TITLE PAGE

Division: Worldwide Development

Information Type: Clinical Protocol

<table>
<thead>
<tr>
<th>Title:</th>
<th>An open-label study to evaluate the preference attributes of the ELLIPTA™ dry powder inhaler (DPI) compared to the HandiHaler™ DPI in subjects with Chronic Obstructive Pulmonary Disease (COPD)</th>
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<td>GW685698+GW642444</td>
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<tr>
<td>Development Phase</td>
<td>IV</td>
</tr>
<tr>
<td>Effective Date:</td>
<td>15-DEC-2015</td>
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<td>Author(s):</td>
<td>PPD</td>
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SPONSOR SIGNATORY:

PPD

Steve coe, MD
Vice President, Respiratory Head Unit Physician

Date
15 Dec 2015
# Medical Monitor/SAE Contact Information:

<table>
<thead>
<tr>
<th>Role</th>
<th>Name</th>
<th>Day Time Phone Number and email address</th>
<th>After-hours Phone/Cell/Pager Number</th>
<th>Fax Number</th>
<th>Site Address</th>
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<tr>
<td>Primary Medical Monitor</td>
<td>PPD</td>
<td>PPD</td>
<td>PPD</td>
<td>PPD</td>
<td>GSK 1250 South Collegeville Rd Collegeville, PA 19462</td>
</tr>
<tr>
<td>SAE contact information</td>
<td>PPD</td>
<td>PPD</td>
<td>PPD</td>
<td>PPD</td>
<td>GSK 5 Moore Drive PO Box 13398 RTP, NC 27709-3398</td>
</tr>
<tr>
<td>SAE Coordinator information</td>
<td>PPD</td>
<td>PPD</td>
<td>PPD</td>
<td>PPD</td>
<td>GSK 1250 South Collegeville Rd Collegeville, PA 19462</td>
</tr>
</tbody>
</table>

**Sponsor Legal Registered Address:**

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

In some countries, the clinical trial sponsor may be the local GlaxoSmithKline Affiliate Company (or designee). If applicable, the details of the alternative Sponsor and contact person in the territory will be provided to the relevant regulatory authority as part of the clinical trial application.

Regulatory Agency Identifying Number(s): **IND No:** 077855
INVESTIGATOR PROTOCOL AGREEMENT PAGE

- I confirm agreement to conduct the study in compliance with the protocol.
- I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described study.
- I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that site staff receives the appropriate information throughout the study.

Investigator Name: ______________________________

Investigator Signature _______________________________ Date _______________________________
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1. PROTOCOL SYNOPSIS FOR STUDY 204983

1.1. Rationale

Inhaled medication plays an important role in the treatment of COPD, and the effectiveness of inhaled medications is strongly influenced by the adherence to these medications [Virchow, 2008].

There has been an increased interest in the area of patient preference and satisfaction over the past decade, as preference for a particular medication or inhaler device may be associated with improved adherence with therapeutic regimens [Anderson, 2005; FDA Patient Preference Initiative, 2015; FDA PP Guidance, 2015].

This study is designed to evaluate patient preference of several inhaler-specific attributes individually between the ELLIPTA™ dry powder inhaler (DPI) and the HandiHaler DPI.

1.2. Objective(s)/Endpoint(s)

<table>
<thead>
<tr>
<th>Objectives</th>
<th>Endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary</strong></td>
<td></td>
</tr>
<tr>
<td>• The primary objective of this study is to evaluate whether more subjects with COPD prefer the ELLIPTA inhaler to the HandiHaler based on the number of steps needed to take medication.</td>
<td>• Inhaler preference based on the number of steps needed to take the medication.</td>
</tr>
<tr>
<td><strong>Secondary</strong></td>
<td></td>
</tr>
<tr>
<td>• To evaluate the subject’s preference of these two inhalers based on how easy it was to tell how many doses were left.</td>
<td>• Inhaler preference based on how easy it was to tell how many doses were left.</td>
</tr>
<tr>
<td>• To evaluate the subject’s preference of these two inhalers based on size of the inhaler.</td>
<td>• Inhaler preference based on the size of the inhaler.</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td></td>
</tr>
<tr>
<td>• To evaluate the preference based on the comfort of the mouthpiece.</td>
<td>• Inhaler preference based on the comfort of the mouthpiece.</td>
</tr>
<tr>
<td>• To evaluate Inhaler preference.</td>
<td>• Inhaler preference.</td>
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</table>

1.3. Overall Design

This is a Phase IV multi-center, randomized, open-label, cross-over, placebo study in subjects with COPD to compare preference attributes of two dry powder inhalers, ELLIPTA and HandiHaler. Approximately 211 subjects will be enrolled from investigational sites in the United States.
Eligible subjects will sign the informed consent form (ICF) at Visit 1 and will be assigned a subject number. Subjects are expected to continue their current COPD medication(s) as prescribed. Subjects can continue to follow up with their regular physician for their COPD healthcare during the study.

1.4. **Treatment Arms and Duration**

Subjects who have not used either the ELLIPTA inhaler or the HandiHaler in the past 6 months will be screened to participate in the study. Eligible subjects will be randomized to determine the sequence of using the two inhalers (ELLIPTA and HandiHaler), neither of which contains active treatment.

- One group will be dispensed the ELLIPTA inhaler at Visit 1 to use during the first period (once daily [QD] for 5-9 days) and the HandiHaler at Visit 2 to use during the second period (QD for 5-9 days).
- The other group will be dispensed the HandiHaler inhaler at Visit 1 to use during the first period (QD for 5-9 days) and the ELLIPTA inhaler at Visit 2 to use during the second period (QD for 5-9 days).

Subjects will have an equal chance of being in either of these two groups (1:1 allocation). Subjects will be educated on how to use each inhaler at the time of study inhaler dispensation according to the patient information leaflet provided by GSK. They will be given an opportunity to familiarize themselves with each inhaler and will be asked to demonstrate back correct use. At the end of the second period (Visit 3), they will complete the study by answering 5 questions to assess their preference of device attributes and dosing regimens between the two inhalers. Two inhaler preference questionnaires will be used: these will ask the same questions, but the ordering of the inhalers in the responses is different. The version of the inhaler preference questionnaire will be assigned at randomization.

1.5. **Type and Number of Subjects**

Approximately 234 subjects will be screened to achieve approximately 211 randomised and 200 evaluable subjects for a total of 100 evaluable subjects per treatment order. This study will be conducted in approximately 15 investigational sites in the United States.

If subjects prematurely discontinue the study, additional replacement subjects may be randomised at the discretion of the Sponsor.

1.6. **Analysis**

The percentages of preference for each specific attribute (i.e., preferring ELLIPTA inhaler, preferring Handihaler inhaler, and no preference) will be summarised by study inhaler use sequence, by preference questionnaire version, by the combination of study inhaler use sequence and preference questionnaire version, and overall (including 95% confidence interval [CI]) and listed. The responses for each specific attribute will be analyzed using a Cochran-Mantel-Haenszel test, adjusted for study inhaler use sequence.
and preference questionnaire version. The Cochran-Mantel-Haenszel test serves as a stratified approximation to Prescott’s test, a variation of a one-sample chi-square test that accounts for study inhaler sequence, preference questionnaire version, and subjects who indicate no preference [Prescott, 1981; Senn, 2002]. Homogeneity among preference questionnaire version with respect to preference will be assessed using a Breslow-Day test.

The primary preference measure must achieve statistical significance at $\alpha=0.05$ level in order to evaluate statistical assessments of the secondary measures. The secondary measures will be subject to multiplicity adjustment using Hochberg’s method [Westfall, 1999]. If all primary and secondary preference measures achieve statistical significance, the ‘other’ preference measure based on the comfort of the mouthpiece will be tested for statistical significance. No multiplicity adjustments will be applied for the statistical tests on the ‘other’ endpoint of overall device preference. However unadjusted p-values will be displayed in the statistical outputs for descriptive purposes only.

2. INTRODUCTION

2.1. Study Rationale

Inhaled medication plays an important role in the treatment of COPD, and the effectiveness of inhaled medications is strongly influenced by the adherence to these medications [Virchow, 2008].

There has been an increased interest in the area of patient preference and satisfaction over the past decade, as preference for a particular medication or inhaler device may be associated with improved adherence with therapeutic regimens [Anderson, 2005; FDA Patient Preference Initiative, 2015; FDA PP Guidance, 2015].

This study is designed to evaluate patient preference of several inhaler-specific attributes individually between the ELLIPTA dry powder inhaler (DPI) and the HandiHaler.

2.2. Background

Chronic obstructive pulmonary disease (COPD) has been defined as a preventable and treatable disease with some significant extra pulmonary effects that may contribute to the severity of COPD in individual patients. The pulmonary component of COPD is characterized by airflow limitation that is not fully reversible, which is usually progressive and associated with an abnormal inflammatory response of the lung to noxious particles or gases. COPD is a major cause of poor health, resulting in millions of deaths annually worldwide [GOLD, 2015] and contributing significantly to health care costs and morbidity [Chapman, 2006; Lopez, 2006]. According to the World Health Organization (WHO), COPD was the fifth leading cause of death worldwide in 2002 and is estimated to be the third leading cause by 2030 [WHO, 2012].

Current published guidelines on COPD state that the goals of pharmacologic therapy should be to control symptoms, improve health status and exercise tolerance, and reduce the frequency of COPD exacerbations [GOLD, 2015].
Personalized medicine, which has so far focused on customizing drugs based on genetic variation, may need to be expanded to also account for the tremendous variation in individual preferences and behaviours [Progressions, 2012]. Patients will value interactive relationships with their healthcare providers and products or services that are segmented according to patients’ preferences.

The first-line options in the pharmacological management of COPD are all inhaler-based medicines. Therefore, the choice of inhaler is an important consideration in managing COPD. Patients’ attitudes toward a particular device, for example, are one factor to evaluate when selecting therapy because patients’ attitudes to the device and their experiences in using it can influence adherence to therapy [Hodder, 2009; Barrons, 2011; Anderson, 2005; FDA Patient Preference Initiative, 2015; FDA PP Guidance, 2015]. Bateman also recommended that three factors are considered when selecting inhalation therapy for COPD patients. These are (1) the characteristics of the inhaler, (2) the patient’s knowledge, attitudes, and preference, and (3) the physician’s familiarity with inhalers and their skill in understanding the patient’s needs and preferences [Bateman, 2005]. In addition, less frequent dosing regimens are indicated as one way to improve adherence to COPD therapy [Ágh, 2011; Lareau, 2010].

The ELLIPTA dry powder inhaler was developed for the delivery of inhaled medication in patients with both chronic obstructive pulmonary disease (COPD) and asthma. This inhaler was designed to be easy to use and requires few steps for correct administration. It also has a large dose counter window with easy-to-read numbers. The ELLIPTA has been designed for the delivery of a new once daily (QD) inhaled corticosteroid/long-acting β2 agonist combination, fluticasone furoate/vilanterol trifenate (FF/VI) and of the long-acting muscarinic antagonist/long-acting β2 agonist combination of umeclidinium/vilanterol trifenate.

### 3. OBJECTIVE(S) AND ENDPOINT(S)

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<td>Inhaler preference based on the number of steps needed to take the medication.</td>
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<td>To evaluate the subject’s preference of these two inhalers based on how easy it was to tell how many doses were left.</td>
<td>Inhaler preference based on how easy it was to tell how many doses were left.</td>
</tr>
<tr>
<td>To evaluate the subject’s preference of these two inhalers based on size of the inhaler.</td>
<td>Inhaler preference based on the size of the inhaler.</td>
</tr>
</tbody>
</table>
### 4. STUDY DESIGN

#### 4.1. Overall Design

<table>
<thead>
<tr>
<th>Placebo ELLIPTA</th>
<th>Placebo HandiHaler</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo HandiHaler</td>
<td>Placebo ELLIPTA</td>
</tr>
</tbody>
</table>

**Visit 1**

**Study Period 1**

7 days (+/-2)

**Visit 2**

**Study Period 2**

7 days (+/-2)

**Visit 3**

End of Study Preference Questionnaire

#### 4.2. Treatment Arms and Duration

This is a Phase IV multi-center, randomized, open-label, cross-over, placebo study in subjects with COPD to compare preference attributes of two dry powder inhalers, ELLIPTA and HandiHaler. Approximately 234 subjects will be screened to achieve approximately 211 randomised subjects who are at least 40 years of age with a diagnosis of COPD as defined by the American Thoracic Society/European Respiratory Society [Celli, 2004] receiving COPD therapy and have no experience with either the ELLIPTA inhaler or Handihaler for the previous 6 months will take part in this study. This study will be conducted in the investigational sites in the United States.

Informed consent will be obtained at Screening/Visit 1 (day 1). Following screening/informed consent, subjects meeting all of the inclusion criteria and none of the exclusion criteria will be randomized to one of the following study groups:

- One group will be dispensed the ELLIPTA inhaler at Visit 1 to use during the first period (QD for 5-9 days), and the HandiHaler inhaler at Visit 2 to use during the second period (QD for 5-9 days).

- The other group will be dispensed the HandiHaler inhaler at Visit 1 to use during the first period (QD for 5-9 days), and the ELLIPTA inhaler at Visit 2 to use during the second period (QD for 5-9 days).
Subjects will continue their COPD medication(s) throughout the study after study eligibility. Subjects should continue to follow up with their regular physician for their COPD medical care during the study.

At Visit 2, subjects will return the first study inhaler and receive the second study inhaler. At Visit 3, subjects will return the second study inhaler and complete the inhaler preference questionnaire. The version of the inhaler preference questionnaire the subject will complete will be assigned at randomization.

4.3. Type and Number of Subjects

Approximately 234 subjects will be screened to achieve approximately 211 randomised and 200 evaluable subjects for a total of 100 evaluable subjects per treatment order. This study will be conducted in approximately 15 investigational sites in the United States.

If subjects prematurely discontinue the study, additional replacement subjects may be randomised at the discretion of the Sponsor.

4.4. Design Justification

The current study offers a design with an aim of assessing inhaler preference in subjects with a diagnosis of COPD. Subjects will have no experience with the ELLIPTA inhaler or the HandiHaler within six months of Visit 1. Subjects will be educated on the correct use of their inhaler (with no active medication) during Visit 1 for their first randomized inhaler and at Visit 2 for their second randomized inhaler. Subjects will continue with their usual daily maintenance COPD medication(s) throughout the study.

Inactive treatment was chosen to avoid the potential bias of clinical improvement on subjects’ attitudes and perceptions (i.e., a subject clinically improves on treatment and feels better and thus prefers that specific inhaler). Adding placebo inhalers to the subject’s existing COPD therapy also avoids the need for wash-in/-out periods and 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.

4.5. Dose Justification

Dose justification is not required as this is a placebo-only study.

4.6. Benefit:Risk Assessment

4.6.1. Risk Assessment

The study involves placebo ELLIPTA inhalers and placebo HandiHalers that do not contain active treatments. The inhalers contain the excipients lactose and lactose blended with magnesium stearate. Excipients of the study inhaler are noted (Section 6.1). 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 5). 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.

During the spirometry testing, subjects may have shortness of breath, coughing, light-headedness or fainting, and/or chest tightness. Subjects experiencing any of these symptoms will receive medical treatment by the study investigator.

<table>
<thead>
<tr>
<th>Potential Risk of Clinical Significance</th>
<th>Summary of Data/Rationale for Risk</th>
<th>Mitigation Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paradoxical bronchospasm, which may occur with an immediate increase in wheezing after inhaling.</td>
<td>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 &lt;1/10,000 including isolated reports.</td>
<td>This should be treated immediately with a fast and shortacting 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.</td>
</tr>
<tr>
<td>Allergic reaction due to hypersensitivity to placebo excipients.</td>
<td>The inhalers contain the excipients lactose and lactose blended with magnesium stearate. There are known allergies to these ingredients.</td>
<td>Subjects with a known hypersensitivity to any of the excipients or a severe milk protein allergy are excluded from the study.</td>
</tr>
<tr>
<td>Shortness of breath, coughing, light-headedness or fainting induced from spirometry testing.</td>
<td>Spirometry testing involves deep breaths with forceful exhalations that can induce the named symptoms.</td>
<td>Subjects experiencing any of these symptoms will receive medical treatment by the study investigator.</td>
</tr>
</tbody>
</table>

4.6.2. **Benefit Assessment**

Subjects will not have direct benefit from participating in the study. Study procedures include physical examination, vital signs, and assessment of adverse events.

4.6.3. **Overall Benefit:Risk Conclusion**

As this is a placebo study, no benefit to the subject, in regards to their COPD is expected. No active treatment is used except for the daily prescribed therapy which an eligible subject should continue. The study activities have negligible risks (e.g. if subjects are hypersensitive to the excipients in the placebo inhaler); however these risks are mitigated by means of the exclusion criteria, which do not allow such subjects from entering the study.
5. SELECTION OF STUDY POPULATION AND WITHDRAWAL CRITERIA

Deviations from inclusion and exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

5.1. Inclusion Criteria

A subject will be eligible for inclusion in this study only if all of the following criteria apply:

<table>
<thead>
<tr>
<th>AGE</th>
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<tbody>
<tr>
<td>1. ≥40 years of age at Visit 1</td>
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<table>
<thead>
<tr>
<th>TYPE OF SUBJECT AND DIAGNOSIS INCLUDING DISEASE SEVERITY</th>
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<tr>
<td>2. <strong>Diagnosis</strong> of COPD with a documented history of COPD for at least 6 months, in accordance with the definition by the American Thoracic Society/European Respiratory Society [Celli, 2004].</td>
</tr>
<tr>
<td>3. <strong>Severity of Disease</strong>: Post albuterol/salbutamol FEV₁/FVC ratio &lt;0.70 and FEV₁ ≤70% of predicted obtained within two years of Visit 1.</td>
</tr>
<tr>
<td>4. <strong>Smoking History</strong>: Current or former (defined as subjects who have quit smoking for at least 3 months prior to Screening/Visit 1) cigarette smokers with a &gt;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)].</td>
</tr>
<tr>
<td>5. <strong>Current COPD Therapy</strong>:</td>
</tr>
<tr>
<td>a. Currently receiving maintenance therapy with one or more long-acting bronchodilators, such as a long-acting muscarinic antagonist (LAMA; also known as a long-acting anti-cholinergic), long-acting beta₂-agonist (LABA), or inhaled corticosteroid (ICS)/LABA combination for the treatment of COPD. 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) or short acting muscarinic antagonist (SAMA) for rescue use.</td>
</tr>
<tr>
<td>b. Has been on current maintenance COPD treatment for at least 4 weeks prior to Screening/Visit 1 and evaluated as unlikely to change COPD treatment within 4 weeks of Visit 1.</td>
</tr>
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SEX
6. Males or
7. Females who are not pregnant or not planning a pregnancy during the study or not lactating

INFORMED CONSENT
8. Capable of giving signed informed consent as described in Section 10.2, which includes compliance with the requirements and restrictions listed in the consent form and in this protocol.
9. Subject understands and is willing, able, and likely to comply with study procedures and restrictions.
10. Subject must be able to read, comprehend, and record information in English.

5.2. Exclusion Criteria

A subject will not be eligible for inclusion in this 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.

2. Recent experience with the ELLIPTA inhaler: Subjects who used any ELLIPTA inhaler (e.g., BREO ELLIPTA, ANORO ELLIPTA, ARNUITY ELLIPTA, INCRUSE ELLIPTA, participated in a clinical study of GW685698, GW642444, GSK573719 [fluticasone furoate, vilanterol, umeclidinium bromide], or any combination of them, or placebo in an ELLIPTA inhaler) within 6 months (i.e., 180 days) prior to Visit 1.

3. Recent experience with the Handihaler inhaler: Subjects who used any Handihaler inhaler (e.g. Spiriva Handihaler, participated in a clinical study of tiotropium, or placebo HandiHaler) within 6 months (i.e., 180 days) prior to Visit 1.

4. Poorly controlled COPD: Subjects with symptoms of poorly controlled COPD such as:
   a. Acute worsening of COPD that is managed by the subject with corticosteroids or antibiotics or that requires treatment prescribed by a physician, in the 4 weeks prior to Visit 1.
b. Hospitalization due to acute worsening of COPD within 4 weeks of Visit 1

c. Use of a total of 8 puffs/day or more of short-acting symptom relief medications such as albuterol and ipratropium for 2 consecutive days or any 3 days within 7 days immediately preceding Visit 1.

d. Changes in COPD symptoms and signs, suggesting worsening COPD health status at Visit 1.

5. Other Disease Abnormalities:

a. Subjects with suspected or evidence of oropharyngeal candidiasis.

b. Historical or current evidence of clinically significant or rapidly progressing or unstable cardiovascular, neurological, renal, hepatic, immunological, endocrine (including uncontrolled diabetes or thyroid disease) or haematological abnormalities that are uncontrolled. Significant is defined as any disease that, in the opinion of the investigator, would put the safety of the subject at risk through participation, or which would affect the analysis if the disease/condition exacerbated during the study.

c. Subjects with a history of psychiatric disease, intellectual deficiency, poor motivation or other conditions that will limit the validity of informed consent to participate in the study

6. Compliance: Subjects at risk of non-compliance, or unable to comply with the study procedures, or unable to continue their current COPD medications.

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**RELEVANT HABITS**

7. **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

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**CONTRAINDICATIONS**

8. **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.

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**DIAGNOSTIC ASSESSMENTS AND OTHER CRITERIA**

9. **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
10. Affiliation with Investigator’s Site: A subject will not be eligible for this study if he/she is an immediate family member of the participating investigator, sub-investigator, study coordinator, or employee of the participating investigator.

5.3. Screening/Baseline/Run-in Failures

Screen failures are defined as subjects who consent to participate in the clinical trial but are never subsequently randomized. In order to ensure transparent reporting of screen failure subjects, meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, and respond to queries from Regulatory authorities, a minimal set of screen failure information is required including Demography, Screen Failure details, Eligibility Criteria, and Serious Adverse Events (see Section 7.4.1.4).

5.4. Withdrawal/Stopping Criteria

Any subject may voluntarily discontinue participation in this study at any time. Further, an investigator may, at his/her discretion, discontinue any subject from participating in the study at any time. All investigators with discontinued subjects from their sites will be required to make every effort to schedule those subjects for an Early Withdrawal Visit as soon as possible. Accordingly, the reasons for each subject’s withdrawal must be recorded in the case report form (CRF) and may include the following: AE, consent withdrawn, lost to follow-up, protocol violation, study closed/terminated, COPD exacerbation, and investigator’s discretion. Specific regards should be given to distinguishing withdrawals due to an AE, COPD exacerbation and protocol violation. The occurrence of a serious adverse event (SAE) that results in withdrawal will be recorded as withdrawal due to “adverse event”. Subjects who are withdrawn from the study may be replaced.

A subject will also be withdrawn from the study if he/she experiences any of the following:

- Subject is not able to demonstrate correct use of the inhalers within three attempts at the dispensation visit.
- COPD exacerbation which requires hospitalization.
- COPD exacerbation which requires emergency treatment, which would in the investigator’s judgement pose continued participation in this study as an unacceptable, risk (i.e. unable to demonstrate correct use), (also see Section 7.4.3 COPD Exacerbations).
- AE/SAE that would, in the investigator’s judgement, make continued participation in the study an unacceptable risk.
- Use of any medication delivered by the ELLIPTA inhaler or HandiHaler (excluding study placebo inhalers).
- Subject reports becoming pregnant during the course of the study.
If a subject is prematurely discontinued from the study, the investigator must make every effort to perform the assessments as specified in the Time and Events at an early withdrawal (EW) visit as soon as possible and then discontinue the subject from the study.

Safety assessments will be completed at the Early Withdrawal Visit; however, inhaler preference questionnaires will not be completed. After completion of the Early Withdrawal Visit, subjects will be discharged from the study.

5.5. Subject and Study Completion

A completed subject is one who has completed all visits of the study.

The end of the study is defined as the last subject’s last visit.

6. STUDY TREATMENT

6.1. Investigational Product and Other Study Treatment

The term ‘study treatment’ is used throughout the protocol to describe any combination of products received by the subject as per the protocol design. Study treatment may therefore refer to the individual study treatments or the combination of those study treatments.
<table>
<thead>
<tr>
<th>Study Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Product name:</strong></td>
</tr>
<tr>
<td><strong>Formulation description:</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Dosage form:</strong></td>
</tr>
<tr>
<td><strong>Unit dose strength(s)/Dosage level(s):</strong></td>
</tr>
<tr>
<td><strong>Route of Administration</strong></td>
</tr>
<tr>
<td><strong>Dosing instructions:</strong></td>
</tr>
<tr>
<td><strong>Physical description:</strong></td>
</tr>
<tr>
<td><strong>Device:</strong></td>
</tr>
<tr>
<td><strong>Method for individualizing dosage:</strong></td>
</tr>
</tbody>
</table>

The ELLIPTA placebo DPI is packaged in a foil over-wrap. The foil overwrap must not be opened immediately prior to use. Once the foil overwrap has been opened the inhaler device has a 30 day in-use shelf life. It should be stored up to 25°C (77°F).

The HandiHaler Placebo will be packed in a carton. Each carton will contain 3 blister strips each containing 5 placebo capsules. Each treatment pack also contains the HandiHaler inhalation device. The HandiHaler inhaler device should be stored up to 30°C (86°F) (Do not freeze).

### 6.2. Study Inhaler Use Sequence and Preference Questionnaire Version Assignment

Subjects will be assigned to a sequence of using the two study inhalers in accordance with the randomization schedule. Once a randomization number has been assigned to a subject, the same number cannot be reassigned to any other subject in the study.

Subjects will be randomized using Registration and Medication Ordering System (RAMOS), an Interactive Voice Response System (IVRS). This is a telephone-based system which will be used by the investigator or designee to register the subject (initially...
at Visit 1, and subsequently at each study visit), randomize the subject to Randomization
Group A, B, C, or D to designate sequence assignment for using the two study inhaler
(Treatment Group 1 or 2 – See Section 4.2 and sequence for preference questionnaire
_Version 1 or Version 2 - See Section 6.3 and Section 12.5).

Eligible subjects will be randomized to receive one of the following 2 possible sequence
of using the two study inhalers (1:1 allocation), and one of the following 2 possible
preference questionnaire versions (1:1 allocation) at Visit 1.

<table>
<thead>
<tr>
<th>Randomization Group</th>
<th>Treatment Group</th>
<th>Sequence of Using the Study Inhalers 1st Period</th>
<th>Sequence of Using the Study Inhalers 2nd Period</th>
<th>Preference Questionnaire Version</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Group 1</td>
<td>ELLIPTA QD</td>
<td>HandiHaler QD</td>
<td>Version 1</td>
</tr>
<tr>
<td>B</td>
<td>Group 1</td>
<td>ELLIPTA QD</td>
<td>HandiHaler QD</td>
<td>Version 2</td>
</tr>
<tr>
<td>C</td>
<td>Group 2</td>
<td>HandiHaler QD</td>
<td>ELLIPTA QD</td>
<td>Version 1</td>
</tr>
<tr>
<td>D</td>
<td>Group 2</td>
<td>HandiHaler QD</td>
<td>ELLIPTA QD</td>
<td>Version 2</td>
</tr>
</tbody>
</table>

6.3. Treatment Assignment

Subjects will be assigned to sequences in accordance with the randomization schedule
generated by Clinical Statistics, prior to the start of the study, using validated internal
software.

6.4. Blinding

This is an open-label study. The subject and the investigator will be able to recognize
study inhaler the subject is receiving. The subject will be informed that the study inhalers
contain no active treatment.

6.5. Packaging and Labeling

The contents of the label will be in accordance with all applicable regulatory
requirements.

6.6. Preparation/Handling/Storage/Accountability

The study inhalers must be stored in a secure area under the appropriate physical
conditions for the product. Access of the study inhalers will be limited to the investigator
or designee. The study inhalers must be dispensed only to subjects enrolled in the study.

No special preparation of study inhaler is required.

- The investigator, institution, or the head of the medical institution (where applicable) is responsible for study inhaler accountability, reconciliation, record
maintenance (i.e. receipt, reconciliation and final disposition records), and
collection of the inhalers at Visit 2 and 3 or Early Withdraw visit.
Further guidance and information for final disposition of unused study inhalers will be provided in the Study Reference Manual (SRM).

6.7. Compliance with Study Treatment Administration

Subject compliance with study inhaler use will be assessed at the beginning and end of each study period based on the dose counter reading on the ELLIPTA inhaler or the number of capsules remaining for the HandiHaler.

6.8. Treatment of Study Treatment Overdose

This is a study using placebo inhalers with no active treatment and therefore management of overdose does not apply.

6.9. Treatment after the End of the Study

Subjects will not receive any additional treatment from GSK after completion of the study because the indication being studied is not life threatening or seriously debilitating and/or other treatment options are available.

The investigator is responsible for ensuring that consideration has been given to the post-study care of the subject’s medical condition, whether or not GSK is providing specific post-study treatment.

6.10. Concomitant Medications and Non-Drug Therapies

Medications (including the current COPD medications) taken during the study (from Visit 1 until Visit 3 or EW) will be recorded in the CRF. In addition, all new medications that are associated with a SAE between Visit 1 and any scheduled follow-up telephone contact, Visit 3, EW are recorded in the CRF.

Selection and modification of the subject’s medications prior to and during study participation is based on the physician’s judgment according to sound medical practice and principles and each subject’s needs. They must not be changed merely for the purpose of enabling the subject’s participation in the study.

6.10.1. Permitted Medications and Non-Drug Therapies

Subjects will continue to use their current maintenance COPD and non-COPD medication(s) throughout the study. All concomitant medications taken during the study and one month prior to the study will be recorded in the eCRF.

6.10.2. Prohibited Medications and Non-Drug Therapies

The use of any of the following therapy is prohibited during the study:

- Any investigational medication taken as part of a different study
• Any medication delivered by the ELLIPTA inhaler or HandiHaler (excluding study placebo study inhalers).

• Any subjects requiring the use of medications to treat their COPD exacerbation outside of those outlined in Section 7.4.3

These restrictions are in addition to the exclusions prior to Visit 1 (Section 5.2).

7. STUDY ASSESSMENTS AND PROCEDURES

Protocol waivers or exemptions are not allowed with the exception of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the Time and Events Table, are essential and required for study conduct.

This section lists the procedures and parameters of each planned study assessment. The exact timing of each assessment is listed in the Time and Events Table Section 7.1.

7.1. Time and Events Table

Table 1 Time and Events Table

<table>
<thead>
<tr>
<th>Procedures</th>
<th>Visit 1 Screen/Randomization</th>
<th>Visit 2 Early Withdrawal</th>
<th>Visit 3 End-of-Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study day – Study Period 1</td>
<td>1</td>
<td>5-9</td>
<td></td>
</tr>
<tr>
<td>Study day – Study Period 2</td>
<td></td>
<td>1</td>
<td>5-9</td>
</tr>
<tr>
<td>Written informed consent</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subject demography</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical/disease history</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Therapy history</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inclusion/exclusion criteria</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spirometry 2, 3</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Health outcome assessments</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preference questions 4</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Safety assessments</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concomitant medication</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Physical examination 3, 5</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vital signs 6</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AEs/SAEs 7</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Dispense subject worksheet 8</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Collect and review subject worksheet</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Study Inhaler</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dispense study inhaler &amp; educate subject on how to use correctly 9</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Collect study inhaler</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Assess study inhaler compliance based on dose counters</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Call into IVRS</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>

1. Subjects will be assigned a subject number at the time when the ICF is signed. The ICF must be signed before any study procedures including drug washout(s). Subjects are expected to continue their current COPD medication(s) except for the restriction prior to spirometry testing at Visit 1.
2. Spirometry testing is done at Visit 1 if documented spirometry measurements that meet the Inclusion Criterion are not available within 24 months preceding Visit 1.
3. Results are recorded in source documents only.
4. Preference questions are completed by a subject at the beginning of Visit 3. Subjects will receive either preference questions Version 1 or Version 2 based on randomization, after using the study inhalers. EW subjects will complete preference questions only if they self-administered at least one dose from each study inhaler.
5. Physician examination includes oropharyngeal examination to exclude subjects with suspected or evidence of oropharyngeal candidiasis. The investigator will evaluate a female subject’s pregnancy status and document in source document during physical examination
6. Vital signs include height, weight, temperature, blood pressure, heart rate, and respiratory rate.
7. Refer to protocol Section 7.4.1.1 for AE/SAE data collection period.
8. Medical Problems/Medications Taken Worksheet - Subjects will record medical problems and medications taken in the worksheet.
9. Subjects will receive one study inhaler at Visit 1 and the other study inhaler at Visit 2 in the order which they were randomized to (Group 1 or Group 2). Subjects will take the first dose for each inhaler at the investigator site after being educated on how to use it correctly.

7.2. Screening and Critical Baseline Assessments

The following will be recorded in the electronic case report form (eCRF) at Visit 1:

- Subject number
- Demographic information including race, gender, ethnic origin, year of birth, height, and weight
- Medical history including COPD (comprised of date of diagnosis and COPD type [emphysema and/or chronic bronchitis], smoking history, COPD exacerbation history, smoking status and previous and/or current medical conditions)
- COPD (within 30 days of Visit 1) and non-COPD concurrent medications
- Concurrent medical conditions
- Details of COPD exacerbation (yes/no status), if applicable
- Inclusion/Exclusion criteria assessment
- Vital signs (including pulse rate and blood pressure measurements)
- SAE assessment (if related to study participation)

7.2.1. Screen Failures

A subject will be assigned a subject number at the time when the ICF is signed.

The following information will be quality-checked and reported on subjects who are screen failures:

- Date of ICF signature
- Demographic information including race, gender, ethnic origin, and date of birth
- Date of screening
- Details of current COPD medications within 30 days of Visit 1
- Details of COPD exacerbation (yes/no status), if applicable
- Screen failure reason: Inclusion/exclusion criteria that was not met
- SAE information, if applicable, only for an SAE considered as related to study participation (e.g., protocol mandated procedures or change in existing therapy)
- Subject number
- Investigator signature page

Subjects who are screen failures cannot be re-screened.

7.3. Premature Discontinuation/Early Withdrawal

Subjects will be considered to have completed the study upon completion of Visit 3 (final clinic visit).

The definition of an early subject withdrawal from the study will be any subject who participates in the study treatment and, for any reason, is withdrawn prior to completion of the Visit 3 procedures.

A subject may voluntarily discontinue participation in the study at any time. The investigator may also, at his/her discretion; discontinue the subject from participating in the study at any time. In addition, the investigator must make every effort to have the subject return to the clinic as soon as possible after discontinuation of study inhaler for an Early Withdrawal Visit. The following evaluations and procedures should be completed and recorded in the eCRF as required:

- Concomitant medication assessment
- Adverse event assessment
- COPD exacerbation assessment
- Collect used study inhaler
- Assess compliance with inhaler

7.4. Safety

Planned time points for all safety assessments are listed in the Time and Events Table (Section 7.1).

7.4.1. Adverse Events (AE) and Serious Adverse Events (SAEs)

The definitions of an AE or SAE can be found in Appendix 2.

The investigator and their designees are responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE.

7.4.1.1. Time period and Frequency for collecting AE and SAE information

- Any SAEs assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK
product will be recorded from the time a subject consents to participate in the study up to and including any follow-up contact.

- AEs will be collected from the start of Study Treatment until the follow-up contact (see Section 7.4.1.3), at the timepoints specified in the Time and Events Table (Section 7.1).
- Medical occurrences that begin prior to the start of study treatment but after obtaining informed consent may be recorded on the Medical History/Current Medical Conditions section of the CRF.
- All SAEs will be recorded and reported to GSK within 24 hours, as indicated in Appendix 2.
- Investigators are not obligated to actively seek AEs or SAEs in former study subjects. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably related to the study treatment or study participation, the investigator must promptly notify GSK.

NOTE: The method of recording, evaluating and assessing causality of AEs and SAEs plus procedures for completing and transmitting SAE reports to GSK are provided in Appendix 2.

7.4.1.2. Method of Detecting AEs and SAEs

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

- “How are you feeling?”
- “Have you had any (other) medical problems since your last visit/contact?”
- “Have you taken any new medicines, other than those provided in this study, since your last visit/contact?”

7.4.1.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs, and non-serious AEs of special interest (as defined in Section 4.6.1) will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up (as defined in Section 5.4). Further information on follow-up procedures is given in Section 12.2.

7.4.1.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to GSK of SAEs related to study treatment (even for non-interventional post-marketing studies) is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a product under clinical investigation are met.
GSK has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. GSK will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and investigators.

Investigator safety reports are prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and GSK policy and are forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a SAE(s) or other specific safety information (e.g., summary or listing of SAEs) from GSK will file it with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

7.4.2. Cardiovascular and Death Events

For any cardiovascular events detailed in Section 12.2 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 for 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.

7.4.3. COPD Exacerbations

A COPD exacerbation is defined as acute worsening of symptoms of COPD requiring the use of antibiotics, systemic corticosteroids or oral corticosteroids (tablets, suspension, or injection), and/or emergency treatment or hospitalization.

Subjects who experience a COPD exacerbation during the treatment period may remain in the study and should continue to use their study inhaler if possible. Treatment of COPD exacerbations with short-term antibiotics and systemic corticosteroids (less than or equal to 14 days) is permitted.

For worsening COPD symptoms/exacerbations requiring:

- Emergency treatment: the decision whether such a subject would continue in the study or be withdrawn would be determined per investigator discretion. The Study Medical Monitor would be available to discuss any related questions with the investigator.
- Hospitalization: such a subject should be withdrawn from the study
If a subject experiences a COPD exacerbation, the COPD exacerbation page of the eCRF should be completed. COPD exacerbations should not be recorded as an Adverse Event, unless they meet the definition of a Serious Adverse Event and these SAEs will be recorded on the appropriate CRF section and should be reported to GSK for all subjects.

The time period for collection of COPD exacerbations will begin from Visit 1 and will end when Visit 3/EW visit has been completed.

Signs and symptoms of COPD included on the diary cards will not be considered AEs and will not be recorded in the eCRF.

### 7.4.4. Pregnancy

- Details of all pregnancies in female subjects will be collected after the start of dosing and until end of study.
- If a pregnancy is reported then the investigator should inform GSK within 2 weeks of learning of the pregnancy and be withdrawn from the study.

### 7.5. Health Outcomes

The preference items that will be used in this study were developed using methods applicable to generation of device preference items. The items were developed based on five prior qualitative research studies of Ellipta, including two studies specific to patients with COPD.

The draft item pool included items that had been used in prior studies and were hypothesized to be relevant and appropriate for patients with COPD. In addition, a new item assessing the use of two inhaler devices was included. The item pool was then evaluated and refined through two iterative rounds of interviews conducted with 15 adults with COPD. Inclusion and exclusion criteria were used to select participants that were similar to the intended clinical trial population. The participants were diverse in terms of ethnicity and educational status. During each round of interviews, participants were asked to provide feedback on their interpretation and understanding of the instructions, questions, and response options, as well as on the relevance and importance of the concept captured by each of the items.

Based on the results of the cognitive interviews, the final measure consisted of five total items. Four of these items assessed inhaler characteristics: size, comfort of the mouthpiece, remaining doses and the number of steps for use and one item assesses use of two inhalers. The results of the conducted qualitative research provided evidence that the final measure adequately and appropriately assesses inhaler preference related to the most important attributes from the patient perspective, thus supporting the measure’s content validity. Furthermore, confirmation was obtained that the wording of the instructions, the questions, and their response options were well understood by adults with COPD.

The final device preference items are scored individually and are not designed to be summed as a total preference score. Preference questions will be answered by each subject once, after completing both periods (after experiencing the ELLIPTA inhaler and
the HandiHaler) at Visit 3 or at EW visit (if the subject administered at least one dose from each study inhaler). Subjects will be randomly assigned to one of two versions of questions. The difference between the two versions of questions is the order of response options (Version 1 presents the HandiHaler as the first response option whereas Version 2 presents the ELLIPTA as the first response option). See Appendix 5 for the list of preference questions.

Paper copies of these preference questions will be used for subjects to answer the questions. The site will enter the answers into the CRF.

7.5.1. Health Outcomes Endpoints

Primary Endpoints

Inhaler preference

- Inhaler preference based on the number of steps needed to take the COPD medication

Secondary Endpoints

Inhaler preference

- Inhaler preference based on how easy it was to tell how many doses were left.
- Inhaler preference based on the size of the inhaler

Other Endpoints

Inhaler preference

- Inhaler preference based on the comfort of the mouthpiece
- Inhaler preference

8. DATA MANAGEMENT

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

9.1. Hypotheses

The primary endpoint of the study is the preference of the device-specific attribute based on the number of steps needed to take the COPD medication. The secondary endpoints include the preference of two other device-specific attributes.

The null hypothesis for device preference for a specific attribute is that there is no difference in preference in that attribute for ELLIPTA vs. Handihaler.

The null hypothesis is $H_0: P_{\text{ELLIPTA}} - P_{\text{HANDIHALER}} = 0$ while the alternative hypothesis is $H_1: P_{\text{ELLIPTA}} - P_{\text{HANDIHALER}} \neq 0$, where $P_{\text{ELLIPTA}}$ is the proportion of subjects that prefer a specific attribute for ELLIPTA, and $P_{\text{HANDIHALER}}$ is the proportion of subjects that prefer a specific attribute for Handihaler.

9.2. Sample Size Considerations

9.2.1. Sample Size Assumptions

The required sample size was calculated using 50,000 simulations of the assumed values. A total of 200 evaluable subjects will provide 90% power to detect a preference for ELLIPTA, where at least 48% of subjects prefer ELLIPTA, 28% prefer HandiHaler and 24% have no preference, using a two-sided test with significance level of 0.05. This equates to a difference between ELLIPTA preference and HandiHaler preference of 20 percentage points.

It is estimated that approximately 5% subjects may be randomized but not complete the study. Therefore, it is anticipated that approximately 211 subjects will be randomized to achieve 200 evaluable subjects.

9.2.2. Sample Size Sensitivity

The power to detect preference for ELLIPTA, assuming the number of evaluable subjects remains as total of 200, is shown in Table 2, based on 50,000 simulations per scenario.
### Table 2  Estimated Power for Different Preference Results

<table>
<thead>
<tr>
<th>Ellipta preference %</th>
<th>No preference %</th>
<th>HandiHaler preference %</th>
<th>Ellipta preference % – HandiHaler preference %</th>
<th>Power (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>55</td>
<td>10</td>
<td>35</td>
<td>20</td>
<td>85</td>
</tr>
<tr>
<td>52.5</td>
<td>15</td>
<td>32.5</td>
<td>20</td>
<td>87</td>
</tr>
<tr>
<td>50</td>
<td>20</td>
<td>30</td>
<td>20</td>
<td>89</td>
</tr>
<tr>
<td>45.5</td>
<td>24</td>
<td>30.5</td>
<td>15</td>
<td>69</td>
</tr>
<tr>
<td>48</td>
<td>24</td>
<td>28</td>
<td>20</td>
<td>90</td>
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<td>50.5</td>
<td>24</td>
<td>25.5</td>
<td>25</td>
<td>98</td>
</tr>
<tr>
<td>47.5</td>
<td>25</td>
<td>27.5</td>
<td>20</td>
<td>91</td>
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<tr>
<td>45</td>
<td>30</td>
<td>25</td>
<td>20</td>
<td>93</td>
</tr>
<tr>
<td>42.5</td>
<td>35</td>
<td>22.5</td>
<td>20</td>
<td>94</td>
</tr>
</tbody>
</table>

9.2.3. **Sample Size Re-estimation or Adjustment**

No sample size re-estimation is planned for this study.

9.3. **Data Analysis Considerations**

9.3.1. **Analysis Populations**

Three populations will be defined for the purposes of data analyses.

- **All Subjects Enrolled (ASE) Population:** This population will comprise all subjects who were screened or who were not screened but experienced a SAE that was assessed as related to study participation between the date of informed consent and the planned date of the Screening Visit. This population will be used for the reporting of reasons for screen failure, COPD exacerbations and SAEs for non-randomized subjects.

- **Intent-to-Treat (ITT) Population:** The ITT Population is defined as all subjects who have been randomized and received one dose of at least one study inhaler. The ITT population will form the basis of all summaries of background, demographic and safety data.

- **Modified Intent-to-Treat (MITT) Population:** The MITT Population will comprise all subjects in the ITT Population who completed at least one question from the 5 preference questions. The MITT population will be used in the analyses of inhaler preference endpoints.

9.3.2. **Interim Analysis**

There will be no interim analyses for this study.
9.4. **Key Elements of Analysis Plan**

9.4.1. **Primary, Secondary and Other Inhaler Preference Analyses**

The percentages of preference for each specific attribute (i.e., preferring ELLIPTA inhaler, preferring Handihaler inhaler, and no preference) will be summarised by study inhaler use sequence, by preference questionnaire version, by the combination of study inhaler use sequence and preference questionnaire version, and overall (including 95% confidence interval [CI]) and listed. The responses for each specific attribute will be analyzed using a Cochran-Mantel-Haenszel test, adjusted for study inhaler use sequence and preference questionnaire version. The Cochran-Mantel-Haenszel test serves as a stratified approximation to Prescott’s test, a variation of a one-sample chi-square test that accounts for study inhaler sequence, preference questionnaire version, and subjects who indicate no preference [Prescott, 1981; Senn, 2002]. Homogeneity among preference questionnaire version with respect to preference will be assessed using a Breslow-Day test. Results of this test will not be reported on the final data display. Cochran-Mantel-Haenszel test will also be adjusted separately for study inhaler use sequence and preference questionnaire version as well as investigator site as a supplementary analysis.

The primary preference measure must achieve statistical significance at \( \alpha = 0.05 \) level in order to evaluate statistical assessments of the secondary measures. The secondary measures will be subject to multiplicity adjustment using Hochberg’s method [Westfall, 1999]. If all primary and secondary preference measures achieve statistical significance, the ‘other’ preference measure based on the comfort of the mouthpiece will be tested for statistical significance. No multiplicity adjustments will be applied for the statistical tests on the ‘other’ endpoint of overall device preference. However unadjusted p-values will be displayed in the statistical outputs for descriptive purposes only.

10. **STUDY GOVERNANCE CONSIDERATIONS**

10.1. **Posting of Information on Publicly Available Clinical Trial Registers**

Study information from this protocol will be posted on publicly available clinical trial registers before enrollment of subjects begins.

10.2. **Regulatory and Ethical Considerations, Including the Informed Consent Process**

The study will be conducted in accordance with all applicable regulatory requirements, and with GSK policy.

The study will also be conducted in accordance with ICH Good Clinical Practice (GCP), all applicable subject privacy requirements, and the guiding principles of the current version of the Declaration of Helsinki. This includes, but is not limited to, the following:

- IRB/IEC review and favorable opinion/approval of the study protocol and amendments as applicable
• Obtaining signed informed consent
• Investigator reporting requirements (e.g. reporting of AEs/SAEs/protocol deviations to IRB/IEC)
• GSK will provide full details of the above procedures, either verbally, in writing, or both.
• Signed informed consent must be obtained for each subject prior to participation in the study
• The IEC/IRB, and where applicable the regulatory authority, approve the clinical protocol and all optional assessments, including genetic research.
• Optional assessments (including those in a separate protocol and/or under separate informed consent) and the clinical protocol should be concurrently submitted for approval unless regulation requires separate submission.
• Approval of the optional assessments may occur after approval is granted for the clinical protocol where required by regulatory authorities. In this situation, written approval of the clinical protocol should state that approval of optional assessments is being deferred and the study, with the exception of the optional assessments, can be initiated.

10.3. Quality Control (Study Monitoring)

• In accordance with applicable regulations including GCP, and GSK procedures, GSK monitors will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and GSK requirements.
• When reviewing data collection procedures, the discussion will also include identification, agreement and documentation of data items for which the CRF will serve as the source document.

GSK will monitor the study and site activity to verify that the:

• Data are authentic, accurate, and complete.
• Safety and rights of subjects are being protected.
• Study is conducted in accordance with the currently approved protocol and any other study agreements, GCP, and all applicable regulatory requirements.

The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents

10.4. Quality Assurance

• To ensure compliance with GCP and all applicable regulatory requirements, GSK may conduct a quality assurance assessment and/or audit of the site records, and the regulatory agencies may conduct a regulatory inspection at any time during or after completion of the study.
• In the event of an assessment, audit or inspection, the investigator (and institution) must agree to grant the advisor(s), auditor(s) and inspector(s) direct access to all relevant documents and to allocate their time and the time of their staff to discuss the conduct of the study, any findings/relevant issues and to implement any corrective and/or preventative actions to address any findings/issues identified.

10.5. Study and Site Closure

• Upon completion or premature discontinuation of the study, the GSK monitor will conduct site closure activities with the investigator or site staff, as appropriate, in accordance with applicable regulations including GCP, and GSK Standard Operating Procedures.

• GSK reserves the right to temporarily suspend or prematurely discontinue this study at any time for reasons including, but not limited to, safety or ethical issues or severe non-compliance. For multicenter studies, this can occur at one or more or at all sites.

• If GSK determines such action is needed, GSK will discuss the reasons for taking such action with the investigator or the head of the medical institution (where applicable). When feasible, GSK will provide advance notification to the investigator or the head of the medical institution, where applicable, of the impending action.

• If the study is suspended or prematurely discontinued for safety reasons, GSK will promptly inform all investigators, heads of the medical institutions (where applicable) and/or institution(s) conducting the study. GSK will also promptly inform the relevant regulatory authorities of the suspension or premature discontinuation of the study and the reason(s) for the action.

• If required by applicable regulations, the investigator or the head of the medical institution (where applicable) must inform the IRB/IEC promptly and provide the reason for the suspension or premature discontinuation.

10.6. Records Retention

• Following closure of the study, the investigator or the head of the medical institution (where applicable) must maintain all site study records (except for those required by local regulations to be maintained elsewhere), in a safe and secure location.

• The records must be maintained to allow easy and timely retrieval, when needed (e.g., for a GSK audit or regulatory inspection) and must be available for review in conjunction with assessment of the facility, supporting systems, and relevant site staff.

• Where permitted by local laws/regulations or institutional policy, some or all of these records can be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken.
• The investigator must ensure that all reproductions are legible and are a true and accurate copy of the original and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the investigator must ensure there is an acceptable back-up of these reproductions and that an acceptable quality control process exists for making these reproductions.

• GSK will inform the investigator of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to that site for the study, as dictated by any institutional requirements or local laws or regulations, GSK standards/procedures, and/or institutional requirements.

• The investigator must notify GSK of any changes in the archival arrangements, including, but not limited to, archival at an off-site facility or transfer of ownership of the records in the event the investigator is no longer associated with the site.

10.7. Provision of Study Results to Investigators, Posting of Information on Publically Available Clinical Trials Registers and Publication

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.

A manuscript will be progressed for publication in the scientific literature if the results provide important scientific or medical knowledge.
11. REFERENCES


12. APPENDICES

12.1. Appendix 1 Abbreviations and Trademarks

12.1.1. Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
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<tbody>
<tr>
<td>AE</td>
<td>Adverse Event</td>
</tr>
<tr>
<td>ASE</td>
<td>All Subjects Enrolled</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence Interval</td>
</tr>
<tr>
<td>COPD</td>
<td>Chronic Obstructive Pulmonary Disease</td>
</tr>
<tr>
<td>CRF</td>
<td>Case Report Form</td>
</tr>
<tr>
<td>CV</td>
<td>Cardiovascular</td>
</tr>
<tr>
<td>DPI</td>
<td>Dry Powder Inhaler</td>
</tr>
<tr>
<td>eCRF</td>
<td>Electronic Case Report Form</td>
</tr>
<tr>
<td>EW</td>
<td>Early Withdrawal</td>
</tr>
<tr>
<td>GSK</td>
<td>GlaxoSmithKline</td>
</tr>
<tr>
<td>ICF</td>
<td>Informed Consent Form</td>
</tr>
<tr>
<td>ITT</td>
<td>Intent to Treat</td>
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<tr>
<td>MedDRA</td>
<td>Medical Dictionary for Regulatory Activities</td>
</tr>
<tr>
<td>MDI</td>
<td>Metered Dose Inhaler</td>
</tr>
<tr>
<td>PP</td>
<td>Patient Preference</td>
</tr>
<tr>
<td>QD</td>
<td><em>quaque die</em>; Once Daily</td>
</tr>
<tr>
<td>SAE</td>
<td>Serious Adverse Event</td>
</tr>
<tr>
<td>MITT</td>
<td>Modified Intent to Treat</td>
</tr>
</tbody>
</table>

12.1.2. Trademark Information

<table>
<thead>
<tr>
<th>Trademarks of the GlaxoSmithKline group of companies</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADVAIR</td>
</tr>
<tr>
<td>ANORO</td>
</tr>
<tr>
<td>ARNUITY</td>
</tr>
<tr>
<td>BREO</td>
</tr>
<tr>
<td>ELLIPTA</td>
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<tr>
<td>INCRUSE</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Trademarks not owned by the GlaxoSmithKline group of companies</th>
</tr>
</thead>
<tbody>
<tr>
<td>HandiHaler</td>
</tr>
<tr>
<td>SAS</td>
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<tr>
<td>Spiriva</td>
</tr>
</tbody>
</table>
12.2. Appendix 2 Definition of and Procedures for Recording, Evaluating, Follow-Up and Reporting of Adverse Events

12.2.1. Definition of Adverse Events

**Adverse Event Definition:**

- An AE is any untoward medical occurrence in a subject or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

- **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 medicinal product.

**Events meeting AE definition include:**

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECGs, radiological scans, vital signs measurements), including those that worsen from baseline, and felt to be clinically significant in the medical and scientific judgement of the investigator.

- 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 prior to the start of the study.

- Signs, symptoms, or the clinical sequelae of a suspected 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 this is an intentional overdose taken with possible suicidal/self-harming intent. This 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. However, the signs and symptoms and/or clinical sequelae resulting from lack of efficacy will be reported if they fulfil the definition of an AE or SAE.

- The signs and symptoms and/or clinical sequelae resulting from lack of efficacy will be reported if they fulfil the definition of an AE or SAE. Also, "lack of efficacy" or "failure of expected pharmacological action" also constitutes an AE or SAE.

**Events NOT meeting definition of an AE include:**

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the
investigator to be more severe than expected for the subject’s condition.

- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject’s condition.
- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is an AE.
- Situations where 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.

12.2.2. Definition of Serious Adverse Events

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

| Serious Adverse Event (SAE) is defined as any untoward medical occurrence that, at any dose: |
| Results in death |
| Is life-threatening |

NOTE:

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

| Requires hospitalization or prolongation of existing hospitalization |
| NOTE: |

- In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician’s office or out-patient setting. Complications that occur during hospitalization are AEs. 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.
Results in disability/incapacity

NOTE:

- The term disability means a substantial disruption of a person’s ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

Is a congenital anomaly/birth defect

Other situations:

- Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious.
- Examples of such events are 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.

Is associated with liver injury and impaired liver function defined as:

- ALT ≥ 3xULN and total bilirubin* ≥ 2xULN (>35% direct), or
- ALT ≥ 3xULN and INR** > 1.5.

* Serum bilirubin fractionation should be performed if testing is available; if unavailable, measure urinary bilirubin via dipstick. If fractionation is unavailable and ALT ≥ 3xULN and total bilirubin ≥ 2xULN, then the event is still to be reported as an SAE.

** INR testing not required per protocol and the threshold value does not apply to subjects receiving anticoagulants. If INR measurement is obtained, the value is to be recorded on the SAE form.

12.2.3. Definition of Cardiovascular Events

Cardiovascular Events (CV) Definition:

Investigators will be required to fill out the specific CV event page of the CRF for the following AEs and SAEs:

- Myocardial infarction/unstable angina
- Congestive heart failure
• Arrhythmias
• Valvulopathy
• Pulmonary hypertension
• Cerebrovascular events/stroke and transient ischemic attack
• Peripheral arterial thromboembolism
• Deep venous thrombosis/pulmonary embolism
• Revascularization

### 12.2.4. Recording of AEs and SAEs

**AEs and SAE Recording:**

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) relative to the event.
- The investigator will then record all relevant information regarding an AE/SAE in the CRF
- It is **not** acceptable for the investigator to send photocopies of the subject’s medical records to GSK in lieu of completion of the GSK, AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by GSK. In this instance, all subject identifiers, with the exception of the subject number, will be blinded on the copies of the medical records prior to submission to GSK.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis will be documented as the AE/SAE and not the individual signs/symptoms.
- Subject-completed Value Evidence and Outcomes questionnaires and the collection of AE data are independent components of the study.
- Responses to each question in the Value Evidence and Outcomes questionnaire will be treated in accordance with standard scoring and statistical procedures detailed by the scale’s developer.
- The use of a single question from a multidimensional health survey to designate a cause-effect relationship to an AE is inappropriate.

### 12.2.5. Evaluating AEs and SAEs

**Assessment of Intensity**

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

- **Mild**: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
- **Moderate**: An event that is sufficiently discomforting to interfere with normal everyday activities.
- **Severe**: An event that prevents normal everyday activities. An AE that is assessed as severe will not be confused with an SAE. Severity is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.
- An event is defined as ‘serious’ when it meets at least one of the pre-defined outcomes as described in the definition of an SAE.

### Assessment of Causality

- The investigator is obligated to assess the relationship between study treatment and the occurrence of each AE/SAE.
- A "reasonable possibility" is meant to convey that there are facts/evidence 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 natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the study treatment will be considered and investigated.
- The investigator will also consult the Investigator Brochure (IB) and/or Product Information, for marketed products, in the determination of 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 when 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 prior to the initial transmission of the SAE data to GSK.**
- The investigator may change his/her opinion of causality in light of follow-up information, amending the SAE data collection tool accordingly.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

### Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as may be indicated or as requested by GSK to
elucidate as fully as possible the nature and/or causality of the AE or SAE.

- The investigator is obligated to assist. This may include additional laboratory tests or investigations, histopathological examinations or consultation with other health care professionals.
- If a subject dies during participation in the study, 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 the designated reporting time frames.

### 12.2.6. Reporting of SAEs to GSK

<table>
<thead>
<tr>
<th>SAE reporting to GSK via electronic data collection tool</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Primary mechanism for reporting SAEs to GSK will be the electronic data collection tool</td>
</tr>
<tr>
<td>• If the electronic system is unavailable for greater than 24 hours, the site will use the paper SAE data collection tool and fax it to the SAE coordinator.</td>
</tr>
<tr>
<td>• Site will enter the serious adverse event data into the electronic system as soon as it becomes available.</td>
</tr>
<tr>
<td>• The investigator will be required to confirm review of the SAE causality by ticking the ‘reviewed’ box at the bottom of the eCRF page within 72 hours of submission of the SAE.</td>
</tr>
<tr>
<td>• After the study is completed at a given site, the electronic data collection tool (e.g., InForm system) will be taken off-line to prevent the entry of new data or changes to existing data</td>
</tr>
<tr>
<td>• If a site receives a report of a new SAE from a study subject or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, the site can report this information on a paper SAE form or to the SAE coordinator by telephone.</td>
</tr>
<tr>
<td>• Contacts for SAE receipt can be found at the beginning of this protocol on the Sponsor/Medical Monitor Contact Information page.</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>SAE reporting to GSK via paper CRF</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the SAE coordinator.</td>
</tr>
</tbody>
</table>
| • 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

- Initial notification via the 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 receipt can be found at this beginning of the protocol on the Sponsor/Medical Monitor Contact Information page.

### SAE reporting to GSK via PIMS

- Facsimile transmission of the following PIMS listings for the corresponding subject is the preferred method to transmit SAE information to the Medical Monitor:
  - SAE listing
  - Demographic listing
  - Study treatment listing
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable, with a copy of all required information sent by overnight mail.
- If the PIMS system is unavailable when the SAE occurs, the site will use the paper SAE form and fax that to the Medical Monitor. The site will enter the SAE data into PIMS as soon as the system becomes available.
12.3. Appendix 3 Collection of Pregnancy Information

12.3.1. Collection of Pregnancy Information

- Investigator will collect pregnancy information on any female subject, who becomes pregnant while participating in this study.
- Information will be recorded on the appropriate form and submitted to GSK within 2 weeks of learning of a subject's pregnancy.
- Subject will be followed to determine the outcome of the pregnancy. The investigator will collect follow up information on mother and infant, which will be forwarded to GSK. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.
- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the investigator, will be reported to GSK as described in Appendix 2. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Any female subject who becomes pregnant while participating will be withdrawn from the study.
12.4. Appendix 4 Country Specific Requirements

No country-specific requirements exist.
12.5. Appendix 5 Inhaler Preference Questionnaires

Inhaler Preference Questionnaire Version 1

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

1. Which inhaler do you prefer based on the number of steps needed to take your COPD medication?
   - HandiHaler
   - Ellipta
   - No preference

2. Which inhaler do you prefer based on how easy it is to tell how many doses you have left?
   - HandiHaler
   - Ellipta
   - No preference

3. Which inhaler do you prefer based on the size of the inhaler?
   - HandiHaler
   - Ellipta
   - No preference

4. Which inhaler do you prefer based on the comfort of the mouthpiece?
   - HandiHaler
   - Ellipta
   - No preference

5. Which inhaler do you prefer for taking your COPD medication?
   - HandiHaler
   - Ellipta
   - No preference
Inhaler Preference Questionnaire Version 2

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

1. Which inhaler do you prefer based on the number of steps needed to take your COPD medication?
   - Ellipta
   - HandiHaler
   - No preference

2. Which inhaler do you prefer based on how easy it is to tell how many doses you have left?
   - Ellipta
   - HandiHaler
   - No preference

3. Which inhaler do you prefer based on the size of the inhaler?
   - Ellipta
   - HandiHaler
   - No preference

4. Which inhaler do you prefer based on the comfort of the mouthpiece?
   - Ellipta
   - HandiHaler
   - No preference

5. Which inhaler do you prefer for taking your COPD medication?
   - Ellipta
   - HandiHaler
   - No preference