EU) European Confiormity (CE) marking (Class I device).

Instructions for medical device use are provided in the SRM, PSSM and in the pack insert for each device.

7.4. Dose Modification

During the treatment period, investigators may modify the dose of a given subject during the study. Subjects in turn may change their dose from 100/25mcg FF/VI to 200/25mcg FF/VI and vice-versa if deemed absolutely necessary by the investigator.

7.5. Method of Treatment Assignment

Assignment of Subject Number

A unique Subject Number will be assigned to any subject who has signed the informed consent at V1. The unique Subject Number will be used to identify individual subjects during the course of the study.

Assignment of Randomisation Number

At V2, V3 or V4 (Run-in visits), subjects meeting the eligibility criteria will be assigned to study treatment using an interactive web response system (IWRS) that will be used by HCP or designee to register the subject, randomise the subject and provide treatment assignment information. Details on how to use RAMOS NG, the IWRS, to register and randomise subjects is provided in the RAMOS NG IWRS manual and SRM.

Once a randomisation number has been assigned to a subject, it cannot be reassigned to any other subject in the study.

Subjects will be assigned to study treatment in accordance with the randomisation schedule. The randomisation code will be generated by GSK using a validated computerised system. A subject will be randomised using RAMOS NG. The study will use central-based randomisation system to allocate treatments.

Subjects will be randomized 1:1:1:1:1 to one of the five treatments arms for the duration of the treatment period. Following the interim analysis and if extra subjects are required in arms 1 and 5, then those subjects will be randomised 1:1 in those arms. See Section 5 for description and numbering of arms.

Each investigator will be provided with sufficient study supplies to respond directly to subject requests for study treatment as required. Additional supplies will be supplied as needed to the sites. Details of how to use the IWRS system (RAMOS NG) to randomise subjects and manage study treatment supplies (including dispensing) is provided in the RAMOS NG IWRS manual and SRM.

7.6. Blinding

The study is open label, neither the subject, HCP, site staff, or sponsor is blinded to treatment assignment.

7.7. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.
2. Only subjects enrolled in the study may receive study treatment and only authorised site staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated)

area in accordance with the labeled storage conditions with access limited to the investigator and authorised site staff.

3. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
4. Further guidance and information for the final disposition of unused study treatment are provided in the SRM.

Under normal conditions of handling and administration, study treatment is not expected to pose significant safety risks to site staff.

A Material Safety Data Sheet (MSDS)/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from GSK.

7.8. Treatment Compliance

The primary measure of treatment compliance for both Relvar/Breo ELLIPTA and Salbutamol MDI will be captured by the respective sensor for those treatments. However, the date of prescription and date of return of the inhaler, as well as start and finished dose count on each Relvar/Breo ELLIPTA, will be recorded in source documents at the dispensing visit and also transferred to the eCRF.

7.9. Concomitant Therapy

All medications for asthma, excluding biological therapy and for other disorders that are not contra indicated in asthma, or prohibited in this study, may be continued throughout the study.

Please consult the prescribing information for the full list of medications which need to be used with caution:

Beta-blockers: Use with caution. May block bronchodilatory effects of beta-agonists and produce severe bronchospasm.

Diuretics: Use with caution. Electrocardiographic changes and/or hypokalemia associated with non-potassium-sparing diuretics may worsen with concomitant beta-agonists.

Non-study asthma medications: A detailed history of previous 1 year, for prescriptions for maintenance medications will be captured in the subjects eCRF and also any other ongoing asthma medications at inclusion.

Any medication or vaccine of relevance to the study or prescribed for safety events, including exacerbations experienced during the study, that the subject is receiving at the time of enrolment or receives during the study must be recorded in the eCRF in addition to medical records. As minimum the following will be needed:

- reason for use

- dates of administration including start and end dates
- dosage information including dose and frequency

Over-the-counter medicines, vitamins, and/or herbal supplements are not required to be captured.

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

7.10. Prohibited Concomitant Medication

Subjects must abstain from taking the following medications from 5 days prior to the first dose of study medication until completion of the follow-up visit.

- Strong cytochrome P450 3A4 inhibitors (e.g., ketoconazole)
- Monoamine oxidase inhibitors and tricyclic antidepressants:
- Subjects must never have been treated with a biological therapy for asthma e.g. omalizumab, mepolizumab.

Patients using Relvar/Breo ELLIPTA should not use another medicine containing a LABA (e.g., salmeterol, formoterol fumarate, arformoterol tartrate, indacaterol) for any reason.

Do not use in combination with an additional medicine containing a LABA because of risk of overdose.

For full list of cautions for use and medicine interactions please consult the prescribing information and/or consult the study Medical Monitor if in doubt.

7.11. Treatment after the End of the Study

There is no plan to continue to provide treatment following the end of the study. The investigator is responsible for ensuring that consideration has been given to the post-study care of the subject's medical condition, whether or not GSK is providing specific post-study treatment.

Medications initiated after completion of the assessments at V10 or the EW visit will not be recorded in the eCRF unless taken to treat an AE or asthma exacerbation. subjects who have completed the EW visit are allowed to use any medications prescribed by the Investigator or primary care physician.

8. DISCONTINUATION CRITERIA

Subjects that permanently stop study treatment are encouraged to remain in the study. Subjects have the right to discontinue study treatment before the end of the study. A subject may also be asked to discontinue study treatment at the investigator's discretion.

Subjects who withdraw from study treatment prematurely (for any reason) should, where possible, continue to be followed-up as per protocol until the completion of the Safety Follow-up assessments. If patients want to discontinue use of the CIS but will continue taking the Relvar/Breo ELLIPTA DPI then they will be given the option to continue to remain in study if they continue using the clip-on sensor for ELLIPTA. If this is not possible, the Investigator must encourage the subject to participate in as much of the study as they are willing (or able) to. Likewise, subjects who change their dose of Relvar/Breo (FF/VI) at the discretion of the investigator during the study will be given the option to remain on the study. For those subjects who do not want to use the sensor during the study, their health outcome information will be collected along with any additional adherence data. For those subjects who change dose, all information will continue to be collected for the duration of the study.

A subject may be withdrawn from study treatment at any time. A reason for premature discontinuation of study treatment must be captured in the eCRF.

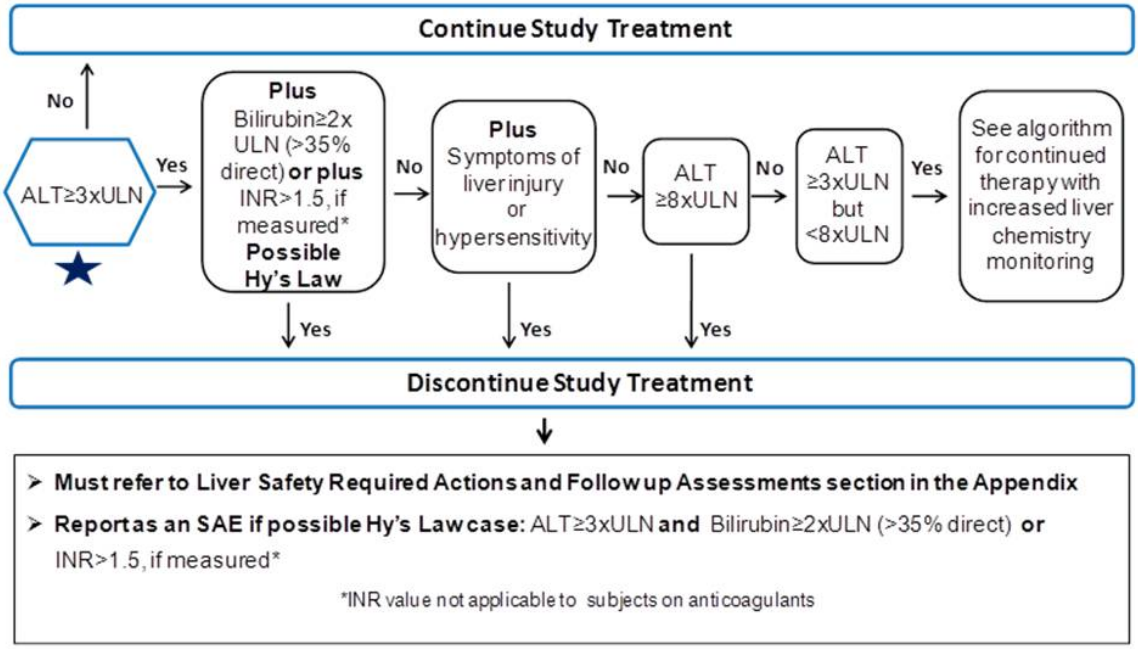
8.1. Discontinuation of Study Treatment

8.1.1. Liver Chemistry Stopping Criteria

There are no scheduled blood tests in this study. If however the subject has a routine blood test during the study and the results suggest abnormal liver function, then the liver stopping criteria will apply.

Liver chemistry stopping and increased monitoring criteria have been designed to assure subject safety and evaluate liver event etiology (in alignment with the FDA premarketing clinical liver safety guidance). These protocol guidelines are in alignment with FDA premarketing clinical liver safety guidance: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf.

Discontinuation of study treatment for abnormal liver tests should be considered by the investigator when a subject meets one of the conditions outlined in the algorithm , see Appendix 6,or if the investigator believes that it is in the best interest of the subject.



8.1.2. QTc Stopping Criteria

ECGs are not planned at Screening or during this study. However, if during the study a subject has an ECG performed the following stopping criteria apply and treatment should be withdrawn:

A subject who meets the bulleted criteria below will be withdrawn from the study:

- QTcF>500 msec or uncorrected QT>600 msec
- Change from V1 baseline: QTcF> 60msec

For patients with underlying **bundle branch block**, follow the discontinuation criteria listed below:

	Discontinuation QTc with Bundle Branch Block
< 450 msec	> 500 msec
450 – 480 msec	≥ 530 msec [Note: QTc(F)>500 msec for Korean subjects]

8.2. Withdrawal from the Study

- A subject may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioural, compliance to protocol or administrative reasons.

- Subjects should be reminded at each visit that if they do choose to withdraw themselves then, they should contact the Investigator or Study staff as soon as possible and arrange an EW visit.
- Female subject will be withdrawn if they produce a positive pregnancy test whilst on the study.
- If the subject withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

Refer to the Section 2 for data to be collected at the time of EW from the study

8.3. Lost to Follow Up

A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.
- Before a subject is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.
- Should the subject continue to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

9. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarised in the Section 2.

Protocol waivers or exemptions are not allowed

Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the subject should continue or discontinue study treatment.

Adherence to the study design requirements, including those specified in the Section 2, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the subject's routine clinical management (e.g., blood count) and obtained before signing of the informed consent form (ICF) may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and was performed within the time frame defined in the Section 2.

9.1. Efficacy Assessments

9.1.1. Primary, Secondary and Other Adherence Measures

The Primary, Secondary and Other adherence endpoint (adherence to maintenance medication) data is collected by the Clip-on Sensor for ELLIPTA and records the time and date when the ELLIPTA cover is opened and closed.

The sensor will be attached to subjects ELLIPTA Relvar/Breo treatment from start of run-in until V10. References and material for fitting the sensors, downloading the app and other aspects of using the CIS are included in the SRM.

9.1.2. Secondary Efficacy Endpoints

9.1.2.1. Asthma Control Test

This assessment is described in Section 9.1.3.1 and will be collected electronically at the site at the timepoints detailed in Section 2. This will be carried out via use of the electronic Patient Reported Outcome (ePRO) device.

9.1.2.2. Rescue Medication Use

Rescue Medication use endpoint data is collected by the Clip on Sensor for salbutamol MDI and records time and date when the MDI is actuated.

The sensor will be attached to the subject's salbutamol MDI treatment from start of run-in until V10. Details for fitting the sensor and other aspects of using the CIS are included in the SRM.

9.1.3. Questionnaires and Interviews

It is preferred that the questionnaires are administered at the same time of day at each visit and that this time of day is the same as when they were originally administered (as is feasible/appropriate), in order to avoid potential bias due to the time of day when responding. The subjects should not be told the results of any diagnostic tests prior to completing the questionnaires and the questionnaires should be completed before any procedures are performed on the subject to avoid influencing the subject's response. Adequate time in a quiet, comfortable location must be allowed to complete all items on the questionnaires and if necessary, the subject must be encouraged to complete any questionnaires or missing items fully.Full guidance for obtaining good quality data from patient-completed questionnaires is included in the SRM.

All the questionnaires will be completed on an ePRO device at the clinical study site and at the time detailed in the Section 2.

Further instructions for completing the questionnaires can be found in the SRM.

9.1.3.1. 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) with a range of 5 to 25. By answering all 5 questions a subject with asthma can obtain a score that may range between 5 and 25, with higher scores indicating better control. An ACT score of 5 to 19 suggests that the subject's asthma is unlikely to be well controlled. A score of 20 to 25 suggests that the subject's asthma is likely to be well controlled. The total score is calculated as the sum of the scores from all 5 questions[Nathan, 2004]. The minimally important difference (MID) for ACT is 3 [Schatz, 2009].

Subjects will complete the ACT at times shown in the Section 2 using the electronic version on the ePRO device at the clinical site.

The ACT has been developed as a measure of subjects' asthma control that can be quickly and easily completed in clinical practice and by telephone. The questions are designed to be self-completed by the subject.

Please refer to the SRM for further details.

9.1.3.2. 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 will be completed on an ePRO device at the clinical study site and at the times detailed in the Section 2.

Please refer to the SRM for further details.

9.1.3.3. St Georges Respiratory Questionnaire (SGRQ)

The St. George's Respiratory Questionnaire is a well established instrument, comprising 50 questions 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 subject with a recall over the past 4 weeks [Jones, 1992]

SGRQ will be completed on an ePRO device at the clinical study site and at the times detailed in the Section 2.

Please refer to the SRM for further details.

9.1.3.4. Patient Activation Measure (PAM)

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 questionnaire will be completed at the times shown in the Section 2.

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].

PAM will be completed by subjects on an ePRO device at the clinical study site and at the times detailed in the Section 2.

Please refer to the SRM for further details.

9.1.3.5. Medication Adherence Report Scale for Asthma (MARS-A), 10-item questionnaire

Reported adherence to medication will be assessed with the Medication Adherence Report Scale for Asthma (MARS-A) questionnaire at times shown in the Schedule of Activities (SoA).

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 has no specified timeframe on which responses should be based but generally refer to the present moment. MARS-A will be completed on an ePRO device at the clinical study site and at the times detailed in the Section 2.

Please refer to the SRM for further details.

9.1.3.6. 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 rated on a 5-point Likert scale [Horne, 2002].

The BMQ General comprises a General Harm scale and a General Overuse scale assessing beliefs about pharmaceuticals as a class of treatment. The General Harm scale assesses beliefs about the intrinsic nature of medicines and the degree to which they are perceived as harmful and should be avoided if possible. The General Overuse scale represents beliefs about the use of medicines and whether they are overprescribed by

clinicians. The BMQ Specific (Asthma) comprises two scales: one assessing patients' beliefs about the necessity of preventer medication for maintaining present and future health (Necessity scale), and the other assessing their concerns about the potential adverse consequences of using it (Concerns scale). Four items were added for use in patients with asthma.

BMQ will be completed on an ePRO device at the clinical study site and at the times detailed in the Section 2.

Please refer to the SRM for further details.

9.1.3.7. Exit Questionnaire

All subjects will complete a questionnaire at the end of the final study visit (V10) to assess the CIS. This questionnaire is designed to understand the subject's perceptions of the CIS. It is self-completed on the ePRO device by subjects. It includes questions relating to the concepts below:

- Overall satisfaction with CIS
- Parts of the CIS that were most /least helpful
- Level of engagement with the CIS
- Challenges/difficulties with using CIS
- Subject perception of the impact of the CIS on asthma
- Subject perception of future use of a similar system
- Impact of CIS on physician interaction

9.1.3.8. Exit Interviews

Exit interviews will be conducted for subjects at selected sites at the visit after they have completed their course of study medication (V11). Exit interviews are qualitative interviews conducted with study subjects to capture a subjects experience on changes in asthma and perceptions of the CIS.

Interview questions are designed to fully assess a subject's experience in a structured format by a trained interviewer. Subject feedback will audio-taped for subsequent transcription and qualitative analysis.

These exit interviews will be conducted by external vendors after subjects have completed V11. The analysis and report of the exit interview will be managed by a separate RAP.

9.2. Serious Adverse Events (SAE), Non-Serious Adverse Events that leads to withdrawal and Non Serious Adverse Drug Reactions (ADR)

The Investigator or site staff will be responsible for detecting, documenting and reporting events that meet the definition of a, non-serious adverse events that leads to withdrawal, non-serious adverse drug reaction (ADR) or SAE.The definition of an ADR is any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, for which there is a reasonable possibility that the untoward occurrence is *causally related* to the medicinal product. ADRs are a subset of AEs for a given medicinal product.

Potential SAEs and associated non serious ADRs may be identified from a subject's primary HCP report or a subjects health records. The HCP will have the ultimate responsibility for determining causality and seriousness.

In some countries extra safety information may be requested as required by local Regulatory Agencies and information providing detail of these extra safety events and how these should be reported are included in Appendix 8.

In this study, only information regarding non- serious adverse drug reactions (ADRs), AEs leading to withdrawal and serious adverse events (SAEs) will be detected, documented and reported. However, the definition of an AE is critical for the definition of non-serious ADRs and SAEs.

The definitions of an AE or SAE can be found in Appendix 4

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious or that caused the subject to discontinue the study (see Section 8.1).

9.2.1. Time Period and Frequency for Collecting AE, ADR and SAE Information

- Any SAEs assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time a subject consents to participate in the study up to and including any follow-up contact.
- AEs leading to withdrawals and ADRs will be collected from the start of Study Treatment until the follow-up contact at the timepoints specified in SoA Section 2
- Medical occurrences that begin prior to the start of study treatment but after obtaining informed consent may be recorded on the Medical History/Current Medical Conditions section of the eCRF.
- All SAEs will be recorded and reported to the sponsor or designee within 24 hours, as indicated in Appendix 4 The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

- Investigators are not obligated to actively seek AEs or SAEs in former study subjects. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify the sponsor.
- The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 4.

9.2.2. Method of Detecting Aes, ADRs and SAEs

Care will be taken not to introduce bias when detecting AE and/or SAE. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrence.

The Investigator or site staff will be responsible for detecting, documenting and reporting events that meet the definition of a non-serious adverse drug reaction (ADR), AE (leading to withdrawal) or SAE.

Potential SAEs, AE (leading to withdrawal) and associated non serious ADRs may be identified from patients medical records. The Investigator will have the ultimate responsibility for determining causality and seriousness. .

In this study, only information regarding non- serious adverse drug reactions (ADRs), AE leading to withdrawal and serious adverse events (SAEs) will be detected, documented and reported.

9.2.3. Follow-up of AEs, ADRs and SAEs

After the initial AE that led to withdrawal/non-serious ADR/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs, will be followed until the event is resolved, stabilized, otherwise explained, or the subject is lost to follow-up (as defined in Section 8.3). Further information on follow-up procedures is given in Appendix 4.

9.2.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a study treatment under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.

- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information e.g., summary or listing of SAE) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

In some countries extra safety information may be requested as required by local Regulatory Agencies and information for this and how these should be reported are included in Appendix 8.

9.2.5. Cardiovascular and Death Events

For any cardiovascular events as detailed in Appendix 4 and all deaths, whether or not they are considered SAEs, specific Cardiovascular (CV) and Death sections of the CRF will be required to be completed. These sections include questions regarding cardiovascular (including sudden cardiac death) and non-cardiovascular death.

The CV CRFs are presented as queries in response to reporting of certain CV Medical Dictionary of Regulatory Activities (MedDRA) terms. The CV information should be recorded in the specific cardiovascular section of the CRF within one week of receipt of a CV Event data query prompting its completion.

The Death CRF is provided immediately after the occurrence or outcome of death is reported. Initial and follow-up reports regarding death must be completed within one week of when the death is reported.

9.2.6. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as SAEs

The following disease related events (DREs) are common in subjects with asthma and can be serious/life threatening:

9.2.6.1. Asthma Exacerbations

For the purposes of this study, severe asthma exacerbations will be collected and recorded on the asthma exacerbation eCRF page from the start of treatment until follow up/or the EW visit for those subjects that withdraw from participation in the study.

A severe asthma exacerbation is defined as deterioration of asthma requiring the use/additional use of systemic corticosteroids (tablets, suspension, or injection), or antibiotics, an inpatient hospitalisation, or emergency department visit due to asthma that required systemic corticosteroids or antibiotics. Further clarification will be present in the SRM.

Asthma exacerbations should not be recorded as an AE unless they meet the definition of an SAE.

These events will be recorded on the DRE page in the subject's eCRF within 24 hours of the physician becoming aware. The time period for collection of exacerbation information in the eCRF will be from the time that the ICF is signed until the Exit visit or EW.

For consistency, exacerbations separated by less than 7 days will be treated as a continuation of the same exacerbation.

9.2.7. Pregnancy

Details of all pregnancies in female subjects will be collected after the start of study treatment and until at least 5 terminal half-lives after the last dose.

If a pregnancy is reported, the investigator should inform GSK within 2 weeks of learning of the pregnancy and should follow the procedures outlined in Appendix 5.

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAE.

9.2.8. Medical Device Incidents (Including Malfunctions)

Procedures for Documenting Medical Device Incidents are provided in Appendix 7.

9.3. Treatment of Overdose

For this study, any dose of Relvar/Breo ELLIPTA greater than the prescribed dose within a 24-hour time period will be considered an overdose.

GSK is not recommending specific treatment guidelines for overdose and toxicity management. The investigator is advised to refer to the relevant document(s) for detailed information regarding warnings, precautions, contraindications, adverse events, and other significant data pertaining to the study drug being used in this study. Such documents may include, but not be limited to, the IB or equivalent document provided by GSK.

In the event of an overdose, the HCP/treating physician should:

1. Contact the Medical Monitor immediately.
2. Document the quantity of the excess dose as well as the duration of the overdosing in the CRF.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the subject.

9.4. Screening and Safety Assessments

Planned time points for all screening and safety assessments are provided in Section 2.

9.4.1. Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the Skin, Cardiovascular, Respiratory, Gastrointestinal and Neurological systems. Height and weight will also be measured and recorded.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

The physical exam is to inform on inclusion and only needs to be recorded in the subjects source/medical notes. Physical exams will be performed at the time points specified in the Section 2.

9.4.2. Vital Signs

Vital signs (systolic and diastolic blood pressure and pulse rate) will be performed at the screening visit only as part of physical exam The measurement will be taken after 5 minutes rest in a semi-supine position. One reading of blood pressure and pulse will be taken.

The vital signs are to inform on inclusion and only needs to be recorded in the subjects source/medical notes.

9.4.3. Clinical Safety Laboratory Assessments

Urine pregnancy tests are performed at timelines detailed in Section 2. The tests will be provided locally. The results of the tests should be recorded in the subject's medical records only.

If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in subject management or are considered clinically significant by the investigator (e.g., SAE or AE), then the results must be recorded in the eCRF.

9.5. Biomarkers

9.5.1. FeNO in breath

FeNO will be measured using a handheld electronic device. Measurements will be obtained in accordance with the American Thoracic Society (ATS)/European Respiratory Society (ERS) Recommendations for Standardized Procedures for the Online and Offline Measurement of Exhaled Lower Respiratory Nitric Oxide and Nasal Nitric Oxide [Silkoff, 2005]. All sites will use standardized equipment provided by a central vendor. For each observation, at least 2 measurements will be obtained to establish reproducibility (up to 8 measurements can be performed). FeNO measurements will be interpreted in accordance with the Official ATS Clinical Practice Guideline: Interpretation of Exhaled Nitric Oxide Levels (FeNO) for Clinical Applications [Dweik, 2011]. FeNO observations must be completed before PEF assessments. Subjects should not use their rescue medication for at least 6 hours before each FeNO assessment, unless

essential for clinical need. Subjects should also withhold Breo/Relvar ELLIPTA for (1 dosing interval) approximately 24 hours prior to FeNO assessment.

9.6. Peak Expiratory Flow (PEF)

At visits where PEF is to be taken the subjects should withhold Salbutamol for 6 hrs before the visit and Relvar/Breo ELLIPTA for approximately 24 hours prior to assessment.

PEF will be performed using a Mini Wright Peak Flow Meter provided by GSK. Details of how this procedure is performed is detailed in the SRM.

PEF will be taken in triplicate at timelines detailed in the Section 2. All 3 measures should be recorded in the subjects record and transferred to the eCRF.

9.7. Prescription Record for Asthma Maintenance Medication

The following will be collected in the eCRF and confirmed by a subjects medical record's, or the prescribing physician. Prescriptions for a subjects asthma maintenance therapy (ICS or ICS/LABA combinations) for the 12 months prior to inclusion.

9.8. Medical Resource Utilisation and Health Economics

Medical resource utilisation associated with medical encounters, will be collected in the eCRF by the investigator and study-site personnel for all subjects throughout the study.

These events should be recorded and reviewed by the HCP or designee with the subject at all study visits and where available confirmed with a subjects medical records.

Protocol-mandated procedures, tests, and encounters are excluded, though visits relating to HCP review of the CIS dashboard will be captured.

The data collected may be used to conduct exploratory health care resource utilization (HCRU) and economic analyses and will include:

- 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
- Number of prescriptions filled/requested for maintenance medication in the 12 months prior to inclusion.
- Annualised rate of severe exacerbations
- Number of unscheduled visits to primary care related to Asthma

10. DATA MANAGEMENT

- For this study, subject data will be entered into a GSK defined eCRF, transmitted electronically to GSK or designee and combined with data provided from other sources in a validated data system.
- Management of clinical data will be performed in accordance with applicable GSK standards and data cleaning procedures to ensure the integrity of the data, e.g., removing errors and inconsistencies in the data.
- Adverse events and concomitant medication terms will be coded using MedDRA (Medical Dictionary for Regulatory Activities) and an internal validated medication dictionary, GSKDrug.
- eCRFs (including queries and audit trails) will be retained by GSK, and copies will be sent to the investigator to maintain as the investigator copy. Subject initials will not be collected or transmitted to GSK according to GSK policy.

11. STATISTICAL CONSIDERATIONS

11.1. Hypothesis

The main purpose of the study is to compare the effect of 6 months use with the CIS on adherence to ELLIPTA maintenance therapy with adherence to ELLIPTA maintenance therapy without CIS use (sensor alone), in subjects with poorly controlled asthma. 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 and

95% confidence intervals. 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, and arms with rescue medication use feedback versus none, 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, in order to obtain estimated mean treatment differences and 95% confidence intervals. This will be a descriptive comparison and no formal inference is planned.

11.2. Sample Size Determination

11.2.1. Sample Size Assumptions

The fixed sample size calculation is based on the primary endpoint, percentage of ELLIPTA doses taken (daily adherence) between Months 4 and 6 as determined by the maintenance sensor and has approximately 90% power to detect an absolute difference of 15% in the primary comparison. The treatment difference is based on the limited published data [Charles, 2007, van Boven, 2016]. This assumes a conservative standard deviation of 28% (based on a previous study [Charles, 2007]) and significance declared at the two-sided 5% level.

Approximately 432 patients will be randomised in order to obtain at least 380 subjects (i.e. 76 subjects per arm) with available data over the last three months of the treatment period, in anticipation of a 12% drop-out within the first three months. Subjects will be randomised to one of five treatment arms with a ratio of 1:1:1:1:1.

Using the above assumptions the smallest observed effect predicted to result in a statistically significant difference between treatment groups is 9% (minimum detectable difference).

11.2.2. Sample Size Sensitivity

Due to limited historical data within GSK, an external party was hired to conduct a literature review. Based on results from the literature review only one paper in an asthmatic adult population provided adherence rates and variability estimates that could be used as assumptions for power calculations [Charles, 2007].

The study presented sample size assumptions for the treatment difference in mean daily % adherence of 10% and a standard deviation of the data of 18% [s1]. The reported raw means (standard deviation) of mean daily % adherence were 88% (16%) and 66% (27%) in the intervention and control groups, respectively. Due to uncertainty in data variability a wide range of values were explored. Table 2 belowpresents the power achieved with the proposed sample size of 76 completers per arm should the assumptions of standard deviation of the data change.

Table 2 Standard Deviation Affect on Power from the Fixed Sample Size

Standard Deviation (%)	Power for Primary Comparison
22	99
24	97
26	94
28	90
30	86
32	81
34	77

11.2.3. Sample Size Re-estimation

Due to the uncertainty on the true treatment effect and data variability, and to reduce the risk of running an underpowered study, it is considered appropriate to adopt an adaptive approach to the sample size for this study. This will offer a mechanism to adjust the sample size in response to updated treatment effect and variability estimates seen at a planned interim analysis [Mehta, 2011] . The proposal is as follows:

- Start with a fixed sample size calculation based on the primary endpoint.
- Independent statistician performs a planned unblinded interim analysis to examine data based on 50% of subjects on each arm having completed the 6 months treatment period.
- Based on the interim results (i.e.: treatment effect, data variability and conditional power) maintain or increase the sample size in order to obtain the desired power of 90%.

The conditional power based on the interim results will assess as to where it falls within certain regions established prior to the trial starting. Should the conditional power be in the favourable or unfavourable range the sample size will not be adjusted and will remain at the fixed size for all treatment arms. Conditional power falling into the promising zone will have a sample size increase applied to treatment arm 1 and 5 only. However, no more than a further 42 subjects will be randomised in to each of the treatment arms 1 and 5 to provide a maximum of approximately 114 (76+38) subjects with data available for the primary analysis in each of those 2 arms such that a total number of 456 subjects in all arms are expected.

The regions and their implications on sample size are detailed below:

Favourable	conditional power at interim (CPinterim) $\geq$ 90%
Promising	CP min $\leq$ CPinterim $<$ 90%
Unfavourable	CPinterim $<$ CP min

Full details of the adaptive method for sample size specified above will be given in the reporting and analysis plan (RAP).

11.3. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All subjects who sign the ICF
Total Population	The Total Population will comprise all subjects screened and for whom a record exists on the study database and will be used for the tabulation and listing of reasons for withdrawal before randomisation.
Intent-to-treat	The Intent–to–Treat (ITT) population is defined as all subjects who have been randomised and exposed to at least one dose of treatment. The ITT population will be used for all endpoint analyses and Outcomes will be reported according to the randomised treatment allocation.

11.4. Statistical Analyses

Where possible, data from subjects who withdraw prematurely from the study treatment or the study will be included in any relevant analyses. Specific details for inclusion will be detailed in the Reporting and Analysis Plan (RAP).

The covariates to be considered in the efficacy analyses include age, sex, region and the baseline values, if relevant. Other covariates, if appropriate, may be considered. Specific details will be provided in the RAP.

11.4.1. Adherence Analyses

Endpoint	Statistical Analysis Methods
Primary	The primary analysis will estimate the treatment effect of 6 months use of the ELLIPTA maintenance therapy with CIS when both the subject and the HCP are supplied with data from the maintenance sensor versus no data supplied to the subject and HCP (Arm 1 vs Arm 5) for the primary endpoint 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. The analysis will be performed on the ITT population. The analysis will be performed on the percentage adherence between Months 4 and 6 measure using an Analysis of Covariance (ANCOVA) model allowing for effects due to randomised treatment, baseline adherence, duration (days) in run-in, region, sex, 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. Any subjects with missing intermittent adherence data will be

	imputed to as non-adherent i.e. 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. Subjects who prematurely discontinue from study will have their post-withdrawal daily adherence data imputed using data from the control arm using an appropriate method of imputation, such as the jump to reference method. This method of assessing the primary endpoint corresponds to a de-facto treatment policy estimand which reflects the anticipated behaviour that subjects will continue to take an asthma combination therapy without the CIS intervention. Missing data due to a medical device incident such as device failure, technical failure of the e-sensor, or data transmission failure will be assumed to be missing at random (MAR). For each subject the percentage adherence measure will be calculated under the assumption that any missing data is MAR, from the proportion of the number of days a subject is adherent divided by the number of days data provided for the last 3 months treatment period. 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 p-value. Summary statistics (mean, standard deviation, median, minimum, maximum) of the primary endpoint will be provided. Where possible, adherence data collected from subjects who withdraw prematurely from study treatment will be included in the analysis. Sensitivity analyses of the primary adherence endpoint will be performed on the ITT population and an assessment of the impact of the missing data will be carried out using multiple imputation methods under different assumptions for missing data for withdrawn subjects. Details will be provided in the RAP.
Secondary	The following secondary analyses 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 subjects versus no data supplied to the subject (Arm 2 vs Arm 5) • Rescue and Maintenance data supplied to subject and HCP versus no data supplied to the subject and HCP (Arm 3 vs Arm 5) • Rescue and Maintenance data only supplied to subject versus no data supplied to the subject (Arm 4 vs Arm 5) for the following secondary endpoints: • 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, • Percentage of ELLIPTA doses taken (daily adherence) 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 The analysis will be performed using an ANCOVA model allowing for effects due to randomised treatment effect, baseline adherence, duration (days) in run-in, region, sex, 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. Any subjects with missing intermittent adherence data will be imputed to as non-adherent i.e. 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. Where possible, adherence data collected from subjects who withdraw prematurely from study treatment will be included in the analysis. Subjects who prematurely discontinue from study will be handled as per the primary endpoint analysis. 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. Summary statistics (mean, standard deviation, median, minimum, maximum) of the secondary endpoint will be provided. If a subject has changed dose during the study, sensitivity analyses on the secondary endpoint(s) regarding ACT will be performed where these subjects are removed from the analysed population. Further details will be provided in the RAP.
Exploratory	Will be described in the RAP.

11.4.2. Safety Analyses

All safety analyses will be performed on the ITT Population.

Endpoint	Statistical Analysis Methods
Safety	SAEs, AEs leading to withdrawal and non-serious ADRs will be collected. Safety endpoints will include: • Incidence and type of serious adverse events • Incidence and type of adverse drug reactions • Incidence and type of non-serious adverse events leading to study withdrawal • Incidence of subjects experiencing a severe exacerbation The incidence of any given adverse event (SAE or ADR) for each treatment group is defined as the proportion of subjects in that group who have experienced at least one such adverse event during the study period.

	The number and percentage of subjects with SAEs, non-serious ADRs and AEs leading to study withdrawal will be summarised by preferred term. The number and percentage of subjects experiencing severe exacerbations over treatment period and the follow-up period will be summarised for each treatment group alongside the primary causes of the exacerbation.

11.4.3. Other Analyses

All other exploratory endpoints, except for qualitative data from exit interviews and questionnaires, will be detailed in the RAP.

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).

11.4.4. Interim Analyses

An interim analysis will be conducted when 50% of subjects complete 6 months of treatment to conduct a sample size re-estimation (refer to Section 11.2.3 for details).

At this interim analysis the adherence data will be reviewed by an independent statistics and programming group independent of the study team. In order to minimise the introduction of any operational bias, good operating procedures will be built into an interim analysis charter which will detail who will access the data, rules for altering the sample size and the procedure to be followed when recommending the sample size alteration. The unblinded interim analysis will be conducted by an internal statistics and programming group independent of the study team and reviewed by an independent interim analysis review committee who will notify of the sample size outcome after 50% of subjects have completed the 6 month treatment period.

This independent statistics and programming group will have access to unblinded data within a restricted and firewalled area to ensure the study team remain blind.

Only the primary endpoint will be analysed at this stage to determine the conditional power of having success at the end of the trial given the interim results.

Further details of the internal statistics and programmer group role, data to be reviewed, committee membership, criteria, decisions and communication plan will be outlined clearly in the charter.

Recruitment will continue while the interim analysis is being conducted.

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13. APPENDICES

13.1. Appendix 1: Abbreviations

ACT	Asthma Control Test
ADR	Adverse Drug Reaction
AE	Adverse Event
ALT	Alanine amino transferase
ANCOVA	Analysis of Covariance
ASE	All Subjects Enrolled
ASUI	Asthma Symptom Utility Index
ATS	American Thoracic Society
BMQ	Beliefs in Medicine Questionnaire
CE	Europen Conformity
CFR	Code of Federal Regulations
CI	Confidence Interval
CIOMS	Council for International Organizations of Medical Sciences
CIS	Connected Inhaler System
CONSORT	Consolidated Standards of Reporting Trials
COPD	Chronic Obstructive Pulmonary Disease
CP	Conditional Power
CRF	Case Report Form
CSR	Clinical Study Report
CV	Cardiovascular
DPI	Dry Powder Inhaler
DRE	Disease Related Event
ER	Emergency Room
ERS	European Respiratory Society
EW	Early Withdrawal
EU-RMP	European Union – Risk Management Plan
FDA	Food And Drug Administration
FeNO	Fractional exhaled Nitric Oxide
FF	Fluticasone Furoate
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GSK	GlaxoSmithKline
HCP	Healthcare Professional
HCRU	Health Care Resource Utilization
HIPAA	Health Insurance Portability and Accountability Act
HPA	Hypothalamic-pituitary adrenal axis
HRT	Hormonal Replacement Therapy
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference On Harmonisation
ICS	Inhaled Corticosteroids
IEC	Independent Ethics Committees

IP	Investigational Product
IRB	Institutional Review Boards
ITT	Intent-to-Treat
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
IWRS	Interactive Web Response System
LABA	Long-Acting Beta2-Agonist
LOCS	Lens Opacities Classification System
MAR	Missing At Random
MARS-A	Medication Adherence Report Scale for Asthma
MDI	Metered Dose Inhaler
MedRA	Medical Dictionary of Regulatory Activities
MHPD	Marketed Health Products Directorate
MID	Minimally Important Difference
MSDS	Material Safety Data Sheet
PAM	Patient Activation Measure
PEF	Peak Expiratory Flow
PIL	Patient Instruction Leaflet
PRO	Patient Reported Outcomes
RAP	Reporting Analysis Plan
SAE	Serious Adverse Event
SGRQ	St Georges Respiratory Questionnaire
SoA	Schedule of Activities
SRM	Study Reference Manual
SUSAR	Suspected Unexpected Serious Adverse Reactions
UFIE	Unusual Failure in Efficacy
VI	Vilantrol
WOCP	Woman Of Childbearing Potential

13.2. Appendix 2: Trademarks

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
BREO
ELLIPTA
GSKDrug
RELVAR

Trademarks not owned by the GlaxoSmithKline group of companies
Amiko and MDI Log
INCA Device
MedDRA
RAMOS NG
Propeller
SmartTrack and SmartTouch

13.3. Appendix 3: Study Governance Considerations

Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with:
    - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
    - Applicable ICH Good Clinical Practice (GCP) Guidelines
    - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IEC/IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects.
- The investigator will be responsible for the following:
    - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC
    - Notifying the IRB/IEC of SAE or other significant safety findings as required by IRB/IEC procedures
    - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR),, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the subject or his/her legally authorized representative and answer all questions regarding the study.

- Subjects must be informed that their participation is voluntary. Subjects or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the subject was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Subjects must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the subject or the subject's legally authorized representative.
- Subjects who are rescreened are required to sign a new ICF.

Data Protection

- Subjects will be assigned a unique identifier by the sponsor. Any subject records or datasets that are transferred to the sponsor will contain the identifier only; subject names or any information which would make the participant identifiable will not be transferred.
- The subject must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the subject.
- The subject must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Dissemination of Clinical Study Data

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.

GSK will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate.

The procedures and timing for public disclosure of the results summary and for development of a manuscript for publication will be in accordance with GSK Policy.

Data Quality Assurance

- All subject data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 25 years from the issue of the final Clinical Study Report (CSR)/ equivalent summary unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

Source Documents

- Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Study and Site Closure

GSK or its designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of GSK. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines

Inadequate recruitment of subjects by the investigator

Discontinuation of further study treatment development

13.4. Appendix 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

AE Definition
An AE is any untoward medical occurrence in a clinical study subject, temporally associated with the use of a study treatment, whether or not considered related to the study treatment. NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study treatment.

Events <u>Meeting</u> the AE Definition
Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease). Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study. Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE. The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE. Also, "lack of efficacy" or "failure of expected pharmacological action" constitutes an AE or SAE.

Events <u>NOT</u> Meeting the AE Definition
Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject’s condition.

The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition.

Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.

Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

A SAE is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AE. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in persistent disability/incapacity

The term disability means a substantial disruption of a person's ability to conduct normal life functions.

This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect
f. Other situations: Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Definition of Cardiovascular Events

Cardiovascular Events (CV) Definition:
Investigators will be required to fill out the specific CV event page of the CRF for the following AEs and SAEs: Myocardial infarction/unstable angina Congestive heart failure Arrhythmias Valvulopathy Pulmonary hypertension Cerebrovascular events/stroke and transient ischemic attack Peripheral arterial thromboembolism Deep venous thrombosis/pulmonary embolism • Revascularization

Recording AE and SAE

AE and SAE Recording
When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) related to the event. The investigator will then record all relevant AE/SAE information in the CRF. It is **not** acceptable for the investigator to send photocopies of the subject's medical records to GSK in lieu of completion of the GSK /AE/SAE CRF page. There may be instances when copies of medical records for certain cases are requested by

GSK. In this case, all subject identifiers, with the exception of the subject number, will be redacted on the copies of the medical records before submission to GSK.

The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

Mild: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.

Moderate: An event that causes sufficiently discomfort and interferes with normal everyday activities.

Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AE and SAE can be assessed as severe.

> An event is defined as ‘serious’ when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

The investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE.

A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

The investigator will use clinical judgment to determine the relationship.

Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.

The investigator will also consult the Investigator’s Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.

For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to** GSK**.**

The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by GSK to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

If a subject dies during participation in the study or during a recognized follow-up period, the investigator will provide GSK with a copy of any post-mortem findings including histopathology

New or updated information will be recorded in the originally completed CRF.

The investigator will submit any updated SAE data to GSK within 24 hours of receipt of the information.

Reporting of SAE to GSK

SAE Reporting to GSK via Electronic Data Collection Tool

The primary mechanism for reporting SAE to GSK will be the electronic data collection tool.

If the electronic system is unavailable for more than 24 hours, then the site will use the paper SAE data collection tool (see next section).

The site will enter the SAE data into the electronic system as soon as it becomes available.

The investigator or medically-qualified sub-investigator must show evidence within the eCRF (e.g., check review box, signature, etc.) of review and verification of the relationship of each SAE to IP/study participation (causality) within 72 hours of SAE entry into the eCRF.

After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.

If a site receives a report of a new SAE from a study subject or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the /medical monitor/SAE coordinator by telephone.

Contacts for SAE reporting can be found in the SRM.

SAE Reporting to GSK via Paper CRF
Scanned transmission of the SAE paper, by email of CRF is the preferred method to transmit this information to the **medical monitor or the SAE coordinator**. In rare circumstances and in the absence of email, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service. Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames. Contacts for SAE reporting can be found in the SRM

13.5. Appendix 5: Contraceptive Guidance and Collection of Pregnancy Information

Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below)

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with ONE of the following:

- Documented hysterectomy
- Documented bilateral salpingectomy
- Documented bilateral oophorectomy

Note: Documentation can come from the site personnel's: review of subject's medical records, medical examination, or medical history interview.

3. Postmenopausal female

- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
- Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance

Female subjects

Female subjects of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in Table 3.

Table 3 Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User Dependent [a] *Failure rate of <1% per year when used consistently and correctly.*
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] • oral • intravaginal • transdermal
Progestogen-only hormonal contraception associated with inhibition of ovulation[b] • injectable
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation[b] • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • bilateral tubal occlusion
Vasectomized partner *(A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.)*
Sexual abstinence (*Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject.)*

NOTES:

a. Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for subjects in clinical studies.

b. Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraceptive method. In this case two highly effective methods of contraception should be utilized during the treatment period and for at least 5 days after the last dose of study treatment

Pregnancy Testing

WOCBP should only be included after a negative highly sensitive urine test

Additional pregnancy testing should be performed during the treatment period as decribed in the SOA and a time (>5 days) corresponding to time needed to eliminate study treatment after the last dose of study treatment and as required locally

Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected

Pregnancy testing, with a sensitivity of [5, 10, 25] mIU/mL will be performed using the test kit provided locally or by the sponsor and in accordance with instructions provided in its package insert

Collection of Pregnancy Information

Female Subjects who become pregnant

Investigator will collect pregnancy information on any female subject, who becomes pregnant while participating in this study.

Information will be recorded on the appropriate form and submitted to GSK within 2 weeks of learning of a subject's pregnancy.

Subject will be followed to determine the outcome of the pregnancy. The investigator will collect follow up information on subject and neonate, which will be forwarded to GSK Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.

Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.

A spontaneous abortion is always considered to be an SAE and will be reported as such.

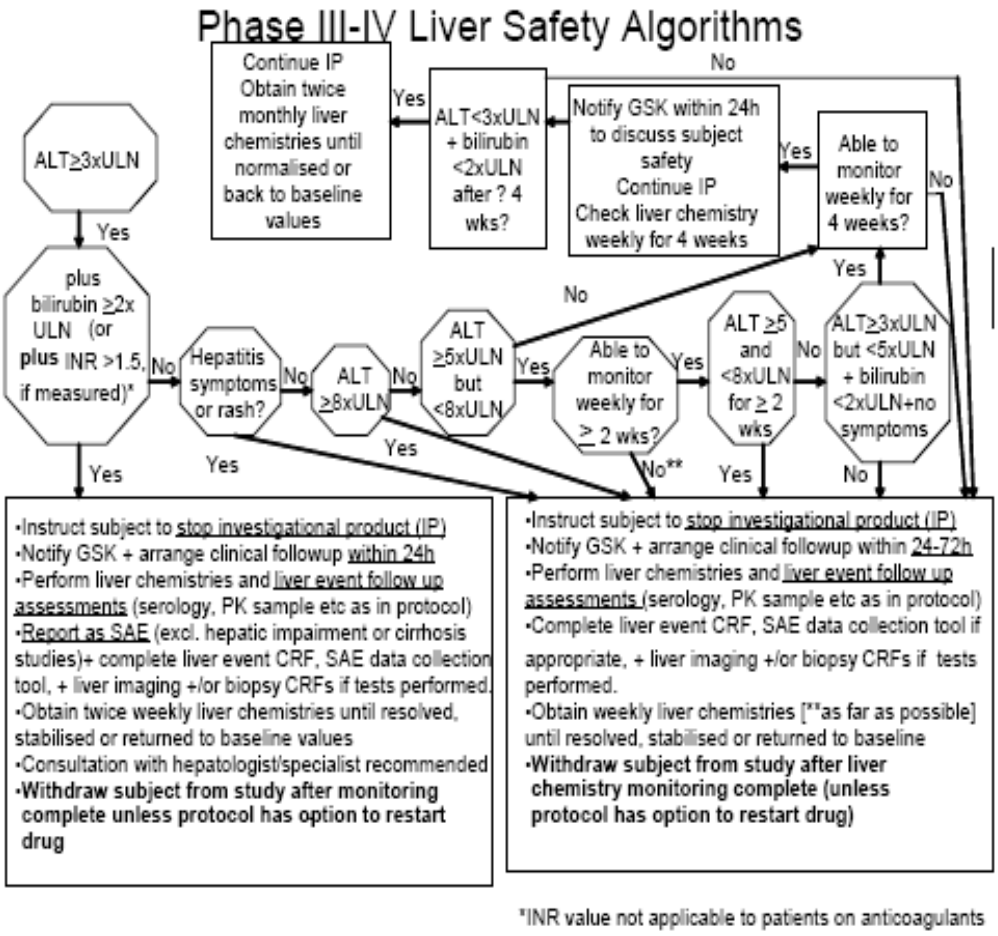
Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the investigator, will be reported to GSK as described in Appendix 4. While the investigator is not obligated to actively seek this information in former study subjects, he or she may learn of an SAE through spontaneous reporting.

Any female subject who becomes pregnant while participating

will discontinue study treatment or be withdrawn from the study

13.6. Appendix 6: Liver Safety: Required Actions, Follow-up Assessments

Phase III-IV liver chemistry stopping criteria and required follow up assessments



Liver Chemistry Stopping Criteria	
ALT-absolute	ALT ≥ 8xULN
ALT Increase	ALT ≥ 5xULN but <8xULN persists for ≥2 weeks ALT ≥ 3xULN but <5xULN persists for ≥4 weeks
Bilirubin[1, 2]	ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin)
INR[2]	ALT ≥ 3xULN **and** INR>1.5, if INR measured
Cannot Monitor	ALT ≥ 5xULN but <8xULN and cannot be monitored weekly for ≥2 weeks ALT ≥ 3xULN but <5xULN and cannot be monitored weekly for ≥4 weeks
Symptomatic[3]	ALT ≥ 3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity

Required Actions and Follow up Assessments	
Actions	**Follow Up Assessments**
• Immediately discontinue study treatment • Report the event to GSK **within 24 hours** • Complete the liver event CRF and complete an SAE data collection tool if the event also meets the criteria for an SAE[2] • Perform liver event follow up assessments • Monitor the subject until liver chemistries resolve, stabilize, or return to within baseline (see **MONITORING** below) • **Do not restart/rechallenge** subject with study treatment • Permanently discontinue study treatment and continue subject in the study for any protocol specified follow up assessments **MONITORING:** **<u>For bilirubin or INR criteria:</u>** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24 hrs**	• Viral hepatitis serology[4] • Obtain INR and recheck with each liver chemistry assessment until the transaminases values show downward trend • Only in those with underlying chronic Hepatitis B at study entry (identified by positive Hepatitis B surface antigen) quantitative Hepatitis B DNA and Hepatitis delta antibody[5]. • Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH). • Fractionate bilirubin, if total bilirubin≥2xULN • Obtain complete blood count with differential to assess eosinophilia • Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form • Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal

• Monitor subjects twice weekly until liver chemistries resolve, stabilize or return to within baseline • A specialist or hepatology consultation is recommended **<u>For All other criteria:</u>** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24-72 hrs** • Monitor subjects weekly until liver chemistries resolve, stabilize or return to within baseline	remedies, other over the counter medications. • Record alcohol use on the liver event alcohol intake case report form (CRF) page **<u>For bilirubin or INR criteria:</u>** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG) or gamma globulins. • Serum acetaminophen adduct high performance liquid chromatography (HPLC) assay (quantifies potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week [James, 2009]). • Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy CRF forms.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that subject if alanine aminotransferase (ALT) ≥ 3xULN **and** bilirubin ≥ 2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin) or ALT ≥ 3xULN **and** INR>1.5, if INR measured which may indicate severe liver injury (possible 'Hy's Law'), **must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**; INR measurement is not required and the threshold value stated will not apply to subjects receiving anticoagulants
3. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia)
4. Includes: Hepatitis A IgM antibody; Hepatitis B surface antigen (HbsAg) and Hepatitis B Core Antibody (IgM); Hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody
5. If Hepatitis delta antibody assay cannot be performed,, it can be replaced with a PCR of Hepatitis D RNA virus (where needed) [Le Gal, 2005] .

13.7. Appendix 7: Medical Device Incidents: Definition and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definition and Documentation of Medical Device Incidents

Definitions of a Medical Device Incident

The detection and documentation procedures described in this protocol apply to all GSK medical devices provided for use in the study (see Section 7.3 for the list of GSK medical devices).

Medical Device Incident Definition
A medical device incident is any malfunction or deterioration in the characteristics and/or performance of a device as well as any inadequacy in the labeling or the instructions for use which, directly or indirectly, might lead to or might have led to the death of a subject/user/other person or to a serious deterioration in his/her state of health.
Not all incidents lead to death or serious deterioration in health. The nonoccurrence of such a result might have been due to other fortunate circumstances or to the intervention of health care personnel.

It is sufficient that:

- An **incident** associated with a device happened and
- The **incident** was such that, if it occurred again, might lead to death or a serious deterioration in health.

A serious deterioration in state of health can include any of the following:

- Life-threatening illness
- Permanent impairment of body function or permanent damage to body structure
- Condition necessitating medical or surgical intervention to prevent one of the above
- Fetal distress, fetal death, or any congenital abnormality or birth defects

Examples of incidents
A subject, user, caregiver, or healthcare professional is injured as a result of a medical device failure or its misuse. A subject's study treatment is interrupted or compromised by a medical device failure. A misdiagnosis due to medical device failure leads to inappropriate treatment. A subject's health deteriorates due to medical device failure.

Documenting Medical Device Incidents

Medical Device Incident Documenting
Any medical device incident occurring during the study will be documented in the subject's medical records, in accordance with the investigator's normal clinical practice, and on the appropriate form. For incidents fulfilling the definition of an AE or an SAE, the appropriate AE/SAE CRF page will be completed as described in Appendix 4 The form will be completed as thoroughly as possible and signed by the investigator before transmittal to the GSK. It is very important that the investigator provides his/her assessment of causality (relationship to the medical device provided by GSK) at the time of the initial report and describes any corrective or remedial actions taken to prevent recurrence of the incident. A remedial action is any action other than routine maintenance or servicing of a medical device where such action is necessary to prevent recurrence of an incident. This includes any amendment to the device design to prevent recurrence.

13.8. Appendix 8: Country-specific requirements

13.8.1. Additional Adverse Event (AE) Reporting: Country-specific requirements for Canadian investigators:

The purpose of this information is to comply with Health Canada guidelines. They state that all events associated with lack of efficacy of marketed investigational products must be documented and reported.

Health Canada requires pharmaceutical manufacturers to expeditiously report domestic cases of unusual failure in efficacy (UFIE) for new drugs to the Marketed Health Products Directorate (MHPD) within 15 days of first notification. This regulation applies to marketed drugs, and used as directed per the Canadian prescribing information, including those drugs used in Phase IV (non CTA filed) clinical trials.

Adverse event (AE): Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding) symptom or disease (new or exacerbated) temporally associated with the use of a Medicinal Product. For a marketed Medicinal Product, this can also include failure to produce expected benefits (i.e. lack of efficacy, with or without an adverse event),

In order for GSK to comply this Canadian regulatory requirement, Canadian investigators are required to collect, record and report lack of efficacy events as per Table 4.

Table 4 Collection and Reporting of Adverse Events and Lack of Efficacy

Adverse Event criteria	Electronic case record form (eCRF) only	Paper form only	Electronic case record form (eCRF) + Paper form
Non serious	Non drug related lack of efficacy reports with associated signs or symptoms or clinical sequelae	Drug related lack of efficacy reports without associated signs or symptoms or clinical sequelae.	Drug related lack of efficacy with associated signs or symptoms or clinical sequelae
Serious	Non drug related lack of efficacy reports with associated signs or symptoms or clinical sequelae	Drug related lack of efficacy reports without associated signs or symptoms or clinical sequelae.	Drug related lack of efficacy reports with associated signs or symptoms or clinical sequelae

The investigator will then record all relevant information regarding an AE/SAE in the electronic CRF “and/or paper form as applicable

For lack of efficacy reports the paper form will be used to submit to GSK as per Table 4.

All paper forms are required to be faxed to GSK Canada’s Drug Safety department at PPD **within 24 hrs of first awareness**.