TITLE PAGE

Protocol Title: An open-label, low interventional clinical study investigating error rates (critical and overall) prior to any retraining in correct use of the ELLIPTA dry powder inhaler (DPI) compared to other DPIs including; DISKUS, Turbuhaler, HandiHaler and Breezhaler as a monotherapy or in combination, in adult patients with Chronic Obstructive Pulmonary Disease (COPD).

Protocol Number: 204981

Short Title: A low interventional clinical study comparing error rates (critical and overall); between the ELLIPTA dry powder inhaler (DPI) and other DPIs, prior to any retraining in correct use, and as prescribed to treat COPD patients.

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SPONSOR SIGNATORY:

PPD

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1. SYNOPSIS

Protocol Title: An open-label, low interventional clinical study investigating error rates (critical and overall) prior to any retraining in correct use of the ELLIPTA dry powder inhaler (DPI) compared to other DPIs including; DISKUS, Turbuhaler, HandiHaler and Breezhaler as a monotherapy or in combination, in adult patients with Chronic Obstructive Pulmonary Disease (COPD).

Short Title: A low interventional clinical study comparing error rates (critical and overall); between the ELLIPTA dry powder inhaler (DPI) and other DPIs, prior to any retraining in correct use, and as prescribed to treat COPD patients.

Rationale: This study will investigate error rates for the ELLIPTA DPI, alone or in combination, when compared to a number of other DPIs (DISKUS, Turbuhaler, HandiHaler and Breezhaler) and combinations of these, as prescribed to COPD patients. This study will aim to provide clinical evidence in COPD patients that the minimal number of steps required to correctly use the ELLIPTA DPI results in fewer errors made by participants. The study will also assess if this lower error rate is then better maintained over time, following any required re-training in correct use.

Objectives and Endpoints: The objectives and endpoints for the study are listed in the table below.

Objectives	Endpoints
Primary	
To compare the number of COPD patients making critical errors when using their current prescribed inhaled medication, at V1 and prior to any re-training in correct use.	The percentage of participants making at least one critical error at V1 for each DPI tested.
Secondary	
To compare the number of COPD patients making overall errors, when using their current prescribed inhaled medication at V1 and prior to any re-training in correct use.	The percentage of participants making at least one overall error at V1 for each DPI tested.
To compare the number of COPD patients making critical and overall errors, when using their current prescribed inhaled medication at V2 (week 6).	• The percentage of participants making at least one critical error at V2 for each DPI tested. • The percentage of participants making at least one overall error at V2 for each DPI tested.
Exploratory	
To explore, across all DPIs tested, if any association between critical errors, and key patients characteristics including: • Age. • Educational Status. • Co-Morbidities (Arthritis (upper limbs), Neurological Disorders & Visual impairment). • Time on current DPI(s). • Time since last trained on DPI(s). • Level of control (COPD Assessment Test (CAT) and Exacerbation History).	Exploration of these characteristics will be investigated using a logistic regression model on the primary endpoint of, the percentage of participants making at least one critical error at V1 for each inhaler tested, including each of these factors as terms in the model. • Age obtained from Demography. • Educational status from time in full time education. • Co-morbidities will be documented as relevant to DPI use. • Time on current DPI(s) and time since last trained will be documented categorically; however time on current DPI(s) will be included in the primary analysis model. • Level of control will be assessed by: o COPD Assessment Test. o Exacerbation History (Previous 1 year and required treatment with antibiotics and/or steroids).

Overall Design:

This is an open-label, low interventional study which does not involve administration of treatment nor placebo. The analysed population will be the Intent to Treat (ITT) population, which is defined as all patients who have demonstrated use in their primary DPI from one or more of the prescribed DPIs listed below.

Screened and confirmed COPD patients will attend the clinic for two visits, where they will demonstrate the use of their prescribed DPI. This will investigate the relative ability of COPD patients to use their prescribed DPI. Participants will demonstrate DPI use over two visits, approximately 6 weeks apart. Their demonstration of DPI use at Visit 1 (V1) will serve as the primary end-point in this study. Visit 2 (V2) will serve as the secondary end-point, where their ability to maintain the correct use of their prescribed DPI will be examined.

Participants taking part in the study must be using one of the listed DPIs as their primary treatment (the term 'primary treatment' is explained in detail in Section 5.1):

- ELLIPTA (RELVAR ELLIPTA™, ANORO ELLIPTA™ or INCRUSE ELLIPTA™)
- Turbuhaler (Symbicort Turbuhaler)
- DISKUS (Seretide DISKUS™)
- HandiHaler. (Spiriva HandiHaler)
- Breezhaler (Ultibro or Seebri Breezhaler)

Participant's use of the above listed DPIs will be assessed for critical and overall errors. Following error assessment, participants will be instructed in correct use of their DPI(s) if they have made any errors during their visit, as they would in general/primary practice. If the participant has used a DPI correctly, they will not receive any instruction on correct use for that DPI, but will be informed of their correct use.

Within 6 weeks, plus or minus 7 days (deemed long enough to establish if any retraining is required, or if no training required, correct use is maintained), participants will attend the clinic for V2 and they will be reassessed for errors made during use of their DPI. Any changes in health and prescriptions will be captured. Upon completion of V2, the participant will be discharged from the study. This is detailed in Figure 1 below.

Figure 1 Study Schematic

Number of Participants:

Sufficient patients with COPD will be screened in order to assure that each arm (outlined in Table 1) consists of 50 patients (A-I). Approximately 450 evaluable participants will complete the study.

Treatment Groups and Duration:

The duration of the study consists of two visits, approximately 6 weeks apart (± 7 days). Patients will continue to use their prescribed medication for the duration of the study. No active or placebo medication will be provided during the course of the study.

Table 1 below defines the treatments groups and treatment comparisons of interest depending on their prescribed treatment and whether they take a monotherapy or combination treatment to treat their COPD.

Table 1 Treatment Groups

<table>
<tr><th colspan="2">Treatments</th><th colspan="2">Combination DPI Treatment Groups</th></tr>
<tr><th colspan="2">Single DPI Treatment Groups</th><td>ICS-LABA With Spiriva HandiHaler (LAMA)</td><td>ICS-LABA With Incruse ELLIPTA™ (LAMA)</td></tr>
<tr><td>Relvar ELLIPTA™ (ICS/LABA)</td><td>A</td><td colspan="2">G</td></tr>
<tr><td>Symbicort Turbuhaler (ICS/LABA)</td><td>B</td><td colspan="2">H</td></tr>
<tr><td>Seretide DISKUS™ (ICS/LABA)</td><td>C</td><td colspan="2">I</td></tr>
<tr><td>Spiriva HandiHaler (LAMA)</td><td>D</td><td></td><td></td></tr>
<tr><td>Incruse ELLIPTA™ (LAMA)</td><td rowspan="2">E</td><td></td><td></td></tr>
<tr><td>Anoro ELLIPTA ™(LAMA/LABA)</td><td></td><td></td></tr>
<tr><td>Ultibro Breezhaler (LAMA/LABA)</td><td rowspan="2">F</td><td></td><td></td></tr>
<tr><td>Seebri Breezhaler (LAMA)</td><td></td><td></td></tr>
</table>

Any participant that is included because of a relevant treatment will also, if using a generic Ventolin Metered Dose Inhaler (MDI) for rescue treatment, have their rescue therapy (MDI) errors also assessed during demonstration.

2. SCHEDULE OF ACTIVITIES (SOA)

	Visit 0 Screening	**Visit 1 Baseline**	**Visit 2**	**Notes**
	Day 1 (Can occur on same day as V1)	**Day 1 (Can occur on same day as V0)**	**Week 6 ± 7 days**	
Procedure				
Screening (V0)				Completed prior to V1 assessments.
Written informed consent	X			V0 can take place on the same day as V1. V1 should be completed no later than 30 days after consent.
Participant demography	X			Age, height, weight, year of birth, sex, ethnicity and geographic ancestry will be recorded.
Medical/disease history including COPD, smoking and Arthritis/Ophthalmic/Neurological history	X			Participant will have a medical history of COPD, smoking history, time on current DPI(s), time since last trained on DPI(s) and any co-morbidities that may affect correct use of DPI recorded.
Exacerbation History	X			Exacerbation history for previous year recorded.
COPD diagnosis	X			Documented confirmation of COPD diagnosis from Physician.
Concomitant medication history including COPD therapy history	X			All current concomitant medication of relevance (Arthritic, Ophthalmic, Neurological medications) or related to an AE will be recorded. A minimum COPD therapy history for the preceding 2 years will be recorded.

	Visit 0 Screening	Visit 1 Baseline	Visit 2	Notes
Inclusion/exclusion criteria	X			All criteria must be met prior to inclusion at V1.
Register the patient	X			To ensure the correct number of patients are included on each arm.
CAT Score	X			Take this for reference (exploratory).
Educational status	X			No. of years spent in full time education.
Study Assessments (V1 +V2)				
Assess participant's ability to correctly use their DPI(s) and MDI(s) with Checklists		X	X	No instruction provided by HCP before or during this assessment.
Correct use of DPI training		X	X	Train participants should they make errors during demonstration.
Adverse event/Serious adverse event assessment		X	X	Collected until completion of study.
Prescriptions and health review		X	X	Review changes in prescription and health between beginning and end of study.

3. INTRODUCTION

3.1. Study Rationale

Please note that Turbohaler and ACCUHALER are the names commonly used within the United Kingdom for these DPIs. However, in other regions and for the purposes of this study, these DPIs are referred to as Turbuhaler and DISKUS respectively in this protocol.

This study is designed to investigate error rates during the use of ELLIPTA DPI, alone or in combination, when compared to a number of other DPI types (DISKUS, Turbuhaler, HandiHaler and Breezhaler) and combinations of these, as prescribed to COPD patients during routine medical practice. This study aims to provide clinical evidence in COPD patients that the reduced number of steps required to use the ELLIPTA DPI could result in fewer errors made by participants, and therefore a more consistent treatment. The study will also assess if this reduced error rate is then better maintained over time, following any required instruction in correct use.

3.2. Background

Chronic Obstructive Pulmonary Disease (COPD) is a progressive obstructive lung disease that is characterised by long-term poor airflow. The disease manifests when noxious particles or gases lead to a modification in a participant's airways, resulting in the development of a chronic inflammatory response. This leads to increasing airflow limitation, breathlessness and other symptoms. Despite being both treatable and preventable, COPD remains one of the leading causes of morbidity and mortality worldwide. Despite recent advances in diagnosis and treatment, the economic and social burden of this disease is increasing [GOLD, 2017].

The goal of COPD treatment is to reduce or relieve symptoms, and reduce risk by preventing exacerbations. The result of which aims to improve both exercise tolerance and health status whilst, preventing disease progression and treating exacerbations, ultimately reducing mortality rates. The current treatment of COPD includes; smoking cessation, inhaled pharmacological therapy, primarily long and short term bronchodilators (β_2-agonists and anti-cholinergics) and inhaled corticosteroid, as well as other non-pharmacological interventions.

The current GOLD treatment guidelines assign COPD patients into four groups from A to D, depending on the severity of their symptoms and associated risk. Assignment usually incorporates both the patient's degree of airflow limitation and exacerbation history. Accordingly, patients belonging to Group A experience the fewest symptoms and are thus classified as low risk on the spectrum. These patients may only need a short acting bronchodilator as required to relieve symptoms. However, as the disease progresses, other inhaled therapies are required in combination in order to maintain airway control. Such that COPD patients from Group D, whom have a high symptom burden, high risk of exacerbations and/or high airflow limitation, may require multiple inhaled therapies including: inhaled corticosteroids (ICS), long-acting β_2-agonists (LABA) and long-acting muscarinic antagonists/anticholinergic agents (LAMA). When all three drugs are administered collectively, this is referred to as triple therapy.

Currently, patients requiring triple therapy can be prescribed ICS/LABA and LAMA, or LABA/LAMA and ICS, from separate inhalers. The specific ICS/LABA/LAMA combination therapy prescribed will determine the variation in inhaler types (and thereby the inhalation techniques) and dosing regimens. Use of different inhaler devices, inhalation techniques and dosing regimens contributes to treatment complexity. This can increase the potential for errors during inhaler use, thus reducing or precluding drug delivery to the site of action in the lungs [Cochrane M, 2000; van der Palen J, 1999]. Fixed-dose combination inhalers that minimise the number of inhalers required could simplify treatment, improve adherence, and reduce errors in inhaler use. An inhaler which incorporates all three treatments consequently, has the potential to more aptly treat the disease [GOLD, 2017].

The ability of COPD patients to correctly use their prescribed inhaler(s) coupled with adequate training in inhaler technique are also critical factors involved in effective drug delivery [Bonini M, 2015; Melani A, 2011]. A review of inhaler use revealed that most common errors made by patients included; a failure to exhale before inhalation, failure to hold breath after inhalation, incorrect positioning of the inhaler, and failure to execute a forceful and deep inhalation. While these mistakes can be remedied by reading the Patient Information leaflet (PIL) or training by a nurse or physician, the reality is that inefficient inhaler technique can lead to reduced drug delivery and lung deposition may result in ineffective treatment of the disease [Lavorini F, 2008].

For any prescribed inhaler, it is thus imperative that the patient follows all the steps in the PIL correctly in order to ensure optimal drug delivery. Furthermore, given the time demands on healthcare professionals, the time required by a primary care nurse, physician, or a community pharmacist to train a patient in correct use of an inhaler(s) at the time of initial prescription, and for any subsequent retraining becomes important. Therefore, an inhaler which is simple to use and requires minimal time to train would be highly advantageous [Bonini M, 2015]. A simple inhaler, which requires fewer steps to deliver the active drug, may be preferred by a COPD patient. This has the potential to improve compliance, and may potentially impact the overall management of the disease [Yun Kirby, 2015].

The ELLIPTA DPI has been designed to be simple for patients to use, and data supports that when using an ELLIPTA DPI COPD patients make fewer critical and overall errors compared with other common DPIs tested [van der Palen J, 2016].The ELLIPTA DPI has also been shown to be preferred by patients for a number of reasons, including simplicity and the reduced number of steps required to receive therapy [van der Palen J, 2016]. The ELLIPTA DPI is already available to deliver a LABA/ICS combination (RELVAR ELLIPTA™), LAMA (INCRUSE ELLIPTA™), and LAMA/LABA combination (ANORO ELLIPTA™). Accordingly, in other clinical studies, the benefit of a once daily, triple therapy where all three active treatments are provided in one ELLIPTA DPI has been assessed and is in review with regulatory agencies.

3.3. Benefit/Risk Assessment

The safety profile of all inhalers used in this study is well characterised. Given the nature of the study, short duration of dosing and the fact that there is no change in dose from

what the participant would otherwise be taking, unexpected safety events are not anticipated to occur.

This study does not involve treatment with sponsor supplied active or placebo medication. Participants who meet the inclusion/exclusion criteria will continue their COPD medication as prescribed by their healthcare provider during their participation in the study. Participants should continue to follow up with their regular physician for their COPD healthcare during the study.

The study procedures include demonstration of the use of the participants prescribed inhaler(s) by the study participant. This will also include a subsequent instruction on correct use by site staff if correct use is not demonstrated as per the PIL.

Adverse events (AEs) and serious adverse events (SAEs) will be collected for the duration of the study.

3.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Paradoxical bronchospasm, which may occur with an immediate increase in wheezing after inhalation.	As with other inhalation therapy, paradoxical bronchospasm may occur with an immediate increase in wheezing after dosing. From post-marketing data, paradoxical bronchospasm has been reported at a frequency of <1/10,000 including isolated reports [Nicklas, 1990].	This should be treated immediately with a fast and short acting inhaled bronchodilator. Investigators will be instructed to assess the participant's condition to determine their eligibility to continue in the study and the need for alternative therapy.

3.3.2. Benefit Assessment

As there is no treatment provided concomitantly to the patient's currently prescribed medication, no benefit to the participant is expected during this study. However, participants may improve their ability to use their DPI as a result of the training involved in this study.

3.3.3. Overall Benefit: Risk Conclusion

The overall potential risk identified is minimal due to the nature of the study, in that no COPD medication, in addition to their already prescribed therapy is provided to participants.

4. OBJECTIVES AND ENDPOINTS

Further information on all endpoints described in this section is provided in Section 10.4.1.

Objectives	Endpoints
Primary	
To compare the number of COPD patients making critical errors when using their current prescribed inhaled medication, at V1 and prior to any re-training in correct use.	The percentage of participants making at least one critical error at V1 for each DPI tested.
Secondary	
To compare the number of COPD patients making overall errors, when using their current prescribed inhaled medication at V1 and prior to any re-training in correct use.	The percentage of participants making at least one overall error at V1 for each DPI tested.
To compare the number of COPD patients making critical and overall errors, when using their current prescribed inhaled medication at V2 (week 6).	• The percentage of participants making at least one critical error at V2 for each DPI tested. • The percentage of participants making at least one overall error at V2 for each DPI tested.
Exploratory	

To explore, across all DPIs tested, if any association between critical errors, and key patients characteristics including:
• Age.
• Educational Status.
• Co-Morbidities (Arthritis (upper limbs), Neurological Disorders & Visual impairment).
• Time on current DPI(s).
• Time since last trained on DPI(s).
• Level of control (COPD Assessment Test (CAT) and Exacerbation History).
	Exploration of these characteristics will be investigated using a logistic regression model on the primary endpoint of, the percentage of participants making at least one critical error at V1 for each inhaler tested, including each of these factors as terms in the model. Further information about these factors is described in Section 9.1.2.
	• Age obtained from Demography.
	• Educational status from time in full time education.
	• Co-morbidities will be documented as relevant to DPI use.
	• Time on current DPI(s) and time since last trained will be documented categorically; however time on current DPI(s) will be included in the primary analysis model.
	• Level of control will be assessed by:
	  ○ COPD Assessment Test.
	  ○ Exacerbation History (Previous 1 year and required treatment with antibiotics and/or steroids).

5. STUDY DESIGN

5.1. Overall Design

This study will be conducted as an open-label, low-interventional study. COPD diagnosed participants will attend the clinic for the screening visit (V0) and subsequent assessment visit (V1). These visits may occur on the same day. They will need to withhold a dose of their prescribed inhaled medicine (maintenance) and bring all of their prescribed inhaled medicines (maintenance and rescue) with them during V1 and V2. Participants will be included in the study if they are prescribed any of the following DPIs for maintenance treatment of their COPD: ELLIPTA (RELVAR ELLIPTA™, ANORO ELLIPTA™ or INCRUSE ELLIPTA™), Turbuhaler (Symbicort Turbuhaler), DISKUS (Seretide DISKUS™), HandiHaler (Spiriva HandiHaler), and Breezhaler (Ultibro or Seebri Breezhaler).

Participants using any other inhalers not listed here to receive maintenance therapy are hereby excluded from participation. For the purposes of this study, these DPIs are defined as primary or secondary, depending on the total number of DPIs prescribed to the patient and the method of combination treatment delivered as described below:

- Participants prescribed therapy via a single DPI, in either a fixed dose combination LABA/ICS (ELLIPTA, Turbuhaler, DISKUS), a monotherapy LAMA (ELLIPTA, HandiHaler, Breezhaler), or a fixed dose combination LAMA/LABA (ELLIPTA, Breezhaler) would have that DPI considered as the primary DPI for analysis.
- For participants receiving prescribed therapy via two of these types of DPI, the DPI from which they receive LABA/ICS (ELLIPTA or Turbuhaler or DISKUS) will be considered the primary DPI for analysis, while the DPI from which they receive LAMA (HandiHaler or ELLIPTA) treatment will be considered secondary during analysis.

Participants will be separated into nine different treatment groups (A-I) in this study depending on their prescribed COPD treatment, as is outlined in Table 1 below. Groups A-F include patients using a single DPI to treat their COPD. Groups G-I consist of patients who are prescribed two DPIs for treatment of their COPD.

Table 1 Treatment Groups

Treatments		**Combination DPI Treatment Groups**	
Single DPI Treatment Groups		ICS-LABA With Spiriva HandiHaler (LAMA)	ICS-LABA With Incruse ELLIPTA™ (LAMA)
Relvar ELLIPTA™ (ICS/LABA)	A	G	
Symbicort Turbuhaler (ICS/LABA)	B	H	
Seretide DISKUS™ (ICS/LABA)	C	I	
Spiriva HandiHaler (LAMA)	D		
Incruse ELLIPTA™ (LAMA)	E		

Treatments		**Combination DPI Treatment Groups**	
Single DPI Treatment Groups		ICS-LABA With Spiriva HandiHaler (LAMA)	ICS-LABA With Incruse ELLIPTA™ (LAMA)
Anoro ELLIPTA ™(LAMA/LABA)	F		
Ultibro Breezhaler (LAMA/LABA)			
Seebri Breezhaler (LAMA)			

The use of all DPIs specified in this study will be assessed for both critical and overall errors. After successful inclusion into the study, participants will have their maintenance DPI's and relevant rescue therapy (MDI) errors (if used by patient) assessed at V1, receiving no training or information on technique from health clinic staff prior to that assessment. Following error assessment, if the participant has made any errors during their visit, they will be instructed on the correct use of their DPI(s) as they would in general/primary practice. If the participant uses their DPI correctly, they will not receive any instruction on correct use for that DPI, but will be informed of their correct use.

Other baseline information including demography, smoking history, symptom score (CAT), medical history, time on each DPI, time since last trained and educational information will be captured at this visit.

Within 6 weeks, plus or minus 7 days (deemed long enough to lose or forget training), participants will attend the clinic for V2 and will be reassessed for errors made during use of their DPI(s). Any changes in health and prescriptions will be captured at this visit. Upon completion of V2, participants will be discharged from the study. They will be referred to their GP for further training if they continue to demonstrate incorrect use of their prescribed DPI. This is detailed in Figure 1 below.

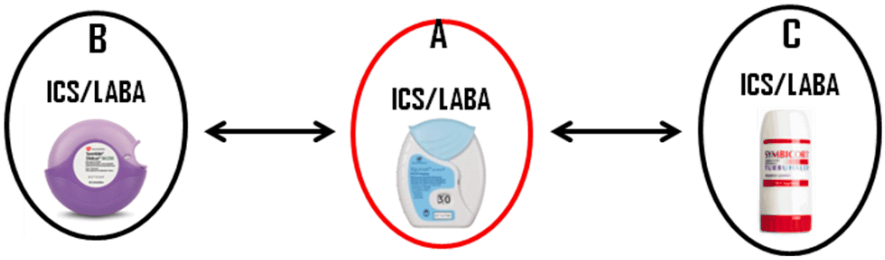
Figure 1 Study Schematic

The primary endpoint for this study will be the percentage of participants making at least one critical error (critical error rate) during the use of their primary DPI. The comparisons that will be made between treatment groups are outlined in Figure 2 below and are as follows:

Primary comparisons:

1. RELVAR ELLPITA DPI vs. any other ICS/LABA (Seretide DISKUS™ or Symbicort Turbuhaler) DPI.

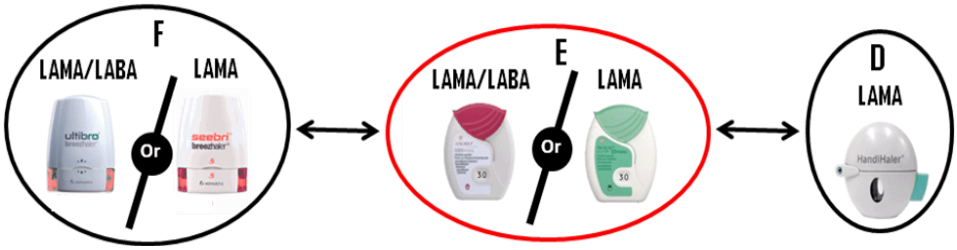
    - *This comparison aims to compare critical error rates in the primary ICS/LABA DPIs.*



- **Group A versus group B**
- **Group A versus group C**

2. INCRUSE ELLIPTA™ or ANORO ELLIPTA™ DPI vs. any other LAMA (Spiriva HandiHaler or Seebri Breezhaler), or LAMA/LABA (Ultibro Breezhaler) DPIs.

    - *This comparison aims to compare critical error rates in the primary LAMA and LAMA/LABA DPIs.*



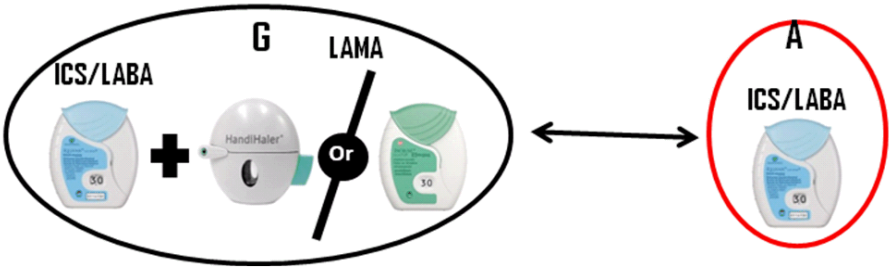
- **Group E versus Group D**
- **Group E versus Group F**

Other comparisons:

3. RELVAR ELLIPTA™ DPI vs. RELVAR ELLIPTA™ with any other LAMA (Spiriva HandiHaler or INCRUSE ELLIPTA™) DPI.

    - *This aims to compare critical error rates in the primary DPI, simulating a triple therapy from one DPI (ELLIPTA) against triple*

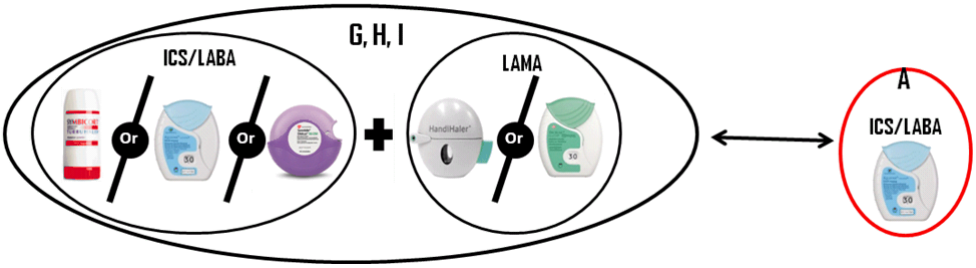
therapy from two ELLIPTA DPIs, or from ELLIPTA DPI with any other LAMA DPI.



- **Group A versus Group G**

4. RELVAR ELLIPTA™ DPI vs. all ICS/LABA (Seretide DISKUS™, RELVAR ELLIPTA™ or Symbicort Turbuhaler) DPIs with a LAMA (Spiriva HandiHaler, Seebri Breezhaler or INCRUSE ELLIPTA™) second DPI.

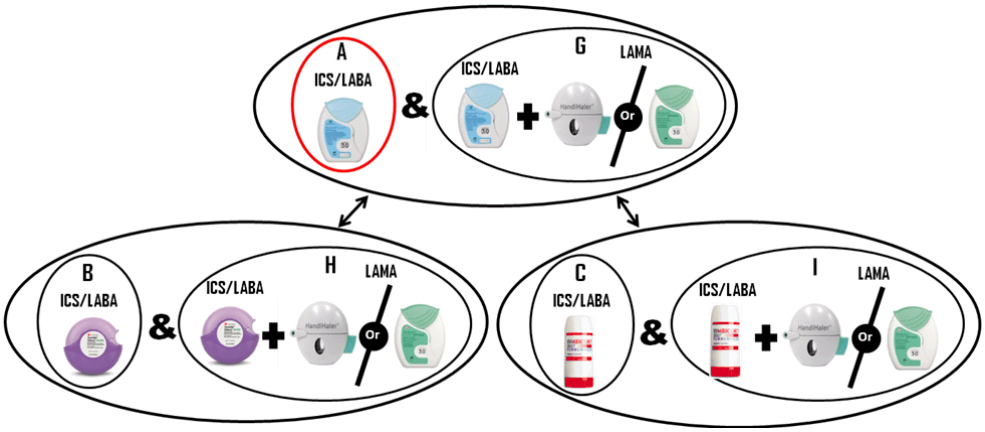
    - *This aims to compare critical error rates in the primary DPI, simulating a triple therapy delivered in one ELLIPTA DPI against a triple therapy from any two other DPIs used in the study.*



- **Group A versus Group G+H+I**

5. RELVAR ELLIPTA™ DPI with or without a LAMA DPI (Spiriva HandiHaler, Seebri Breezhaler or INCRUSE ELLIPTA™) vs. any other ICS/LABA (Seretide DISKUS™ or Symbicort Turbuhaler) DPI with or without a LAMA (Spiriva HandiHaler or Seebri Breezhaler) DPI.

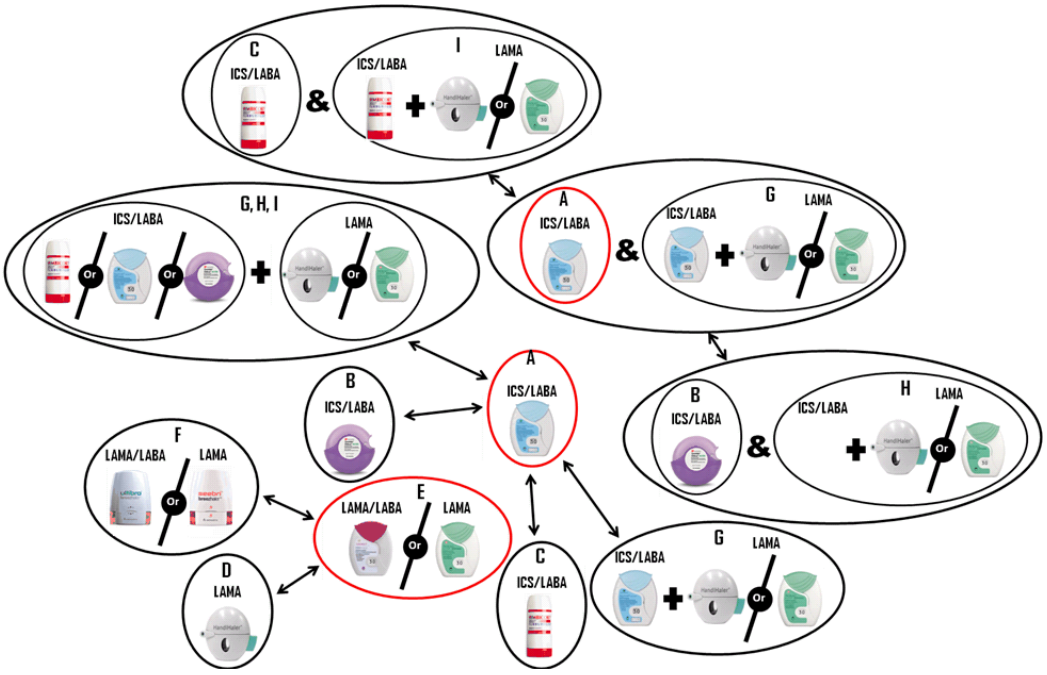
    - *This aims to compare critical error rates in the primary DPI, simulating a triple therapy delivered in one ELLIPTA DPI or combination of DPIs against a triple therapy using any other ICS/LABA delivering primary DPI.*



- **Group A+G versus B+H**
- **Group A+G versus C+I**

All comparisons investigated are outlined in Figure 2 below:

Figure 2 Comparisons



The secondary endpoints will be tested in the same way as the primary endpoints and will also involve the same comparisons, however it will assess the percentage of participants making at least one overall error at V1 for each DPI tested, or one critical and/or overall error at V2 for each DPI tested.

If the participant cannot demonstrate correct use by the end of V2, they will be referred to their General Practitioner (GP) for additional training.

5.2. Number of Participants

Sufficient patients with COPD will be screened to ensure that approximately 450 participants will be enrolled to achieve 50 evaluable participants per treatment group (A-I). An evaluable participant is defined in the Intent-to-Treat population in Section 10.3.

If participants prematurely discontinue the study, additional replacement participants may be recruited at the discretion of the Sponsor.

5.3. Participant and Study Completion

A participant is considered to have completed the study if he/she has completed all phases of the study including the last scheduled procedure shown in the Schedule of Activities.

The end of the study is defined as the date of the last visit of the last participant in the study.

5.4. Scientific Rationale for Study Design

The study design has been chosen in order to appropriately capture the ability of COPD patients to use their DPI in a low interventional setting. It involves an investigation of the error rate in the ELLIPTA DPI, alone or in combination, when compared to a number of other DPIs (DISKUS, Turbuhaler, HandiHaler and Breezhaler) and combinations of these, as prescribed to COPD patients. It will also investigate whether upon correction of these errors during retraining at V1, the patient after approximately 6 weeks at V2 maintains correct use regardless of whether they were trained by the HCP or not.

This information will aim to provide clinical evidence in COPD patients that the reduced number of steps required by the ELLIPTA DPI results in fewer errors made by the participants. It will also help determine the extent to which this reduced error rate is maintained over time after appropriate retraining in correct use, as would occur in a real world setting where patients are trained/retrained by a doctor (GP), nurse or pharmacist.

5.5. Dose Justification

Not applicable as no active treatment will be provided in this study

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

Participants are eligible to be included in the study only if all of the following criteria apply:

TYPE OF PARTICIPANT AND DIAGNOSIS
1. Participants with documented Physician's diagnosis of COPD, and currently receiving maintenance therapy 2. Aged ≥ 40 years of age at inclusion. 3. Using one of the maintenance therapies of interest described in Table 1, for at least 3 months prior to inclusion on the study.
SEX
4. Males or Females
INFORMED CONSENT
5. Capable of giving signed informed consent, which includes compliance with the requirements and restrictions listed in the consent form and in the protocol.

6.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

CONCURRENT MEDICATIONS/MEDICAL HISTORY
1. Asthma: Participants with a current diagnosis of asthma. Participants with a prior history of asthma are eligible if they have a current diagnosis of COPD.
RELEVANT HABITS
2. Drug/alcohol abuse: Participants with a known or suspected alcohol or drug abuse history at screening (V0) that in the opinion of the investigator could interfere with the participant's proper completion of the protocol requirement.
DIAGNOSTIC ASSESSMENTS AND OTHER CRITERIA
3. Investigational Product: Participants who have received an investigational drug and/or medical device within 30 days of entry into this study (Screening/V1), or within five half-lives of the investigational drug, whichever is longer. 4. Investigational Product: Participants who have been trained during participation in any device study in the 6 months prior to entry into this study.

6.3. Lifestyle Restrictions

There are no lifestyle restrictions.

6.3.1. Meals and Dietary Restrictions

There are no meal or dietary restrictions.

6.3.2. Activity

There are no restrictions on activity.

6.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants 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).

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once. Rescreened participants should be assigned a new participant 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 participant according to the study protocol. The term 'study treatment' is used throughout the protocol, however it must be reiterated that there will not be any administration of a study treatment, neither placebo, nor investigational treatment during this study. Participants will be taking their own prescribed COPD treatment and dosage.

7.1. Treatments Administered

This study does not involve the administration of any new treatments. It assesses the ability of the participant to use their currently prescribed treatment (DPI).

7.1.1. Medical Devices

- Medical devices (not manufactured by or for GSK) that will be used in this study are HandiHaler and Breezhaler.

7.2. Method of Treatment Assignment

All participants will be assigned to their relative treatment groups based on their current prescribed treatment. Participants will be assigned in equal numbers to one of the nine groups tested in the study (A-I) based on the current medication that they are prescribed. The nine treatment groups are outlined in Table 1 and assignment of participants to their respective treatment arms will cease once the required number of participants has been reached.

7.3. Blinding

This is an open label study, as the participants are providing their own prescribed medication for the duration of the study. There will be no blinding.

7.4. Preparation/Handling/Storage/Accountability

As the study does not involve the administration of any new treatment and the patient will only be taking their prescribed medication, relevant instructions how to prepare, handle and store the medication will be outlined in detail in the respective PIL for the participants prescribed treatment.

7.5. Treatment Compliance

Not applicable as the participant is not being provided any new treatment during this study

7.6. Concomitant Therapy

A detailed history of previous and ongoing COPD medications, in particular any types of inhalers used to deliver these medications for the previous 24 months from V0 should be

recorded in order to correctly place the participant in the relevant treatment group. This is a three visit study unless V0 and V1 occur on the same day and patients should continue to take their medication as prescribed by their physician throughout the course of the 6 week study.

However, any medication or vaccine of relevance to the study (Arthritis, Visual Impairment or Neurological Disorders) or prescribed for an AE experienced during the study that the participant is receiving at the time of enrolment or receives during the study must be recorded along with:

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

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

7.7. Treatment after the End of the Study

Not applicable as there is no active treatment provided in this two visit study. Participants will be taking their prescribed medication for the duration of this study and will not receive any specific post-study treatments.

8. DISCONTINUATION CRITERIA

8.1. Discontinuation of Study Treatment

Not applicable as the participants are not introduced to any new treatment(s).

8.1.1. Liver Chemistry Stopping Criteria

Not applicable as the participants are not introduced to any new treatment(s).

8.1.2. QTc Stopping Criteria

Not applicable as the participants are not introduced to any new treatment(s).

8.2. Withdrawal from the Study

- A participant 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 or administrative reasons.
- If the participant 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 SoA for data to be collected at the time of the follow-up visit and for any further evaluations that need to be completed.

8.3. Lost to Follow Up

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

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant 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 SoA.
- Participant registration will be described in the Study Reference Manual (SRM).
- 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 participant should continue or discontinue the study.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management and obtained before signing of ICF may be utilised for screening or baseline purposes provided the procedure met the protocol-specified criteria and was performed within the time frame defined in the SoA.

9.1. Efficacy Assessments

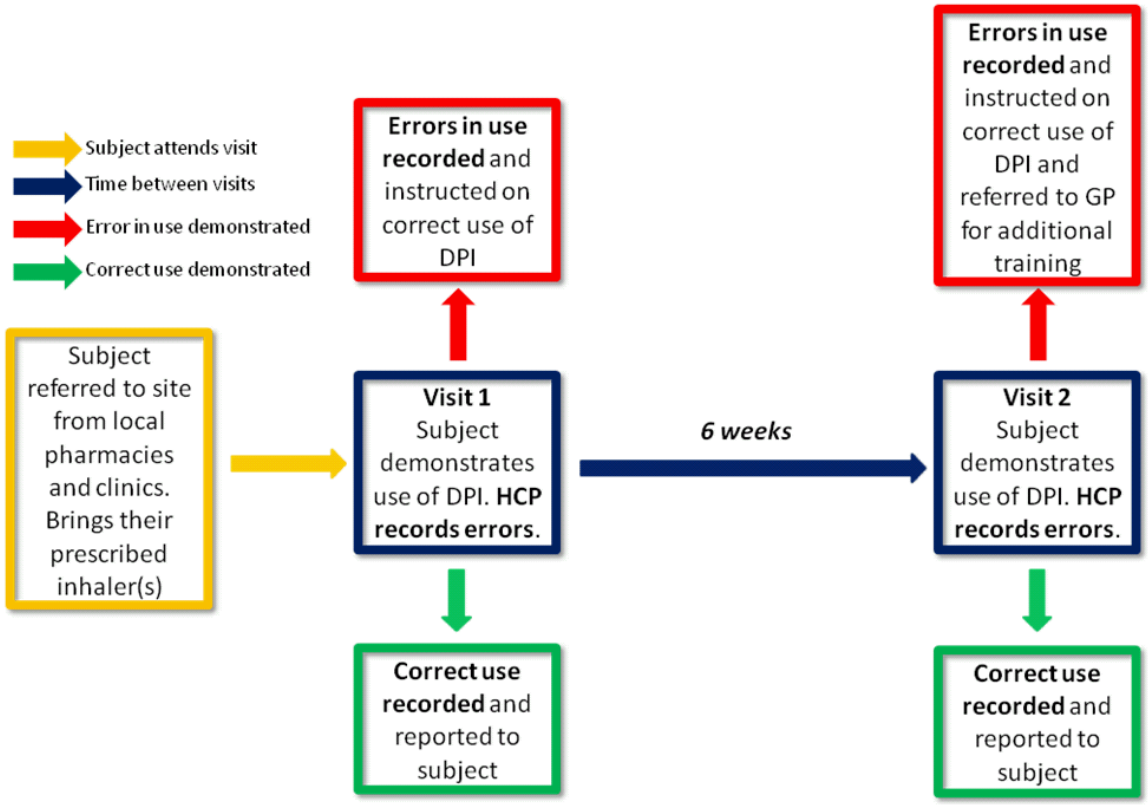
9.1.1. Assessment of Errors in Use of DPI(s)

Participants will be assessed on their use of their prescribed DPI. A checklist for each DPI will be provided to HCPs for scoring errors during the study conduct. The checklists will be provided in the Study Reference Manual and are located in Appendix 12.2.

The errors listed will be aligned with the correct use information from the respective DPI PILs, in the form of a checklist. The errors made during the demonstration by participants are defined as "critical", when the participant receives a lesser/no dose, and "non-critical", when the dose may not be affected, but the participant has demonstrated improper use of their DPI, as per the PIL. The combination of all errors made will be described as overall errors.

At V1, participants will be asked to demonstrate use of their prescribed DPI and MDI if applicable. Any errors (critical or non-critical) made by the participant will be recorded by the HCP on the checklists provided in Appendix 2. If the participant makes no errors, this will also be recorded and reported back to the participant by the HCP. There will be no further assessment at this visit. However, if the participant makes any errors during the demonstration, the HCP will provide instruction on the correct use of their DPI. At V2, approximately 6 weeks after V1, the same exact procedure will be carried out. However, if the HCP deems the participant still unable to correctly use their prescribed DPI, after a third instruction, the participant should be referred to their GP for further assessment. This is illustrated below in Figure 3.

Figure 3 Outline of study procedure and evaluation of errors in DPI use process



9.1.2. Other Study assessments

9.1.2.1. Arthritis, Visual Impairment and Neurological Disorders

- This information will be collected via simple questions at the screening visit.

9.1.2.2. Age and Education

- Age will be collected from the participant's demography information. Education information will include time in full time education. This will be documented as number of years in full time education, including primary, secondary and tertiary education.

9.1.2.3. Time on current DPI and time since last trained

- Time on current DPI will be determined categorically as described below:
  - 3 months $> x \leq$ 6 months
  - 6 months $> x \leq$ 1 year
  - 1 year $> x \leq$ 2 years
  - 2 years $> x \leq$ 3 years
  - $x >$ 3 years
- Time since last trained on DPI will be captured in the same way as time on current DPI; however, it will not be used as a term in the primary analysis model.

9.1.2.4. Level of control and exacerbation history

- Level of control will be assessed at the screening visit (V0) and will include:
  - Participants will undertake the COPD assessment test (CAT) during V0 to determine their level of control
  - Participants will have their exacerbation history for the previous 1 year collected at V0.

9.2. Adverse Events

The definitions of an AE or SAE can be found in Appendix 12.4.

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, considered related to the study treatment or the study, or that caused the participant to discontinue the study (see Section 8).

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

- All SAEs and AEs will be collected from the signing of the ICF until the time point specified in the SoA (Section 2).
- Medical occurrences that begin before obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the case report form (CRF) not the AE section.
- All SAEs will be recorded and reported to the sponsor or designee within 24 hours, as indicated in Appendix 12.4. 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 participants. However, if the investigator learns of any SAE, including a death, at any time after a participant 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 12.4.

9.2.2. Method of Detecting AEs 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 participant is the preferred method to inquire about AE occurrence.

9.2.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, will be followed until the event is resolved, stabilised, otherwise explained, or the participant 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 participants 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 eg, 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.

9.2.5. Cardiovascular and Death Events

For any cardiovascular events 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.

9.3. Safety Assessments

There are no mandated safety assessments, other than monitoring for AEs and SAEs and this is described in detail in Section 9.2.

9.4. Pharmacokinetics

PK parameters are not evaluated in this study.

9.5. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

9.6. Genetics

Genetics are not evaluated in this study.

9.7. Biomarkers

Biomarkers are not evaluated in this study.

9.8. Health Economics OR Medical Resource Utilisation and Health Economics

Health Economics/Medical Resource Utilisation and Health Economics parameters are not evaluated in this study.

10. STATISTICAL CONSIDERATIONS

10.1. Hypotheses

The primary purpose of this study is to assess the number of critical errors made by COPD patients for each DPI tested.

The primary endpoint of the study is the percentage of participants making at least one critical error (critical error rate) for each DPI at V1. This will be analysed using logistic regression and will be adjusted for the covariate of time on current DPI.

For each DPI comparison, the null hypotheses are no difference between DPIs:

H_0: $p_1=p_2$

The alternative hypothesis is that there is a difference between DPIs:

H_A: $p_1 \neq p_2$

The DPIs and treatment comparisons for this study are outlined in Section 5.1 and Table 1.

10.2. Sample Size Determination

The sample size calculation is based on the primary endpoint, the percentage of participants making at least one critical error in each primary DPI at V1.

Based on reported critical error rates [Molimard M, 2004] and results from study [NCT02184624, 200301], a critical error rate (i.e. the proportion of participants making at least one critical error using the DPI after reading the patient information leaflet) for each of the DPIs has been assumed. The rates in Molimard were generally lower than those seen in 200301 for those DPIs present in both, suggesting a difference between the reporting within those studies. The ELLIPTA DPI critical error rate has been assumed as 5%, which is the lowest of the rates observed in the 200301 sub-studies. The rationale for choosing the lowest rate is the choice of critical error rate for the other DPIs is assumed to be 30%, based on the rates observed in Molimard (Accuhaler 11%; Turbohaler 32%), whereas in 200301 we observed higher rates of 44-48%.

A total of 50 participants in each treatment/DPI group will provide > 94% power to show a statistically significant difference between the critical error rate of each of the paired treatment/DPI comparisons assuming a true critical error rate of 5% for the ELLIPTA DPI and 30% for each of the other DPIs.

A two-sided 5% significance level was assumed to test the difference between critical error rates for each of the treatment/DPI comparisons of interest.

10.3. Populations for Analyses

The analysis population will be the Intent-to-treat population (ITT), defined as all participants who have demonstrated DPI use in their primary DPI. The ITT population will be used in all analysis for all endpoints.

Population	Description
All Participants Enrolled ASE	All participants who sign the ICF and for whom a record exists in the study database, including screen failures and any participant who was not screened but experienced an SAE between the date of informed consent and the planned date of the screening visit.
Intent-To-Treat (ITT)	All participants who have been enrolled and demonstrated use of their primary DPI.
Safety	This population will be the same as the Intent-To-Treat population

10.4. Statistical Analyses

10.4.1. Efficacy Analyses

Endpoint	Statistical Analysis Methods
Primary	The primary endpoint is the percentage of participants making at least one critical error when using the DPI which forms part of their current prescribed inhaled medication, at V1 prior to any re-training in correct use. This endpoint will be analysed using logistic regression with treatment option as fixed effects and adjusting for the covariate of time on current DPI. The odds ratio, 95% CI and p-value will be presented for the comparison between DPIs. It will be based on a two-sided hypothesis testing approach of superiority. This analysis will be performed for each of the primary and other treatment comparisons detailed in Section 5.1 and Table 1. For all formal treatment comparisons, the errors used are for the primary DPI within each treatment/DPI group. Sensitivity analyses may be performed to take into account patients who have changed their medication during the study. This will be detailed further in the RAP. There will be no adjustment for multiple comparisons on multiple endpoints in the analysis.
Secondary	The following secondary endpoints will be analysed in the same way as for the primary endpoint and using the same treatment comparisons:

Endpoint	Statistical Analysis Methods
	• The percentage of participants making at least one overall error at V1 for each DPI tested • The percentage of participants making at least one critical error at V2 for each DPI tested • The percentage of participants making at least one overall error at V2 for each DPI tested For all formal statistical analyses where more than one DPI has been used, the comparison will be between the critical errors recorded on the primary DPI. Error rates will not be combined when dual DPIs are being used. There will be no adjustment for multiple comparisons on multiple endpoints in the analysis.
Exploratory	To explore, across all DPIs tested, if any association between critical errors, and key patients characteristics including: • Age. • Educational Status. • Co-Morbidities (Arthritis (upper limbs), Neurological & Visual Impairment) • Time on current DPI(s) (Note: This is already included in the primary analysis model, however the parameter may be used in further exploratory analyses). • Time since last trained on DPI(s) (collected but not used in the primary analysis model). • Level of control- CAT and Exacerbation History. How these variables will be collected is described in Section 9.1.2. Exploration of these characteristics will be investigated using a logistic regression model on the primary endpoint of the percentage of participants making at least one critical error at V1 for each DPI tested, including each of these factors as terms in the model.

10.4.2. Safety Analyses

All safety analyses will be performed on the ITT Population.

Adverse events (AEs) will be coded using the standard GSK dictionary, Medical

Dictionary for Regulatory Activities (MedDRA), and grouped by body system. The number and percentage of participants experiencing at least one AE of any type, AEs within each body system and AEs within each preferred term will be presented for each treatment group. Separate summaries will be provided for all AEs, drug related AEs, fatal SAEs, non-fatal SAEs, AESIs and AEs leading to withdrawal.

Deaths and SAEs, if applicable, will be documented in case narrative format.

10.4.3. Other Analyses

All other analyses will be described in the reporting and analysis plan.

10.4.4. Interim Analyses

No interim analyses are planned.

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12. APPENDICES

12.1. Appendix 1: Abbreviations and Trademarks

ASE	All Participants Enrolled
COPD	Chronic Obstructive Pulmonary Disease
CONSORT	Consolidated Standards of Reporting trials
CRF	Case Report Form
CV	Cardiovascular
DPI	Dry Powder Inhaler
GP	General Practitioner
HCP	Healthcare professional
ICS	Inhaled Corticosteroids
IEC	Independent Ethics Committees
IRB	Institutional Review Boards
ITT	Intent-to-Treat
LABA	Long Acting β_2-Agonist
LAMA	Long Acting Anticholinergic
MedRA	Medical Dictionary of Regulatory Activities
PIL	Patient instruction Leaflet
SABA	Short Acting β_2-Adrenergic Agonist
SAE	Serious Adverse Effects
SAMA	Short Acting Muscarinic Antagonist
SoA	Schedule of Activities
SRM	Study Reference Manual
SUSAR	Suspected Unexpected Serious Adverse Reactions

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
ANORO ELLIPTA
INCRUSE ELLIPTA
RELVAR ELLIPTA
SERETIDE DISKUS

Trademarks not owned by the GlaxoSmithKline group of companies
Seebri Breezhaler
Spiriva HandiHaler
Symbicort Turbuhaler
Ultibro Breezhaler

12.2. Appendix 2: Inhaler specific errors for the inhalers used in this study

There are no universally agreed checklists that define critical errors and overall errors for specific inhalers. The checklist and critical errors for use in this study have been developed by GSK for each inhaler based upon:

- A review of the PIL for each inhaler and the steps defined therein for correct use
- The available literature which is exhaustive for a number of the commonly used inhalers
- Review of these errors with a group of external inhaler experts

The critical errors checklists are, therefore, as robust as possible. Furthermore, GSK has selected sites with trained assessors to ensure as much consistency as possible in the valuation of errors in study participants. Checklist of instructions for correct use will be based on the steps listed in the PIL(s) for each inhaler. Some of the steps outlined in the PIL(s) require several actions to be identified and checked by the HCP.

Critical Errors are identified in underlined text in the list below. A critical error is defined as an error that is most likely to result in no or significantly reduced medication being inhaled. The specific errors outlined in these checklists will NOT change, however, their formatting or layout may change prior to use by the site.

Protocol Identifier **204981**	**Participant Identifier** ☐☐☐☐☐☐	**ELLIPTA (RELVAR, INCRUSE and ANORO Checklist** **Visit #**

Date of Assessment:	☐☐ DAY ☐☐☐ MONTH ☐☐ YEAR
Attempt Number:	☐ PIL (1) ☐ HCP (2) ☐ HCP (3)

PIL Step	PIL Wording (Relvar, Incruse and Anoro ELLIPTA™ June 2016)	Error (Underlined text indicates a critical error)	Completed Correctly	Not Completed Correctly
2	**Prepare a dose** Wait to open the cover until you are ready to take your dose. Do not shake the inhaler. • Slide the cover down until you hear a click.	Failed to open cover	☐	☐
		Shook the device after dose preparation	☐	☐
3	**Inhale your medicine** • While holding the inhaler away from your mouth, breathe out as far as is comfortable. Do not breathe out into the inhaler. • Put the mouthpiece between your lips, and close your lips firmly around it. Do not block the air vent with your fingers. • Take one long, steady, deep breath in. Hold this breath for as long as possible (at least 3-4 seconds). • Remove the inhaler from your mouth. • Breathe out slowly and gently.	No exhalation before an inhalation	☐	☐
		Exhaled directly into mouthpiece	☐	☐
		No seal by the lips round the mouthpiece during the inhalation	☐	☐
		Inhalation manoeuvre **was not** : - long - steady - deep	☐	☐
		Blocked air inlet during inhalation manoeuvre	☐	☐

PIL Step	PIL Wording (Relvar, Incruse and Anoro ELLIPTA™ June 2016)	Error (Underlined text indicates a critical error)	Completed Correctly	Not Completed Correctly
		Did not hold breath	☐	☐
4	• Close the inhaler	Did not close the device (Note: this is an error but one which does not affect the medication that is inhaled)	☐	☐
Other comments:				

Staff Name – Print **Staff Signature** **Date**

Protocol Identifier **204981**	**Participant Identifier** ☐☐☐☐☐☐	**DISKUS Checklist** **Visit #**

Date of Assessment:	☐☐ DAY ☐☐☐ MONTH ☐☐ YEAR
Attempt Number:	☐ PIL (1) ☐ HCP (2) ☐ HCP (3)

PIL Step	PIL Wording (Seretide DISKUS™ March 2015)	Error (Underlined text indicates a critical error)	Completed Correctly	Not Completed Correctly
1	• Hold the outer case in one hand and put thumb of your other hand on the thumbgrip. • Push your thumb away from you as far as it will go • You will hear a click. This will open a small hole in the mouthpiece	Failed to open cover	☐	☐
2	• Hold your inhaler with the mouthpiece towards you (You can hold it in either your right or left hand). • Slide the lever away from you as far as it will go (you will hear a click). This places dose in the mouthpiece.	Lever is not pushed back	☐	☐
		Shook the device after dose preparation	☐	☐
3	• Hold the inhaler away from your mouth, breathe out as far as is comfortable. • Do not breathe into the inhaler.	No exhalation before an inhalation	☐	☐
		Exhaled directly into mouthpiece	☐	☐
4	• Put the mouthpiece between your lips. • Breathe in, steadily and deeply through	No seal by the lips round the mouthpiece during the inhalation	☐	☐

PIL Step	PIL Wording (Seretide DISKUS™ March 2015)	Error (Underlined text indicates a critical error)	Completed Correctly	Not Completed Correctly
	the inhaler, not through your nose. • Remove the inhaler from your mouth. • Hold your breath for about 10 seconds or for as long as is comfortable • Breathe out slowly.	Inhalation manoeuvre **was not** : - steady - deep	☐	☐
		Did not hold breath	☐	☐
5	After use, rinse your mouth with water and spit it out, and/or brush your teeth.		NOT REQUIRED	
6	• To close the inhaler, slide the thumbgrip back towards you, as far as it will go. You will hear a click.	Did not close the device (Note: this is an error but one which does not affect the medication that is inhaled)	☐	☐
Other comments:				

Staff Name – Print **Staff Signature** **Date**

Protocol Identifier	**Participant Identifier**	**HandiHaler Checklist**
204981		**Visit #**

Date of Assessment:	DAY	MONTH	YEAR
Attempt Number:	PIL (1)	HCP (2)	HCP (3)

PIL Step	PIL Wording (Spiriva HandiHaler November 2014)	Error (Underlined text indicates a critical error)	Completed Correctly	Not Completed Correctly
3	• Remove capsule from blister pack (only immediately before use, see blister handling) and place it in the centre chamber, as illustrated. It does not matter which way the capsule is placed in the chamber.	Failed to remove capsule	☐	☐
		Failed to insert capsule into the chamber	☐	☐
4	• Close the mouthpiece firmly until you hear a click, leaving the dust cap open.	Did not completely close device capsule chamber (heard click when satisfactory)	☐	☐
5	• Hold the inhaler device with the mouthpiece upwards and press the piercing button completely in only once, and release This makes holes in the capsule and allows the medication to be released when you breathe in.	Did not pierce the capsule (HCP should check capsule was pierced)	☐	☐
		Shook the device after dose preparation	☐	☐
6	• Breathe out completely. • Please avoid breathing into the mouthpiece at any time	No exhalation before an inhalation	☐	☐
		Exhaled directly into mouthpiece	☐	☐
7	• Raise the inhaler to your mouth and close your lips tightly around the mouthpiece. • Keep your head in an upright position and breathe in slowly and deeply but at a rate sufficient to hear or feel the capsule vibrate.	No seal by the lips round the mouthpiece during the inhalation	☐	☐
		Inhalation manoeuvre **was not** : - slow	☐	☐

	• Breathe until your lungs are full; then hold your breath as long as comfortable and at the same time take the inhaler out of your mouth.	- deep		
	• Resume normal breathing. Repeat steps 6 and 7 once, in order to empty capsule completely.	Capsule did not rattle	☐	☐
		Blocked air inlet during inhalation manoeuvre	☐	☐
		Did not hold breath	☐	☐
		Did not check inside the capsule chamber if powder was left/ did not make second inhalation	☐	☐
Other Comments:				

Staff Name – Print **Staff Signature** **Date**

Protocol Identifier	**Participant Identifier**	**Turbuhaler Checklist**
204981		**Visit #**

Date of Assessment:	DAY	MONTH	YEAR
Attempt Number:	PIL (1)	HCP (2)	HCP (3)

PIL Step	PIL Wording (Symbicort Turbuhaler October 2015)	Error (Underlined text indicates a critical error)	Completed Correctly	Not Completed Correctly
1	• Unscrew the cover and lift it off. You may hear a rattling sound	Failed to remove cap	☐	☐
2	• Hold your Inhaler upright with the red grip at the bottom.	Did not hold device upright (± 45° OK) during dose preparation	☐	☐
3	• Do not hold the mouthpiece when you load your inhaler. To load your inhaler with a dose, turn the red grip as far as it will go in one direction. Then turn it as far as it will go in the other direction (it does not matter which way you turn it first). • You should hear a click sound. Your inhaler is now loaded and ready to use. Only load your inhaler when you need to use it.	Base not twisted fully backwards and forwards, no click heard	☐	☐
		Device tipped downwards after dose preparation	☐	☐
		Shook the device after dose preparation	☐	☐
4	• Hold your inhaler away from your mouth. Breathe out gently (as far as is comfortable). • Do not breathe out through your inhaler	No exhalation before inhalation	☐	☐
		Exhaled directly into mouthpiece	☐	☐
5	• Place the mouthpiece gently between your teeth. Close your lips. • Breathe in as deeply and as hard as you can through your mouth. Do not chew or	No seal by the lips round the mouthpiece during inhalation	☐	☐

	bite on the mouthpiece.	Inhalation manoeuvre **was not** : - forceful - deep *Note to HCP: it is important that the inhalation is forceful and deep from the start for this inhaler*	☐	☐
		Blocked air inlet during inhalation manoeuvre	☐	☐
6	• Remove the inhaler from your mouth. • Breathe out gently. The amount of medicine that is inhaled is very small. This means you may not be able to taste it after inhalation. If you have followed instructions, you can still be confident that you have inhaled the dose and the medicine is now in your lungs.	Did not hold breath	☐	☐
7	• If you are to take a second inhalation, repeat steps 2 to 6.		NOT REQUIRED	
8 + 9	• Replace cover tightly after use	Did not close the device (Note: this is an error but one which does not affect the medication that is inhaled)	☐	☐
Other comments:				

Staff Name – Print **Staff Signature** **Date**

Protocol Identifier	**Participant Identifier**	**Breezhaler Checklist**
204981		**Visit #**

Date of Assessment:	DAY	MONTH	YEAR
Attempt Number:	PIL (1)	HCP (2)	HCP (3)

PIL Step	PIL Wording (Seebri and Ultibro Breezhaler October 2015)	Error (Underlined text indicates a critical error)	Completed Correctly	Not Completed Correctly
1	**Remove the cap**		NOT REQUIRED	
2	**Open inhaler** •Hold the base of the inhaler firmly and tilt the mouthpiece. This opens the inhaler		NOT REQUIRED	
3	**Prepare capsule** • Separate one of the blisters from the blister card by tearing along the perforation. Take one blister and peel away the protective backing to expose the capsule. •Do not push capsule through foil.		NOT REQUIRED	
4	**Remove a capsule** • Capsules should always be stored in the blister and only removed immediately before use. With dry hands, remove capsule from the blister. • Do not swallow the capsule.	Failed to remove capsule	☐	☐
5	**Insert capsule** • Place the capsule into the capsule chamber. • Never place a capsule directly into the mouthpiece.	Failed to insert capsule into the chamber	☐	☐

PIL Step	PIL Wording (Seebri and Ultibro Breezhaler October 2015)	Error (Underlined text indicates a critical error)	Completed Correctly	Not Completed Correctly
6	**Close the Inhaler** • Close the inhaler until you hear a "**click**".	Did not completely close device capsule chamber (heard click when satisfactorily)	☐	☐
7	**Pierce the capsule:** • Hold the inhaler upright with the mouthpiece pointing up. • Pierce the capsule by firmly pressing together both side buttons at the same time. **Do this only once.** • You should hear a "**click**" as the capsule is being pierced.	Did not pierce the capsule and failed to release piercing buttons fully before inhalation (HCP to check that capsule was pierced and that piercing buttons were released	☐	☐
8	**Release the side buttons fully,**	Shook the device after dose preparation	☐	☐
9	**Breathe out:** • Before placing the mouthpiece in your mouth, breathe out fully **Do not blow into the mouthpiece**	Exhaled directly into the mouthpiece	☐	☐
10	**Inhale the medicine:** • To breathe the medicine deeply into your airways: • Hold the inhaler as shown in the picture. The side buttons should be facing left and right. Do not press the side buttons. • Place the mouthpiece in your mouth and close your lips firmly around it. • Breathe in rapidly but steadily, as deeply as you can. **Do not press the side buttons.**	No seal by the lips round the mouthpiece during the inhalation	☐	☐
		Inhalation manoeuvre **was not :** -Rapid -Steady -Deep	☐	☐
11	**If you do not hear a whirring noise**: The capsule may be stuck in the capsule chamber. If this happens: • Open the inhaler and carefully loosen the capsule by tapping the base of the inhaler. **Do not press the side buttons.** • Inhale the medicine again by repeating steps 9 and 10.	Capsule did not rattle	☐	☐
		Blocked air inlet during inhalation manoeuvre	☐	☐
12	**Hold breath:** **After you have inhaled the medicine:** • Hold your breath for at least 5-10 seconds	Did not hold breath	☐	☐

PIL Step	PIL Wording (Seebri and Ultibro Breezhaler October 2015)	Error (Underlined text indicates a critical error)	Completed Correctly	Not Completed Correctly
	or as long as you comfortably can while taking the inhaler out of your mouth. • Then breathe out. • Open the inhaler to see if any powder is left in the capsule.			
13	**If there is powder left in the capsule**: • Close the inhaler. • Repeat steps 9 to 12.	Did not check inside the capsule chamber if powder was left / did not make a second inhalation	☐	☐
Other comments:				

Staff Name – Print **Staff Signature** **Date**

Protocol Identifier	**Participant Identifier**	**Generic MDI Checklist**
204981		**Visit #**

Date of Assessment:	DAY	MONTH	YEAR
Attempt Number:	PIL (1)	HCP (2)	HCP (3)

PIL Step	PIL Wording (Generic MDI March 2015)	Error (Underlined text indicates a critical error)	Completed Correctly	Not Completed Correctly
2	• Remove the mouthpiece cover/cap	Failed to remove cap.	☐	☐
3	Shake the inhaler 4-5 times to ensure that: • Any loose objects are removed • The contents of the inhaler are evenly mixed	Did not shake the device.	☐	☐
4	• Hold the inhaler upright with your thumb on the base, below the mouthpiece. • Breathe out as far as is comfortable. • Do not breathe in again yet.	Did not inhale within 5 seconds of shaking the device.	☐	☐
		No exhalation before inhalation.	☐	☐
5	• Place the mouthpiece in your mouth between your teeth. •Close your lips around it. •Do not bite.	Failed to place device in mouth.	☐	☐
6	• Breathe in through your mouth. • Just after starting to breathe in, press down on the top of the canister to release a puff of medicine. • Do this while still breathing in slowly and deeply.	Inhalation manoeuvre **was not** : - slow - deep (Note: if it lasts for <2 seconds, then it is too fast)	☐	☐
		No dose actuated during an inhalation manoeuvre.	☐	☐

PIL Step	PIL Wording (Generic MDI March 2015)	Error (Underlined text indicates a critical error)	Completed Correctly	Not Completed Correctly
		Dose coordination so poor that patient is likely to have received no dose or only received minimal dose.	☐	☐
		Dose coordination was sup-optimal but patient likely to have received some dose.	☐	☐
7	• Hold your breath, take the inhaler from your mouth and your finger from the top of the inhaler. •Continue holding your breath for a few seconds, or as long as is comfortable.	Did not hold breath	☐	☐
8	• If your doctor has told you to take two puffs, wait about half a minute before taking another puff by repeating steps 3 to 7	More than one dose actuation during inhalation procedure	☐	☐
9	• After use always replace the mouthpiece cover straight away to keep dust out. Replace the cover by firmly pushing and clicking into position		NOT REQUIRED	
Other comments:				

Staff Name – Print **Staff Signature** **Date**

12.3. 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 Organisations 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 (eg, 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 participants.
- 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 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 participant or his/her legally authorised representative and answer all questions regarding the study.

- Participants must be informed that their participation is voluntary. Participants or their legally authorised 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 centre.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorised person obtaining the informed consent must also sign the ICF.
- Participants 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 participant or the participant's legally authorised representative.
- Participants who are rescreened are required to sign a new ICF.

Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant 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 participant.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorised 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 participants, 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 participant 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 authorised site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants 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 participant 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.
- Definition of what constitutes source data can be found in source data agreement or source data verification form.

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 participants by the investigator
- Discontinuation of further study treatment development

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

Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a clinical study participant, 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 Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, 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 NOT 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 participant'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 participant's condition. • Medical or surgical procedure (eg, 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 (eg, hospitalisation 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 participant 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 hospitalisation or prolongation of existing hospitalisation In general, hospitalisation signifies that the participant 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 hospitalisation or fulfils any other serious criteria, the event is serious. When in doubt as to whether "hospitalisation" occurred or was necessary, the AE should be considered serious. Hospitalisation 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, diarrhoea, influenza, and accidental trauma (eg, 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 hospitalisation but may jeopardise the participant 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 hospitalisation, 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
- Revascularisation

Recording AE and SAE

AE and SAE Recording
• When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, 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 participant'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 participant identifiers, with the exception of the participant 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 participant, 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 participant dies during participation in the study or during a recognised 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 participant 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 by telephone.
- Contacts for SAE reporting can be found in the SRM.

SAE Reporting to GSK via Paper CRF

- Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the **medical monitor.**
- In rare circumstances and in the absence of facsimile equipment, 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.

12.5. Appendix 5: Protocol Amendment History

N/A