TITLE PAGE

Protocol Title: A randomized, open-label, cross-over, placebo-device study investigating critical and over all errors, training/teaching time, and preference attributes of the ELLIPTA dry powder Inhaler (DPI) as compared to HandiHaler DPI used in combination with either DISKUS DPI or Turbuhaler DPI, in adult patients with Chronic Obstructive Pulmonary Disease (COPD)

Protocol Number: 206215

Short Title: A clinical study assessing critical errors, training/teaching time, and preference attributes of the ELLIPTA dry powder inhaler, in comparison to combinations of dry powder inhalers used to provide triple therapy, in patients with COPD.

Compound Number: GSK573719+GW642444+GW685698 (GSK2834425)

Sponsor Name and Legal Registered Address:

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Regulatory Agency Identifying Number(s): Not Applicable

Approval Date: 15-SEP-2016

SPONSOR SIGNATORY:

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Date

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1. SYNOPSIS

Protocol Title: A randomized, open-label, cross-over, placebo-device study investigating critical and over all errors, training/teaching time, and preference attributes of the ELLIPTA dry powder Inhaler (DPI) as compared to HandiHaler DPI used in combination with either DISKUS DPI or Turbuhaler DPI, in adult patients with Chronic Obstructive Pulmonary Disease (COPD)

Short Title: A clinical study assessing critical errors, training/teaching time, and preference attributes of the ELLIPTA dry powder inhaler, in comparison to combinations of dry powder inhalers used to provide triple therapy, in patients with COPD.

Rationale: This study is designed to assess the benefits of delivering triple therapy using a single ELLIPTA™ DPI (Closed Triple therapy) *versus* delivering triple therapy using two different types of inhalers (open triple therapy) to patients with Chronic Obsttructive Pulmonay Disease (COPD). It will assess the proportion of COPD subjects who make critical errors when using a single ELLIPTA™ DPI *versus* those using combinations of commercially available and commonly used DPIs: DISKUS used in combination with HandiHaler, or Turbuhaler used in combination with HandiHaler. This study would also assess training/teaching time and preference attributes for closed triple therapy as compared to the open triple therapy.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
To compare the number of critical errors made by COPD patients, after a subject has read the respective patient information leaflet(s) (PIL), for each treatment option tested	• The percentage of subjects making at least one critical error after reading the PIL(s)
Secondary	
To compare the number of critical errors made by COPD patients after instruction from the Healthcare Professional (HCP) for each treatment option tested	The percentage of subjects making at least one critical error after the: • first instruction from the HCP • second instruction from the HCP
To compare the number of overall (critical and non-critical) errors made by COPD patients, after a subject has read the PIL(S) or after Instruction from the HCP for each treatment option tested	• The percentage of subjects making at least one overall error after reading the PIL(s) • The percentage of subjects making at least one overall error after the first instruction from the HCP • The percentage of subjects making at least one overall error after the second instruction from the HCP

Objectives	Endpoints
To compare the number of instructions (maximum of 2) from a HCP which is needed to demonstrate correct inhaler use	The number of instructions (0, 1 or 2 times) from the HCP which are needed to demonstrate correct inhaler use
To compare the Training/Teaching Time required to demonstrate correct inhaler use	• The total amount of time taken to demonstrate correct inhaler use (T1+T2). • The amount of time taken to read the patient information leaflet and demonstrate correct inhaler use (T1) • The amount of time taken to be given instruction by the HCP (up to 2 times) on use of the inhaler and to demonstrate correct inhaler use (T2)
Preference attributes for each treatment option tested	Treatment preference, from questionnaire for: • Number of steps required to take COPD medication • Over all treatment preference

Overall Design: The study will be conducted as a multi-centre, randomized, open-label, placebo-device, cross-over study, with a 2x2 complete block design.

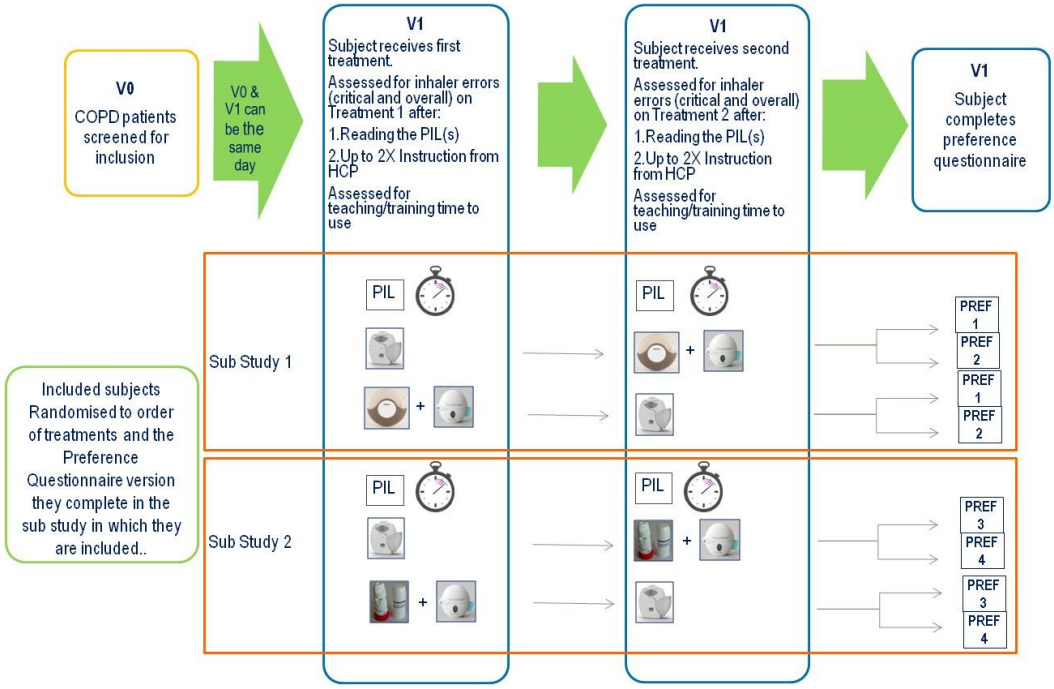
It will comprise of two sub-studies:

- Sub-study 1: Will compare ELLIPTA DPI to DISKUS-HandiHaler DPI combination
- Sub-study 2: Will compare ELLIPTA DPI to Turbuhaler-HandiHaler DPI combination.

The study has 2 visits (V0 and V1) and both can be completed on the same day.

Each sub-study may run independently or in parallel of the other sub study. Each will start dependent on the availability of the placebo DPIs required for that sub-study. The data from the 2 sub studies may be reported independently and as each sub study completes.

Study Schematic



Number of Participants: Sufficient patients with COPD will be screened to ensure approximately 160 participants will be randomized, such that approximately 144 evaluable participants complete the study. Approximately 72 participants completing in each sub study.

Treatment Groups and Duration: Duration is a single visit and subjects are randomised to receive treatments below; dependent on which sub-study they are included in.

There is no active treatment and subjects will continue to take their own prescribed COPD medication for the duration of the study.

Sub Study 1 Treatment Sequences

Sequence	Period 1	Period 2	Preference Questionnaire
A	ELLIPTA	DISKUS + HandiHaler	1
B	DISKUS + HandiHaler	ELLIPTA	2
C	ELLIPTA	DISKUS + HandiHaler	2
D	DISKUS + HandiHaler	ELLIPTA	1

Sub Study 2 Treatment Sequence

Sequence	Period 1	Period 2	Preference Questionnaire
E	ELLIPTA	Turbuhaler + HandiHaler	3
F	Turbuhaler + HandiHaler	ELLIPTA	4
G	ELLIPTA	Turbuhaler + HandiHaler	4
H	Turbuhaler + HandiHaler	ELLIPTA	3

2. SCHEDULE OF ACTIVITIES (SOA)

Visit Number	V0	V1	Notes
Study Day	**1**	**1**	V0 can take place on the same day as V1. V1 should be completed no later than 30 days after consent.
Procedure:			
Screening Assessments			Completed prior to randomisation
Written informed consent	X		Informed consent may take place prior to V0 for logistical reasons. Subjects should be included and randomised within 30 days of providing consent.
Subject demography	X		Age, height, weight, year of birth, sex, ethnicity and geographic ancestry will be recorded
Medical/disease history including Chronic Obstructive Pulmonary Disease (COPD)	X		Subject will have a medical history of COPD, previously confirmed by spirometry.
Concomitant medication history including COPD Therapy History	X		Current concomitant medication will be recorded. A minimum COPD therapy history for the preceding 2 years from inclusion will be recorded
Inclusion/exclusion criteria	X		All criteria must be meet prior to randomisation at V1
Study Assessments			Completed once a subject is included on study
Randomisation		X	Randomised to treatment order and preference questionnaire
Assess the number of inhaler errors (critical and overall) on each treatment after reading the Patient information leaflet (PIL) for Inhaler tested		X	No instruction is provided by the Health Care Professional (HCP) for this assessment.
Assess the number of inhaler errors (overall and critical) on each treatment after each of 2 attempts following instruction by HCP			If a subject cannot show correct use after reading the PIL, then the HCP has up to 2 attempts to instruct the subject to attain this.

Visit Number	V0	V1	Notes
Teaching-Training Time for each inhaler includes the following: • The amount of time taken to read the patient information leaflet and demonstrate inhaler use • The amount of time taken to be given instruction by the HCP on use of the inhaler and demonstrate inhaler use • The total amount of time taken to demonstrate inhaler use		X	• First assessment is attempt one, including time to read PIL and demonstrate use. • Second assessment will be time for HCP to correct errors and subject to show use for up to 2 more attempts • The Cumulative time for all assessments needed by subject and any HCP instruction to demonstrate no errors will also be captured.
Preference Questionnaire		X	Subject will complete version of Preference Questionnaire they have been randomised to.
SAE/AE assessment		X	Collected until completion of final study assessment at V1.

3. INTRODUCTION

3.1. Study Rationale

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

This study is designed to assess the benefits of delivering triple therapy using a single ELLIPTA ™ Dry Powder Inhaler (DPI) (Closed Triple therapy) *versus* delivering triple therapy using two different types of inhalers (open triple therapy) to patients with COPD. It will assess the proportion of COPD subjects who make critical errors when using a single ELLIPTA DPI *versus* those using combinations of commercially available and commonly used DPIs: DISKUS used in combination with HandiHaler, or Turbuhaler used in combination with HandiHaler. This study would also assess training/teaching time and preference attributes for closed triple therapy as compared to the open triple therapy.

3.2. Background

Chronic Obstructive Pulmonary Disease (COPD) is a progressive disease of the airways. Noxious particles or gases lead to a modification in subject's airways which develop a chronic inflammatory response to these environmental factors. This leads to increasing airflow limitation, breathlessness and other symptoms. Despite being both treatable and preventable, COPD is a leading cause of morbidity and mortality worldwide. The economic and social burden of this disease has not been reduced and is increasing despite advances in diagnosis and treatment. [GOLD 2016]

The current treatment goals for COPD are to reduce and relieve symptoms and thereby improve exercise tolerance and health status, whilst reducing risk by preventing disease progression, preventing and treating exacerbations, and reducing mortality

Smoking cessation, inhaled pharmacological therapy, primarily long and short term bronchodilators (beta2-agonists and anti-cholinergics) and inhaled corticosteroids, and other non pharmacological interventions are currently used to achieve the treatment goals.

The current GOLD treatment guidelines, place patients in 4 groups from A to D, dependent on severity of symptoms and assessment of risk; with Group A patients having the fewest symptoms and a low risk as assessed by degree of airflow limitation and/or exacerbation history. COPD patients in Group A may just need a short acting bronchodilator as needed to relieve symptoms. However, as disease progresses, other inhaled therapies are added on to maintain control, such that COPD patients in Group D, who have many symptoms and a high risk of exacerbations and/or high airflow limitation, may need multiple inhaled therapies (inhaled corticosteroids (ICS), long-acting beta2-agonist (LABA) and long-acting anticholinergic (LAMA)).

Currently, subjects requiring triple therapy can be prescribed ICS/LABA and LAMA in separate inhalers. The specific ICS/LABA and LAMA prescribed determine whether the inhaler types (and thereby the inhalation techniques) and the dosing regimens are similar or different. Use of different inhaler types with different inhalation techniques and dosing regimens can add to treatment complexity, and also increase the potential for errors in inhaler use that reduce or preclude drug delivery to the site of action in the lungs [Cochrane, 2000, Van der Palen, 1999]. Fixed-dose combination inhalers that minimise the number of inhalers required would simplify treatment, improve adherence, reduce errors in inhaler use, and potentially lead to better outcomes [GOLD 2016].

The skill and ability of the COPD patient to use the prescribed inhaler/s correctly coupled with adequate training in inhaler technique are also critical to ensure effective drug delivery [Cochrane, 2000, Melani, 2011]. For any prescribed inhaler, the patient needs to follow all the steps in the patient leaflet correctly in order to ensure optimal drug delivery. In this regard, the time needed for a primary care nurse or physician, or a community pharmacist to train a patient in correct use of an inhaler at the time of initial prescription, and for any subsequent retraining becomes important. Given the time demands on healthcare professionals, a device which is simple to use and requires minimal time to train would be desirable [Bonini, 2015]. Further, patients may prefer easy-to-use inhalers having fewer steps to deliver drug; this has the potential to improve compliance and thereby impact outcomes.

ELLIPTA DPI has been designed to be simple for patients to use. In COPD patients' naïve to Ellipta and comparator inhalers, data has shown that patients make fewer critical and overall errors when using ELLIPTA as compared to other common DPIs tested [Van Der Palen, 2016(a)]. ELLIPTA DPI was also shown to be preferred by patients for a number of attributes, including number of steps and training time required to receive therapy [Van Der Palen, 2016(b), Van Der Palen, 2016(c), Komase, 2014]. ELLIPTA is already available to deliver a LABA/ICS combination (BREO ELLIPTA), LAMA

(INCRUSE ELLIPTA), and LAMA/LABA combination (ANORO ELLIPTA). Closed triple therapy (ICS/LAMA/LABA) is currently being assessed in clinical studies to deliver all 3 active treatments from a single ELLIPTA DPI.

3.3. Benefit/Risk Assessment

The study involves use of placebo inhalers (placebo ELLIPTA, placebo DISKUS, placebo Turbuhaler and placebo HandiHaler) that do not contain active treatments and subjects will continue to take their own prescribed COPD medication and other concomitant medication for the duration of the study.

The placebo inhalers and placebo capsules for HandiHaler contain the excipients lactose or lactose blended with magnesium stearate. Excipients of the study inhaler are noted in Section 7.1. Subjects with a known hypersensitivity to any of these or severe milk protein allergy that could contraindicate study participation are excluded from the study (Section 6). Subjects who meet the inclusion/exclusion criteria will continue their COPD treatment as prescribed by their healthcare provider during their participation in the study. Subjects should continue to follow up with their regular physician for their COPD healthcare during the study.

The study procedures include reading of the inhaler patient information leaflets and demonstration of inhaler use by the study subjects and instruction in correct-inhaler use by the site staff.

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 inhaling.	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.	This should be treated immediately with a fast and short acting inhaled bronchodilator. Investigators will be instructed to assess the subject's condition to determine their eligibility to continue in the study and the need for alternative therapy.
Allergic reaction due to hypersensitivity to placebo excipients.	The placebo inhalers and placebo capsules (for HandiHaler) contain the excipients lactose and lactose blended with magnesium stearate. There are known allergies to these ingredients.	Subjects with a known hypersensitivity to any of these, or severe milk protein allergy that could contraindicate study participation are excluded from the study (Section 6.2). If an allergic reaction occurs, it should be treated immediately with a fast and short acting inhaled bronchodilator. Investigators will be instructed to assess the subject's condition to determine their eligibility to continue in the study and the need for alternative therapy

3.3.2. Benefit Assessment

As this is a placebo study, no benefit to the subject is expected. No active treatment is being administered. The subjects will continue to receive their own COPD therapy as prescribed.

3.3.3. Overall Benefit: Risk Conclusion

The overall potential risk identified is minimal, due to the nature of the study.

4. OBJECTIVES AND ENDPOINTS

The study will compare critical errors, training time, and patient preference for closed triple therapy received from a single ELLIPTA inhaler *versus* open triple therapy received from HandiHaler in combination with either DISKUS or Turbuhaler. These comparisons will be performed as separate sub studies and the endpoints and objectives listed here will be the same for the treatment comparisons in each sub study:

- Sub study 1: ELLIPTA (Treatment option 1) versus the combination of DISKUS-HandiHaler (Treatment Option 2)
- Sub study 2: ELLIPTA ((Treatment option 1) versus the combination of Turbuhaler-HandiHaler (Treatment Option 3)

Objectives	Endpoints
Primary	
To compare the number of critical errors [a] made by COPD patients, after a subject has read the respective patient information leaflet(s) (PIL), for each treatment option tested	• The percentage of subjects making at least one critical error after reading the PIL(s)
Secondary	
To compare the number of critical errors made by COPD patients after instruction from the Healthcare Professional (HCP) for each treatment option tested	The percentage of subjects making at least one critical error after the: • first instruction from the HCP • second instruction from the HCP [d]
To compare the number of overall [a] (critical and non-critical) errors made by COPD patients, after a subject has read the PIL(S) or after Instruction from the HCP for each treatment option tested	• The percentage of subjects making at least one overall error after reading the PIL(s) • The percentage of subjects making at least one overall error after the first instruction from the HCP • The percentage of subjects making at least one overall error after the second instruction from the HCP [d]

Objectives	Endpoints
To compare the number of instructions (maximum of 2) from a HCP which is needed to demonstrate correct inhaler use[c]	The number of instructions (0, 1 or 2 times) from the HCP which are needed to demonstrate correct inhaler use
To compare the Training/Teaching Time required to demonstrate correct inhaler use	• The total amount of time taken to demonstrate correct inhaler use (T1+T2). • The amount of time taken to read the patient information leaflet and demonstrate correct inhaler use (T1) [d] • The amount of time taken to be given instruction by the HCP (up to 2 times) on use of the inhaler and to demonstrate correct inhaler use (T2) [d]
Preference attributes for each treatment option tested [b]	Treatment preference, from questionnaire for: • Number of steps required to take COPD medication • Over all treatment preference

a. Over all and critical errors for each inhaler tested, as well as an explanation of how these endpoints were defined, are listed in Appendix 2
b. Preference Questionnaires for each sub-study are included in Appendix 3
c. To show correct inhaler use a subject demonstrates the use of the inhaler without making any critical or non-critical error
d. Endpoint will be treated as 'other endpoint' and not secondary for the statistical analysis

5. STUDY DESIGN

5.1. Overall Design

The study will be conducted as a multi-centre, randomized, open-label, placebo-device, cross-over study, with a 2x2 complete block design.

It will comprise of two sub-studies:

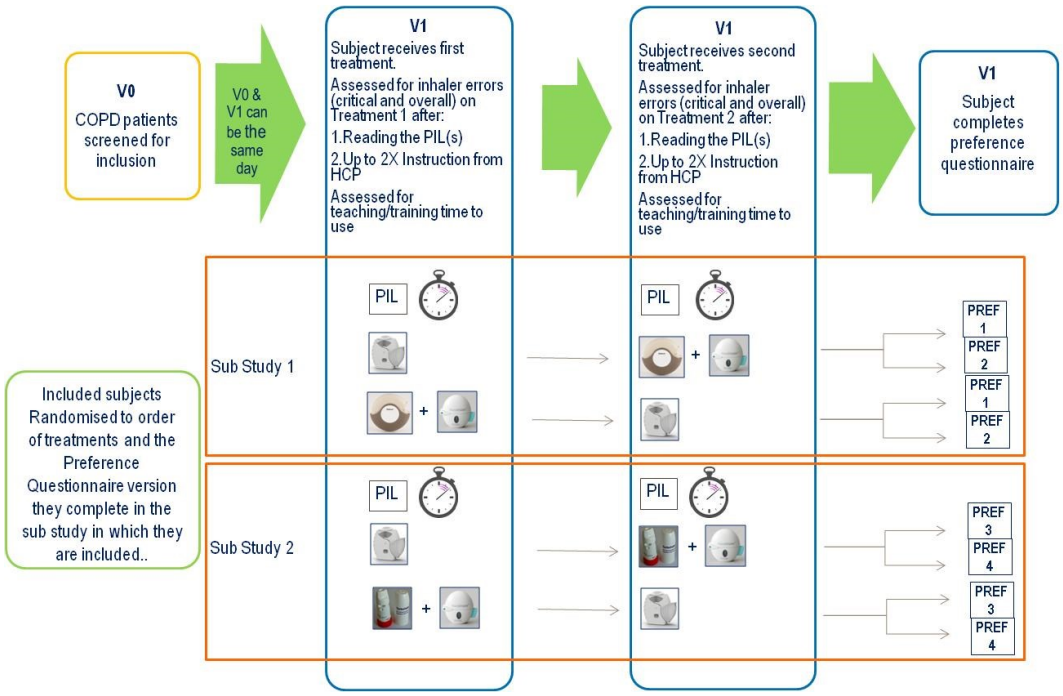
- Sub-study 1: Will compare ELLIPTA DPI (Treatment option 1) to DISKUS-HandiHaler DPI combination (Treatment option 2)
- Sub-study 2: Will compare ELLIPTA DPI (Treatment option 1) to Turbuhaler-HandiHaler DPI combination (Treatment option 3).

The study has 2 visits (V0 and V1) and both can be completed on the same day.

Each sub-study may run independently or in parallel of the other sub study. Each will start dependent on the availability of the placebo DPIs required for that sub-study. The data from the 2 sub studies will be reported independently and as each sub study completes and the data have been cleaned. The database will be locked when all of the sub-studies have completed and data are cleaned.

The study subjects will be randomised to order of treatment and preference questionnaire in each of the 2 sub studies. This is shown in further detail in Figure 1.

Figure 1 Study Schematic



5.2. Number of Participants

Sufficient patients with COPD will be screened to ensure approximately 160 participants will be randomized, such that approximately 144 evaluable participants complete the study. An evaluable subject is defined in the intent to treat population in Section 10.3. Approximately 72 participants completing in each sub study.

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

This design has been used in previous studies looking at critical errors and/or preference of inhalers in patients with COPD and naive to the inhalers tested. The cross-over design was chosen to allow the subjects to serve as their own control in their ability to use both the ELLIPTA DPI and the other combination DPIs. A single visit is suitable for assessing these endpoints and reduces inconvenience of multiple visits for subject included.

Placebo inhalers are used to remove any bias due to treatment effect, avoid the need for wash-in/-out periods, and to avoid the need to withhold or discontinue current COPD medications, which may affect the subject's clinical status (improvement or decline) and perceptions, as noted above.

5.5. Dose Justification

Not applicable as this is a placebo-only 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:

AGE
1. ≥40 years of age at Visit 1
TYPE OF SUBJECT AND DIAGNOSIS
2. Diagnosis of COPD with a documented history of COPD, in accordance with the definition by the European Respiratory Society [Celli, 2004]. 3. Current COPD Therapy: Currently receiving maintenance therapy with a fixed dose combination of a long-acting beta 2-agonist (LABA) and inhaled corticosteroid (ICS). Subject may also be receiving long-acting muscarinic antagonist (LAMA; also known as a long-acting anti-cholinergic). Subjects must be able to continue using their currently prescribed COPD maintenance inhaler therapy throughout the study and as needed short acting beta-adrenergic agonist (SABA) and/or short acting muscarinic antagonist (SAMA) for rescue use. 4. Has been on current maintenance ICS/LABA COPD treatment for at least 4 weeks prior to V0 and evaluated as unlikely to change treatment within 4 weeks of Visit 1.
SMOKING HISTORY
5. Smoking History: Current or former (defined as subjects who have quit smoking for at least 3 months prior to V0/V1) cigarette smokers with a >10 pack-year smoking history [Number of pack years = (number of cigarettes per day ÷ 20) x number of

years smoked (e.g., 10 pack-years is equal to 20 cigarettes per day for 10 years, or 10 cigarettes per day for 20 years].
SEX
6. Males or Females who are not pregnant or not planning a pregnancy during the study or not lactating
INFORMED CONSENT
7. Capable of giving signed informed consent as described in Appendix 4 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

6.2. Exclusion Criteria

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

CONCURRENT CONDITIONS/MEDICAL HISTORY
1. Asthma: Subjects with a current diagnosis of asthma. Subjects with a prior history of asthma are eligible if they have a current diagnosis of COPD.
CONCOMITANT MEDICATIONS
2. **Recent experience with the ELLIPTA inhaler:** Subjects who used any ELLIPTA inhaler (e.g., RELVAR ELLIPTA, ANORO ELLIPTA, ARNUITY ELLIPTA, INCRUSE ELLIPTA, participated in a clinical study of GW685698, GW642444, GSK573719 [fluticasone furoate, vilanterol, umeclidinium bromide], or any combination thereof, or placebo in an ELLIPTA inhaler study) within 24 months prior to Visit 0. 3. **Recent experience with any capsule inhaler:** Subjects who used any capsule system inhaler (e.g. Spiriva HandiHaler, Seebri/Ultibro Breezhaler, or participated in a clinical studies of these, including placebo inhalers) within 24 months prior to Visit 0. 4. Dependent on which sub-study a subject is included on they should not have any recent experience, within 24 months of V0 of the following inhaler for the sub study included on: • **Sub Study 1: DISKUS inhaler** (e.g. Seretide DISKUS or placebo DISKUS) • **Sub Study 2:Turbuhaler** (e.g. Symbicort Turbuhaler or placebo Turbuhaler)
RELEVANT HABITS
5. Drug/alcohol abuse: Subjects with a known or suspected alcohol or drug abuse at Visit 1 which in the opinion of the investigator could interfere with the subject's proper completion of the protocol requirement

CONTRAINDICATIONS
6. Drug/Food Allergy: A history of hypersensitivity to any components of the study inhaler (e.g., lactose, magnesium stearate). In addition, subjects with a history of severe milk protein allergy that, in the opinion of the study physician, contraindicates participation will also be excluded.
DIAGNOSTIC ASSESSMENTS AND OTHER CRITERIA
7. Investigational Product: Subjects who have received an investigational drug and/or medical device within 30 days of entry into this study (Screening/Visit 1), or within five drug half-lives of the investigational drug, whichever is longer 8. Inability to Read: In the opinion of the investigator, any subject who is unable to read and/or would not be able to complete a questionnaire and understand verbal instructions.

6.3. Lifestyle Restrictions

There are no lifestyle restrictions.

6.3.1. Meals and Dietary Restrictions

There are no meals or dietary restrictions.

6.3.2. Caffeine, Alcohol, and Tobacco

There are no caffeine, alcohol, and tobacco restrictions, other than those for a subject's inclusion and any local restrictions whilst the subject is in the clinic.

6.3.3. 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 randomized. 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. Rescreened participants should be assigned a new subject number.

7. TREATMENTS

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

7.1. Treatments Administered

Study Treatment Name:	**ELLIPTA placebo DPI**	**DISKUS placebo DPI**	**HandiHaler DPI and placebo Capsules**	**Turbuhaler placebo DPI**
Dosage formulation:	Placebo DPI with two strips with 30 blisters per strip. First strip: lactose monohydrate Second strip: lactose monohydrate blended with magnesium stearate	Placebo DPI with one blister strip containing lactose monohydrate.	DPI with placebo capsules containing lactose monohydrate	Placebo DPI containing lactose monohydrate
Route of Administration	Oral Inhalation	Oral Inhalation	Oral Inhalation	Oral Inhalation
Dosing instructions:	As directed	As directed	As directed	As directed
Packaging and Labelling	Study Treatment will be provided in the appropriate container and will be labelled as required per country requirement.	Study Treatment will be provided in the appropriate container and will be labelled as required per country requirement.	Study Treatment will be provided in the appropriate container and will be labelled as required per country requirement.	Study Treatment will be provided in the appropriate container and will be labelled as required per country requirement.
Manufacturer	GSK	GSK	Boehringer Ingelheim	AstraZeneca
Device	NA	NA	HandiHaler	NA

7.1.1. Medical Devices

- Other medical device (not manufactured by or for GSK) provided for use in this study is HandiHaler Dry Powder Inhaler

- Any extra instructions for medical device will be provided in the Study Reference Manual.

7.2. Method of Treatment Assignment

All participants will be centrally randomized using an Interactive Web Response System (IWRS). Before the study is initiated, the log in information & directions for the IWRS will be provided to each site.

Participants will be assigned in equal numbers to one of four sequences for the sub-study they are included on, in accordance with the randomization schedule generated by Clinical Statistics, prior to the start of the study and using validated internal software.

The possible sequences for each sub study are shown in Table 1 and Table 2

Table 1 Sub Study 1 Treatment Sequences

Sequence	Period 1	Period 2	Preference Questionnaire
A	ELLIPTA	DISKUS + HandiHaler	1
B	DISKUS + HandiHaler	ELLIPTA	2
C	ELLIPTA	DISKUS + HandiHaler	2
D	DISKUS + HandiHaler	ELLIPTA	1

Table 2 Sub Study 2 Treatment Sequence

Sequence	Period 1	Period 2	Preference Questionnaire
E	ELLIPTA	Turbuhaler + HandiHaler	3
F	Turbuhaler + HandiHaler	ELLIPTA	4
G	ELLIPTA	Turbuhaler + HandiHaler	4
H	Turbuhaler + HandiHaler	ELLIPTA	3

Study treatments will be dispensed at the study visit summarized in SOA

7.3. Blinding

This is an open-label study; however, the order of treatment and preference questionnaire answered by a participant will be assigned using an IWRS. The site will contact the IWRS prior to study treatment administration for each participant. The site will record the treatment assignment on the applicable case report form, if required. Potential bias will be reduced by randomising the order of treatment and the preference questionnaire version answered by subjects.

7.4. Preparation/Handling/Storage/Accountability

- The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment. Details of transit and storage conditions for study treatments will be included in the SRM.
- Only participants enrolled in the study may receive study treatment and only authorized site staff may supply study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
- The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
- Further guidance and information for the final disposition of unused study treatment are provided in the Study Reference Manual.
- Under normal conditions of handling and administration, study treatment is not expected to pose significant safety risks to site staff.

7.5. Treatment Compliance

Participants receive study treatment only at the clinical site and they will receive study treatment directly under supervision of the investigator or designee.

The date and time of each dose administered in the clinic will be recorded in the source documents.

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 inform on the subject's inclusion.

This is a single visit study, and the subject should continue to take their usual COPD and other medications through the conduct of the study.

However, any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) 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

There is no active treatment; this is a single visit, placebo only study and participants will not receive any specific post study treatments.

8. DISCONTINUATION CRITERIA

8.1. Discontinuation of Study Treatment

Not applicable as this is a single-visit study with no active treatment; all subjects will receive placebo treatment only.

8.1.1. Liver Chemistry Stopping Criteria

Not applicable as this is a single-visit study with no active treatment; all subjects will receive placebo treatment only. .

8.1.2. QTc Stopping Criteria

Not applicable as this is a single-visit study with no active treatment; all subjects will receive placebo treatment only.

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.
- This is a single visit, placebo only study, if a subjects withdrawals during this single visit there are no assessments that would need to be completed following withdrawal.

8.3. Lost to Follow Up

Not applicable as this is a single visit study.

9. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA.
- 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 study treatment.
- 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 (e.g., to confirm diagnosis of COPD) and obtained before signing of ICF may be utilized for screening provided the procedure met any protocol-specified criteria and was performed within the time frame defined in the SoA.
- Prior to randomisation, at V1, all assessments to confirm inclusion at V0 will be completed. The details of these assessment are provided in the SoA

9.1. Efficacy Assessments

9.1.1. Assessment of Errors in Use of Device

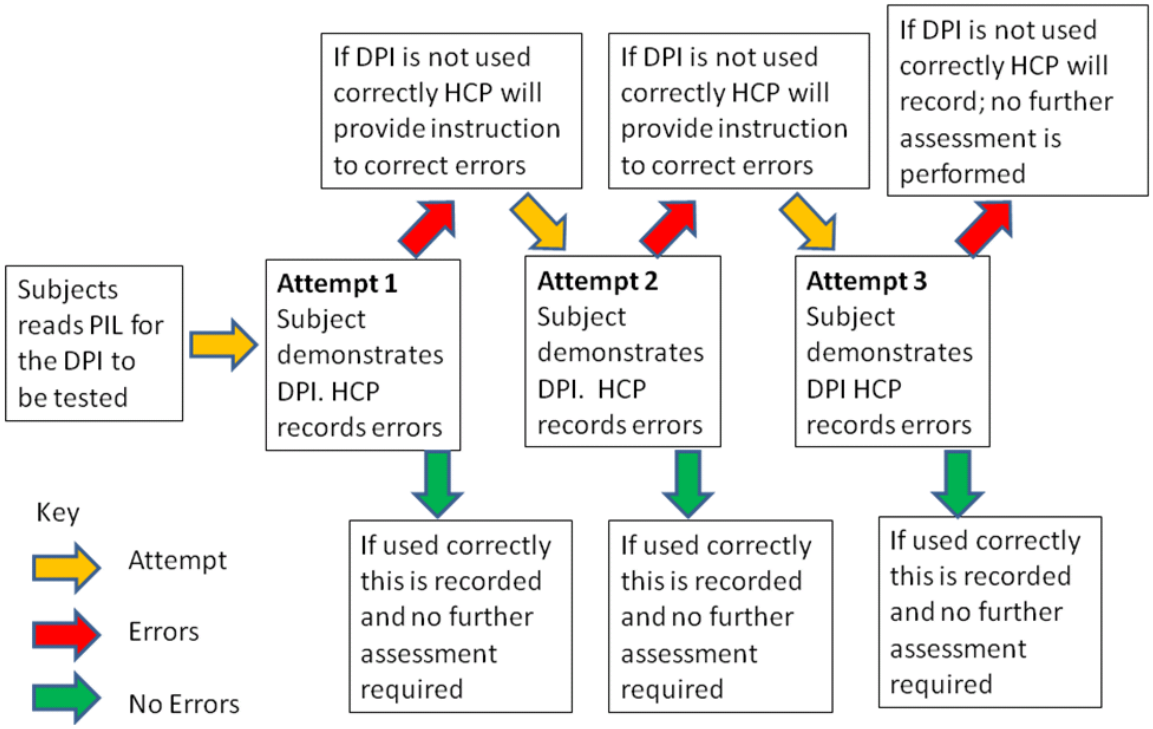
Within each sub-study, subjects will be randomised for the order of treatment. One treatment will require subjects to demonstrate use of a single inhaler (ELLIPTA), while the other treatment will require the subject to demonstrate use of 2 inhalers (DISKUS-HandiHaler in Sub Study 1 or Turbuhaler-HandiHaler in Sub Study 2).

Subjects will be provided with the relevant section of the PIL, explaining correct use, for each inhaler they are to be tested on. The critical and over all errors per inhaler and how these have been defined are included in Appendix 2.

The errors listed will be in aligned with the correct use information from the respective PILs, in a checklist for each inhaler and these will be provided to HCPs for scoring errors during the study conduct. The checklists will be provided in the Study Reference Manual.

Figure 2 depicts the process flow for assessing inhaler use errors and further details are provided, for each treatment, in Section 9.1.1.1 and Section 9.1.1.2.

Figure 2 Assessment of errors in use for each DPI tested



9.1.1.1. Assessment of ELLIPTA error in use

Subject will be asked to read the patient instruction leaflet for ELLIPTA and then demonstrate ELLIPTA use. Any errors (critical or non-critical) made by the subject while using the ELLIPTA will be recorded by the HCP on the checklist provided. If the subject makes no errors, this will also be recorded by the HCP, and there will be no further assessments. If the subject makes any error in the use of the ELLIPTA, the HCP will provide instruction in the correct use of the ELLIPTA to the subject. The subject will then demonstrate ELLIPTA use again. If the subject makes no errors, this will be recorded by the HCP and there will be no further assessments. If the subject again makes errors in the use of the ELLIPTA any errors will be recorded by the HCP. The HCP will again provide instruction in the correct use for the final time, following which the subject will then demonstrate ELLIPTA use one final time. Any errors made during this demonstration will be recorded. There will be no further assessments. In total, the HCP can provide instruction in the use of the inhaler up to two times.

9.1.1.2. Assessment of DISKUS-HandiHaler in Sub Study 1, or Turbuhaler-HandiHaler in Sub Study 2, for error in use

Subjects will be provided with 2 inhalers and 2 PILs dependent on which sub study they are included in.

Subjects should be tested on each DPI provided consecutively, they will be tested in the following order for each sub study.

- Sub Study 1: DISKUS followed by HandiHaler

- Sub Study 2: Turbuhaler followed by HandiHaler

Subjects will be asked to read the patient instruction leaflet for the first DPI (DISKUS or Turbuhaler) and then demonstrate first DPI use. Any errors (critical or non-critical) made by the subject while using the first DPI will be recorded by the HCP on the checklists provided. If the subject makes no errors, this will also be recorded by the HCP and there will be no further assessment for this first DPI. If the subject makes any error in the use of the first DPI, the HCP will provide instruction in the correct use of the inhaler to the subject. The subject will then demonstrate inhaler use again. If the subject makes no errors, this will also be recorded by the HCP and there will be no further assessments for this DPI. If the subject again makes errors in the use of the DPI, the HCP will record the errors and provide instruction in correct use for the final time. The subject will then demonstrate use of first DPI for one final time. Any errors or correct use after this demonstration will be recorded, and there will be no further assessments for this DPI. In total, the HCP can provide instruction in the use of the first DPI up to two times.

This assessment will then be repeated with HandiHaler.

9.1.1.3. Time Taken to Use Device

Time taken to use the device will be recorded as follows:

- T1: the time from when the subject starts to read the patient instruction leaflet until they have completed demonstration of device use (i.e., with no investigator support).
- T2: the time from when the HCP starts to instruct subject until correct use is demonstrated (up to a maximum of two attempts only).
- T1+T2: the time from when the subject starts to read the patient information leaflet until correct use is demonstrated (up to a maximum of three attempts, once after reading the PIL and following instruction, up to 2 times, by HCP).

The HCP will start recording (clock start) the time from when T1 begins and will stop when device use has been demonstrated. The clock re-starts when T2 begins and stops once correct use has been demonstrated, or when three failed attempts have been made. Note: T2 includes the time used by the investigator for re-instructing the Subjects throughout.

For subjects who demonstrate correct inhaler use after reading the PIL, T2 will be 0.

9.1.2. Assessments of Preference

After completing the errors in use assessment for both treatments, the HCP will ask the subject questions from the assigned preference questionnaire. The wording of the questionnaires is included in Appendix 3.

9.2. Adverse Events

The definitions of an AE or SAE can be found in Appendix 5.

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 will be collected from consent until the time point specified in the SoA (Section 2).
- All AEs will be collected from randomisation until the time point specified in the SoA (Section 2).
- Medical occurrences that begin before the start of study treatment but after 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 5. 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 5.

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, stabilized, otherwise explained, or the participant is lost to follow-up). Further information on follow-up procedures is given in Appendix 5.

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 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 Utilization and Health Economics

Health Economics/Medical Resource Utilization 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, after a subject has read the patient information leaflet(s) (PIL) for each treatment option tested. This is a superiority study.

There are two sub-studies and these will be analysed separately. There is no overlap of subjects and so these are considered independent. Hence there will be no adjustment for multiplicity.

The primary endpoint is the percentage of subjects making at least one critical error after reading the PIL(s) on Treatment Option 1 compared with each of Treatment Option 2 (Sub-study 1) and Treatment Option 3 (Sub-study 2).

For each sub-study, the null hypotheses are no difference between treatment options:

H_0: $p_1=p_i$; i=2, 3

The alternative hypothesis is that there is a difference between treatment options.

H_A: $p_1 \neq p_i$; i=2,3

10.2. Sample Size Determination

The sample size calculation for each sub-study is based on the primary endpoint, the percentage of subjects making at least one critical error in each device combination (Ellipta or DISKUS - HandiHaler or Turbuhaler - HandiHaler) after reading the patient information leaflet(s).

Based on the results from studies 201301 and 201330, a range of critical error rates (at least one critical error using each device after reading the patient information leaflet) for each of the treatment options (ELLIPTA, DISKUS - HandiHaler and Turbuhaler - HandiHaler) were explored.

Using 10000 simulations, a total of 72 subjects in each sub-study will provide at least 90% power to show a statistically significant difference between the critical error rate of each of the paired treatment options (Sub-study 1: Treatment option 1 vs. Treatment Option 2; Sub-study 2: Treatment option 1 vs. Treatment Option 3) assuming the following true critical error rates.

Treatment Option 1:	**Treatment Option 2:**	**Treatment Option 3:**
ELLIPTA Critical Error Rate	**DISKUS - HandiHaler Critical Error rate**	**Turbuhaler - HandiHaler Critical Error rate**
11%	**>=37%**	**>=37%**
10%	**>=35%**	**>=35%**
9%	**>=34%**	**>=34%**
8%	**>=32%**	**>=32%**
7%	**>=31%**	**>=31%**
6%	**>=29%**	**>=29%**

The error rates for the combined treatment options were based on the studies 201301 and 201330 and a conservative assumption that the critical error rate for the combined treatment was the same as the critical error rate for a single device i.e. subjects who made errors made them on both devices.

Conditional logistic regression and a two-sided 5% significance level were used as the analysis method in the simulations. No withdrawal is expected in this single visit study however up to 80 subjects may be randomised to each sub-study to ensure we have 72 evaluable subjects in each sub-study.

10.3. Populations for Analyses

All analysis will be performed by individual sub-study. Each sub-study data may be analysed when the sub-study has completed and the data have been cleaned. The database will be locked when all of the sub-studies have completed and data are cleaned.

For purposes of analysis, the following populations are defined for each sub-study:

Population	Description
All Subjects Enrolled (ASE)	• All participants who sign the ICF and for whom a record exists in the study database, including screen failures and any subject who was not screened but experienced an SAE between the date of informed consent and the planned date of the Screening visit

Population	Description
Randomised	• All participants who were randomised.
Intent-to-treat (ITT)	• All randomised subjects, excluding those who were randomised in error and made at least one critical error assessment from one treatment option device. A subject who is recorded as a screen or run-in failure and also randomized will be considered to be randomized in error. Any other subject who receives a randomization number will be considered to have been randomized. • Displays will be based on the treatment to which the subject was randomized.
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 subjects making at least one critical error after reading the PIL(s). This endpoint will be analysed using conditional logistic regression with subject as fixed strata, and treatment option and period as fixed effects. The odds ratio, 95% CI and p-value will be presented for the comparison between treatment options. It will be based on a two-sided hypothesis testing approach of superiority.
Secondary	The following endpoints will be analysed in the same way as for the primary endpoint if there are sufficient subjects making errors otherwise the data will be summarised only: • The percentage of subjects making at least one critical error after the first instruction from the HCP • The percentage of subjects making at least one overall error after reading the PIL(s) • The percentage of subjects making at least one overall error after the first instruction from the HCP The number of instructions (0, 1 or 2 times) from the HCP which are needed to demonstrate correct inhaler use will be analysed using the Wilcoxon signed rank test. The total amount of time taken to demonstrate correct inhaler use (T1+T2)

Endpoint	Statistical Analysis Methods
	will be analysed using Kaplan-Meier methods. Treatment preference from questionnaire will be analysed using a Cochran-Mantel-Haelszel test, adjusted for study inhaler use sequence.
Other	Analysis of the following other endpoints will be defined in the Reporting and Analysis Plan. • The percentage of subjects making at least one critical error after the second instruction from the HCP • The percentage of subjects making at least one overall error after the second instruction from the HCP • The amount of time taken to read the patient information leaflet and demonstrate correct inhaler device use (T1) • The amount of time taken to be given instruction by the HCP on use of the inhaler and demonstrate correct inhaler use (T2)

10.4.2. Safety Analyses

All safety analyses will be performed on the Safety 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 subjects 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 AEs, 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

Any other analyses will be described in the reporting and analysis plan

10.4.4. Interim Analyses

No interim analyses are planned.

The protocol consists of two sub-studies to assess the following treatment comparisons: ELLIPTA DPI (treatment option 1) versus the combination of DISKUS-HandiHaler (treatment option 2) in Sub-study 1 and ELLIPTA DPI (treatment option 1) versus the combination of Turbuhaler-HandiHaler (treatment option 3) in Sub-study 2.

Sub-study 1 will report out independently of Sub-study 2.

11. REFERENCES

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12. APPENDICES

12.1. Appendix 1: Abbreviations and Trademarks

Abbreviations

ASE	All Subjects Enrolled
COPD	Chronic Obstructive Pulmonary Disease
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CV	Cardiovascular
DPI	Dry Powder Inhaler
HCP	Healthcare Professional
ICS	Inhaled Corticosteroids
IEC	Independent Ethics Committees
IRB	Institutional Review Boards
ITT	Intent-to-treat
IWRS	Interactive Web Response System
LABA	Long-Acting Beta2-Agonist
LAMA	Long-Acting Anticholinergic
MedRA	Medical Dictionary of Regulatory activities
PIL	Patient Instruction Leaflet
SABA	Short Acting Beta-Adrenergic Agonist
SAE	Serious Adverse Events
SAMA	Short Acting Muscarinic Antagonist
SRM	Study Reference Manual
SUSAR	Suspected Unexpected Serious Adverse Reactions

Trademark Information

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

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

12.2. Appendix 2: Inhaler Specific Errors for the inhalers used in the study

There are no universally agreed checklists that define critical errors and over all 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 patient information leaflet 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 checklist are, therefore, as robust as possible. Furthermore, GSK has used selected sites with trained assessors to ensure as much consistency as possible in the valuation of errors in study subjects.

Checklist of instructions for correct use will be based on the steps listed in the patient information leaflets/package insert for each device. Some of the steps outlined in the patient information leaflets/package inserts require several actions to be identified and checked by the HCP.

Critical Errors are identified in **bold 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.

These errors will be captured in a checklist provided for HCP assessment of DPI use.

DISKUS/ACCUHALER
Failed to open cover
Lever is not pushed back
Shook the device after dose preparation
No exhalation before an inhalation
Exhaled directly into mouthpiece
No seal by the lips round the mouthpiece during the inhalation
Inhalation manoeuvre: - steady - deep
Did not hold breath
Did not close the device (*Note: this is an error but one which does not affect the medication that is inhaled)*
Any other comments: [free text box]

ELLIPTA
Failed to open cover
Shook the device after dose preparation
No exhalation before an inhalation
Exhaled directly into mouthpiece
No seal by the lips round the mouthpiece during the inhalation
Inhalation manoeuvre: - long - steady - deep
Blocked air inlet during inhalation manoeuvre
Did not hold breath
Did not close the device (*Note: this is an error but one which does not affect the medication that is inhaled)*
Any other comments: [free text box]

TURBUHALER
Failed to remove cap
Did not hold device upright (±45% OK) during dose preparation
Base not twisted fully backwards and forwards, no click heard
Device tipped downwards after dose preparation
Shook the device after dose preparation
No exhalation before an inhalation
Exhaled directly into mouthpiece
No seal by the lips round the mouthpiece during the inhalation
Inhalation manoeuvre: - 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
Did not hold breath
Did not close the device (*Note: this is an error but one which does not affect the medication that is inhaled)*
Any other comments: [free text box]

HANDIHALER
Failed to remove capsule
Failed to insert capsule into the chamber
Did not completely close device capsule chamber (heard click when satisfactory)
Did not pierce the capsule *(HCP should check capsule was pierced)*
Shook the device after dose preparation
No exhalation before an inhalation
Exhaled directly into mouthpiece
No seal by the lips round the mouthpiece during the inhalation
Inhalation manoeuvre: - slow - deep
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 a second inhalation
Any other comments: [free text box]

12.3. Appendix 3: Inhaler Preference Questionnaires

Inhaler Preference Questionnaire Version 1

Instructions: Please complete the following questions related to the treatments you used during this study. Check only one response for each question.

1. Which treatment do you prefer based on the number of steps needed to take your COPD medication?

   □ DISKUS and HandiHaler
   □ ELLIPTA
   □ No preference

2. Which treatment do you prefer for taking your COPD medication?

   □ DISKUS and HandiHaler
   □ ELLIPTA
   □ No preference

Inhaler Preference Questionnaire Version 2

Instructions: Please complete the following questions related to the treatments you used during this study. Check only one response for each question.

1. Which treatment do you prefer based on the number of steps needed to take your COPD medication?

   □ ELLIPTA
   □ DISKUS and HandiHaler
   □ No preference

2. Which treatment do you prefer for taking your COPD medication?

   □ ELLIPTA
   □ DISKUS and HandiHaler
   □ No preference

Inhaler Preference Questionnaire Version 3

Instructions: Please complete the following questions related to the treatments you used during this study. Check only one response for each question.

1. Which treatment do you prefer based on the number of steps needed to take your COPD medication?

   □ Turbuhaler and HandiHaler
   □ ELLIPTA
   □ No preference

2. Which treatment do you prefer for taking your COPD medication?

   □ Turbuhaler and HandiHaler
   □ ELLIPTA
   □ No preference

Inhaler Preference Questionnaire Version 4

Instructions: Please complete the following questions related to the treatments you used during this study. Check only one response for each question.

1. Which treatment do you prefer based on the number of steps needed to take your COPD medication?

   □ ELLIPTA
   □ DISKUS and HandiHaler
   □ No preference

2. Which treatment do you prefer for taking your COPD medication?

   □ ELLIPTA
   □ DISKUS and HandiHaler
   □ No preference

12.4. Appendix 4: Study Governance Considerations

Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with:
    - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
    - Applicable ICH Good Clinical Practice (GCP) Guidelines
    - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (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 authorized representative and answer all questions regarding the study.

- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study 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 authorized 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 authorized representative.

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 authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Publication Policy

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

Dissemination of Clinical Study Data

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided

reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.

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

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

Data Quality Assurance

- All 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 authorized 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 after study completion 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

12.5. Appendix 5: 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 <u>Meeting</u> 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 fulfill 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 fulfill the definition of an AE or SAE. Also, "lack of efficacy" or "failure of expected pharmacological action" constitutes an AE or SAE.

Events <u>NOT</u> Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety

assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the 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, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

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

a. Results in death

b. Is life-threatening

The term 'life-threatening' in the definition of 'serious' refers to an event in which the 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 hospitalization or prolongation of existing hospitalization

In general, hospitalization 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 hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

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

d. Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza,

and accidental trauma (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 hospitalization but may jeopardize 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 hospitalization, or development of drug dependency or drug abuse.

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 recognized follow-up period, the investigator will provide GSK with a copy of any post-mortem findings including histopathology.

- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to GSK within 24 hours of receipt of the information.

Reporting of SAE to GSK

SAE Reporting to GSK via Electronic Data Collection Tool
• The primary mechanism for reporting SAE to GSK will be the electronic data collection tool. • If the electronic system is unavailable for more than 24 hours, then the site will use the paper SAE data collection tool (see next section). • The site will enter the SAE data into the electronic system as soon as it becomes available. • 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, or a scanned version sent by email, 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.