TITLE PAGE

Protocol Title: A randomized, open-label, cross-over, placebo inhaler study to evaluate the correct use of ELLIPTA™ dry powder inhaler (DPI) compared to DISKUS™ DPI used in combination with HandiHaler DPI in participants with Chronic Obstructive Pulmonary Disease (COPD).

Protocol Number: 206901/01

Short Title: A clinical study evaluating the correct use of the placebo ELLIPTA dry powder inhaler, in comparison to combinations of placebo dry powder inhalers used to provide fixed-dose combination triple therapy, in participants with COPD.

Compound Number: GSK2834425 (GW685698+GSK573719+GW642444)

Sponsor Name and Legal Registered Address:

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

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

Regulatory Agency Identifying Number(s): IND No. 114873

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SPONSOR SIGNATORY:

PPD

Steve PPD e, MD
Vice President, Respiratory Head Unit Physician

17th May 2017
Date

PPD

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY		
Document		**Date**
Amendment 1	2016N305948_01	17-MAY-2017
Original Protocol	2016N305948_00	27-Feb-2017

Amendment 01 17-MAY-2017

Overall Rationale for the Amendment: Amendment 01 applies to all study centers participating in the 206901 study. Amendment 01 was created to make the following changes: to extend the time a participant must not have used the ELLIPTA, DISKUS, or HandiHaler inhalers prior to Visit 1, to delete one of the withdrawal criteria, to add an exclusion criteria for participants that are only taking a SABA, and to add some clarification to the overall study design. Minor clerical errors are also being corrected.

The specific areas where changes were made to the protocol are listed below.

SECTION # AND NAME	DESCRIPTION OF CHANGE	BRIEF RATIONALE
Section 1 Synopsis (2nd Secondary Objective) and Section 4 Objectives and Endpoints (2nd Secondary Objective)	Original Text: To evaluate the relative proportions of critical errors for COPD participants using an ELLIPTA inhaler compared to those using a DISKUS and HandiHaler to receive their COPD medications. New Text: To evaluate the relative proportions of critical errors for COPD participants using an ELLIPTA inhaler compared to those using a DISKUS + HandiHaler combination to receive their COPD medications.	Updated DISKUS and HandiHaler to DISKUS + HandiHaler combination for consistency.
Section 1 Synopsis (Other Objectives and Endpoints)	Original Text: Not Present New Text: Objective: • To evaluate whether more participants with	Added additional "Other" objective/ endpoint to capture inhaler preference based upon inhaler regimen and number of steps needed to take the

SECTION # AND NAME	DESCRIPTION OF CHANGE	BRIEF RATIONALE
and Section 4 Objectives and Endpoints (Other)	COPD prefer the ELLIPTA inhaler to the DISKUS + HandiHaler combination inhalers regimen based on the number of steps needed to take the medication. Endpoint: • Inhaler regimen preference based on the number of steps needed to take the medication.	medication.
Section 2 Schedule of Activities (SOA) Procedures	Original Text: Assess participant's ability to correctly use the newly dispensed inhaler (following participant reading patient instruction leaflet (PIL) then demonstrating correct use)[5] New Text: Assess participant's ability to correctly use the newly dispensed inhaler (s) (following participant reading patient instruction leaflet (PIL) then demonstrating correct use)[5]	Added (s) to inhaler as there could be the possibility of 2 inhalers being dispensed.
Section 2 Schedule of Activities (SOA) Preference Questionnaire/Visit 3	Original Text: Not Present New Text: Footnote [8] added: Safety assessments will be completed at the Early Withdrawal Visit: however, inhaler preference questionnaires will not be completed.	Added footnote to clarify that Preference Questionnaires will not be completed at the Early Withdrawal Visit as documented in Section 8.2.
Section 5.1 Overall Design (2rd paragraph from the end)	Original Text: Assessment of errors will be conducted by health care professionals trained in the correct inhaler use of three inhalers prior to the start of the study by face-to-face and videotaped instruction training	Deleted face-to face training along with videotaped instruction. Training will be explained in the

SECTION # AND NAME	DESCRIPTION OF CHANGE	BRIEF RATIONALE
	based on the checklist of errors. After randomization, participants will be asked to read the PIL of the first inhaler and then asked to demonstrate correct inhaler use, if they do not demonstrate correct use they will be instructed on correct use by the HCP. A baseline assessment will be conducted when the participant is initially dispensed the inhaler and a second assessment will be conducted after each 28 day dosing period. After demonstrating correct use at Visit 1, the participant will be sent home with the inhaler for the first 28 day treatment period. At Visit 2, two checklists shall be completed, the first checklist will be for the Day 28 assessment of the first inhaler and the second checklist will be another baseline assessment for the second inhaler which has been dispensed. New Text: Assessment of errors will be conducted by health care professionals trained in the correct use of the three inhalers prior to the start of the study based on the checklist of errors. After randomization, participants will be asked to read the PIL of the first inhaler (s) and then asked to demonstrate correct inhaler use, if they do not demonstrate correct use they will be instructed verbally on correct use by the HCP. A baseline assessment will be conducted when the participant is initially dispensed the inhaler (s) and a second assessment will be conducted after each 28 day	SRM. Clarified that this next attempt at training will be given verbally. Added that the PIL will be sent home with the participant. Added (s) to inhaler as there could be the possibility of 2 inhalers being dispensed. Deleted wording

SECTION # AND NAME	DESCRIPTION OF CHANGE	BRIEF RATIONALE
	dosing period. After demonstrating correct use at Visit 1, the participant will be sent home with the inhaler (s) and the PIL for the first 28 day treatment period. At Visit 2, two checklists shall be completed, the first checklist will be for the Day 28 assessment of the first inhaler (s) and the second checklist will be another baseline assessment for the second inhaler (s) dispensed.	
Section 5.1 Overall Design (3rd paragraph from the end)	Original Text: This study offers a design aimed at assessing the correct use and the number of errors made by the participant using each inhaler [after reading the instructions in the patient information leaflet and after healthcare professional (HCP) instruction] and participant preference of the inhalers. New Text: This study offers a design aimed at assessing the correct use and the number of errors made by the participant using each inhaler [after reading the instructions in the patient information leaflet (PIL) and after 28 days of use] and participant preference of the inhalers.	Clarified that the number of errors assessed for each inhaler will be addressed after the participant has read the PIL and after 28 days of use and not after verbal HCP instruction. Added PIL abbreviation for the patient information leaflet.
Section 5.1 Overall Design (last paragraph)	Original Text: Either the ELLIPTA checklist or the DISKUS + HandiHaler combination checklist will be utilized after 28 days of treatment depending on the inhalers returned. Individual checklist assessment of the DISKUS and the HandiHaler will not be assessed. Compliance with returned	Clarified compliance with returned inhalers based upon the dose counters and capsules returned.

SECTION # AND NAME	DESCRIPTION OF CHANGE	BRIEF RATIONALE
	inhalers (based on the dose counter and remaining capsules) will also be assessed by study staff at Visits 2 and 3. A Preference Questionnaire will also be administered and reviewed by study staff at Visit 3 or the last clinic visit. New Text: Either the ELLIPTA checklist or the DISKUS + HandiHaler combination checklist will be utilized after 28 days of treatment depending on the inhaler (s) returned. Individual checklist assessment of the DISKUS and the HandiHaler will not be assessed. Compliance with returned inhalers (based on the dose counter for the ELLIPTA and DISKUS and remaining capsules for the HandiHaler) will also be assessed by study staff at Visits 2 and 3. A Preference Questionnaire will also be administered and reviewed by study staff at Visit 3 or the last clinic visit.	
Section 6.1 Inclusion Criteria and Section 6.2 Exclusion Criteria	Original Text: Bulleted text New Text: Numbered text. Added numbers to formally bulleted text for both Inclusion (1-9) and Exclusion (1-13) Criteria	Added numbers to Inclusion and Exclusion Criteria to help capture potential Screen Failure reason in e-CRF
Section 6.1 Inclusion Criteria (Type of Participant and	Original Text: Participants must have a diagnosis of COPD with a documented history of COPD for at least 6 months, in accordance with the definition by the American Thoracic	Updated the time participants must have a documented history of COPD from 6 to 12

SECTION # AND NAME	DESCRIPTION OF CHANGE	BRIEF RATIONALE
Diagnosis)	Society/European Respiratory Society [Celli, 2004]. New Text: Participants must have a diagnosis of COPD with a documented history of COPD for at least 12 months, in accordance with the definition by the American Thoracic Society/European Respiratory Society [Celli, 2004].	months.
Section 6.1 Inclusion Criteria (COPD Medications)	Original Text: All participants should be able to stay on their prescribed maintenance COPD treatment without change throughout the entire treatment period. New Text: All participants should be able to stay on their prescribed maintenance COPD inhaler (s) without change throughout the entire treatment period.	Clarified that it's the change in inhalers not treatment that should remain stable throughout the treatment period.
Section 6.2 Exclusion Criteria (Prior/Concomitant COPD Therapy)	Original Text: Participants must not have used the ELLIPTA, DISKUS, or HandiHaler inhalers in the 6 months prior to Visit 1. New Text: Participants must not have used the ELLIPTA, DISKUS, or HandiHaler inhalers in the 12 months prior to Visit 1.	Extended the time a participant should be naive to inhaler use prior to Visit 1.
Section 6.2 Exclusion Criteria (Prior/Concomitant COPD Therapy)	Original Text: Not Present New Text: Participants must not be receiving only inhaled short-acting beta-adrenergic agonists, i.e., albuterol as their daily COPD therapy (as needed [prn]	Clarified that participants only taking SABAs are not eligible for the study

SECTION # AND NAME	DESCRIPTION OF CHANGE	BRIEF RATIONALE
	or regularly scheduled).	
Section 6.2 Exclusion Criteria (Other Diseases/Abnormalities)	Original Text: Historical or current evidence of clinically significant or rapidly progressing or unstable cardiovascular, neurological, cardiovascular, neurological, renal, hepatic, immunological, endocrine (including uncontrolled diabetes or thyroid disease) or hematological abnormalities that are uncontrolled. New Text: 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 hematological abnormalities that are uncontrolled.	Deleted duplicate text.
Section 7.7 Concomitant Therapy (First paragraph)	Original Text: A detailed history of previous and ongoing COPD medications, in particular any types of inhalers used to deliver these medications for the previous 6 months from Visit 1, should be recorded in order to determine the participant's inclusion in the study. New Text: A detailed history of previous and ongoing COPD medications, in particular any types of inhalers used to deliver these medications for the previous 12 months from Visit 1, should be recorded in order to determine the participant's inclusion in the study.	Clarified the time for which previous and ongoing COPD medications will be captured prior to Visit 1.

SECTION # AND NAME	DESCRIPTION OF CHANGE	BRIEF RATIONALE
Section 8.2 Withdrawal/Stopping Criteria (first bullet)	Original Text: Participant is not able to demonstrate correct use of the inhalers within two attempts at the dispensation visit. New Text: Text deleted.	Participant will not be withdrawn after two attempts to demonstrate correct use. There are no protocol specific number of attempts to demonstrate correct use. Verbal training should be given until correct use has been demonstrated prior to releasing the participant from the clinic.
Section 9.1.3 Other Endpoints	Original Text: Not Present New Text: Inhaler regimen preference based on the number of steps needed to take the medication	Added additional endpoint to capture inhaler preference based upon inhaler regimen and number of steps needed to take the medication.
Section 10.3 Populations for Analyses (All Subjects Enrolled (ASE) – Description)	Original Text: All participants who sign the ICF and for whom a record exists in the study database, including screen failures and any participant who was not screened but experienced a SAE between the date of informed consent and the planned date of the Screening visit. New Text: All participants who sign the ICF and for whom a record exists in the study database, including screen failures and any participant who was not screened but experienced a SAE between signing the informed consent	Clarified the All Subjects Enrolled Population regarding when SAE information will be collected after signing the ICF and screening.

SECTION # AND NAME	DESCRIPTION OF CHANGE	BRIEF RATIONALE
	and screening.	
Section 10.4.1 Efficacy Analyses (Other Endpoint)	Original Text: Not Present New Text: Inhaler regimen preference based on the number of steps needed to take the medication	Added additional endpoint to capture inhaler preference based upon inhaler regimen and number of steps needed to take the medication.

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1. SYNOPSIS

Protocol Title: A randomized, open-label, cross-over, placebo inhaler study to evaluate the correct use of ELLIPTA dry powder inhaler (DPI) compared to DISKUS DPI used in combination with HandiHaler DPI in participants with Chronic Obstructive Pulmonary Disease (COPD).

Short Title: A clinical study evaluating the correct use of the placebo ELLIPTA dry powder inhaler, in comparison to combinations of placebo dry powder inhalers used to provide fixed-dose combination triple therapy, in participants with COPD.

Rationale: This study is designed to assess the benefits of delivering triple therapy using a single ELLIPTA™ DPI (fixed-dose combination triple therapy) versus delivering triple therapy using two different types of inhalers (open triple therapy) to participants with Chronic Obstructive Pulmonary Disease (COPD). It will assess correct inhaler use when using a single ELLIPTA™ DPI versus using combinations of commercially available and commonly used DPIs: DISKUS™ used in combination with HandiHaler This study will also assess critical errors and preference attributes for fixed-dose combination triple therapy as compared to the open triple therapy.

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

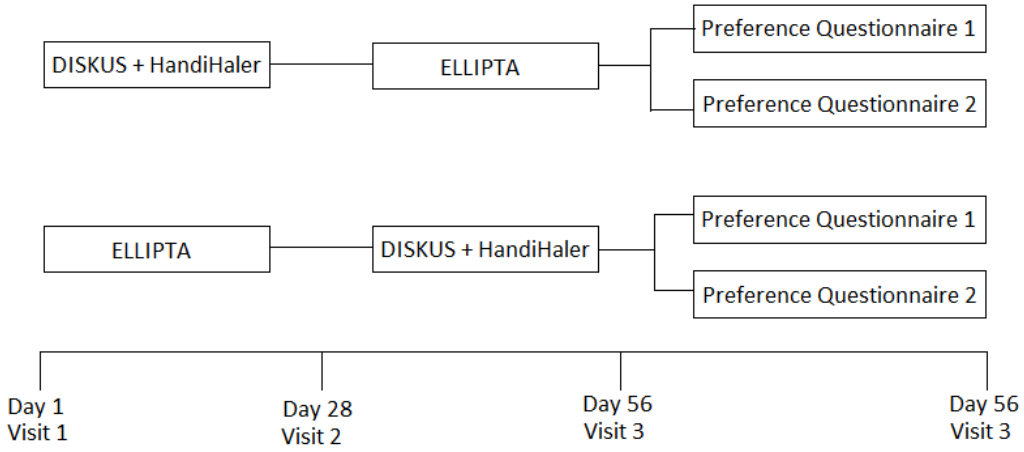
Objective	Endpoint
Primary	
• To evaluate the relative proportions of COPD participants who correctly use an ELLIPTA inhaler compared to those who correctly use a DISKUS + HandiHaler combination to receive their COPD medications.	• Comparison of the correct inhaler use as defined by the percentage of participants with zero errors after 28 days of use.
Secondary	
• To evaluate the overall correct use of an ELLIPTA inhaler compared to the DISKUS + HandiHaler combination in COPD participants.	• Number of errors by type for each inhaler after 28 days of use. • Number and change in errors per participant for each treatment group (V2 and V3) after 28 days of use. • Number and change in errors for each treatment group in participants with one or more errors after 28 days of use.

Objective	Endpoint
• To evaluate the relative proportions of critical errors for COPD participants using an ELLIPTA inhaler compared to those using a DISKUS + HandiHaler combination to receive their COPD medications.	• Comparison of correct inhaler use as defined by the percentage of participants with zero critical errors after 28 days of use.
Other	
• To evaluate the impact of number of COPD maintenance inhalers on study inhaler errors (ELLIPTA and DISKUS + HandiHaler) after 28 days of use.	• Comparison of correct inhalers use as defined by the percentage of participants with zero errors after 28 days of use, including the number of prescribed maintenance inhalers as a covariate.
• To evaluate the number of overall errors made by COPD participants after a participant has read the Patient Instruction Leaflet (PIL(s)).	• The comparison of participants making zero errors after reading the PIL (s) at the start of each treatment period.
• To evaluate the participant's preference of these inhaler options based on how easy it was to tell how many doses were remaining.	• Inhaler preference based on how easy it was to tell how many doses remain.
• To evaluate inhaler preference of taking a regimen that was one inhaler, once a day versus multiple inhalers with a varied dosing regimen.	• Inhaler dosing regimen preference.
• To evaluate whether more participants with COPD prefer the ELLIPTA inhaler to the DISKUS + HandiHaler combination inhalers regimen based on the number of steps needed to take the medication.	• Inhaler regimen preference based on the number of steps needed to take the medication.

Overall Design: This study will be conducted as a randomized, multi-center, open-label, cross-over study comparing placebo ELLIPTA (GSK) with placebo DISKUS (GSK) + HandiHaler [Boehringer Ingelheim (BI)] to assess correct inhaler use. A sufficient number of participants with COPD will be randomized such that 216 participants complete the study. Participants will continue taking their usual COPD maintenance treatment and rescue medications during the entire 56-day study period.

This study has 3 visits and will be completed in approximately 56 days.

Study Schematic:



Number of Participants: Approximately 300 participants with COPD will be screened to ensure approximately 240 participants will be randomized, such that approximately 216 evaluable participants complete the study.

Treatment Groups and Duration: Duration is 3 clinical visits over approximately 56 days.

There is no active treatment and participants will continue to take their own prescribed COPD maintenance and rescue medication during the entire 56-day study period.

The treatment groups are the following:

- At Visit 1 (Day 1) approximately half of the participants will be randomized to receive a placebo ELLIPTA (QD) inhaler for use during the first 28 day treatment period. The remaining half of the participants will receive a placebo DISKUS (BID) + placebo HandiHaler (QD) for use during the first 28 day treatment period.

- At Visit 2 (Day 28) participants previously receiving the placebo DISKUS + placebo HandiHaler inhalers at Visit 1 will receive a placebo ELLIPTA (QD) inhaler for the second 28 day treatment period. Those participants initially receiving a placebo ELLIPTA inhaler at Visit 1 will receive a placebo DISKUS (BID) inhaler + a placebo HandiHaler (QD) inhaler for the second 28 day treatment period.

- At Visit 3 (Day 56) after conducting their last correct inhaler use assessments, the participants will answer either preference questionnaire 1 or preference questionnaire 2 depending on their randomization schedule.

Randomization Group	Sequence of Using the Inhalers		Preference Questionnaire Version
	1st Period	2nd Period	
A	ELLIPTA	DISKUS + HandiHaler	1
B	ELLIPTA	DISKUS + HandiHaler	2
C	DISKUS + HandiHaler	ELLIPTA	1
D	DISKUS + HandiHaler	ELLIPTA	2

Participants will use the assigned placebo inhaler, in each period to match the dose in the prescribing information for the medication that they match. ELLIPTA DPI and HandiHaler DPI will both be taken as one inhalation, once daily. DISKUS DPI will be taken as one inhalation, twice daily.

Study endpoints will be based on evaluation of participant's correct use and preference questionnaires.

The aim of this study is to further evaluate the participant handling errors on ELLIPTA relative to a subset of other available inhalers. The overall correct use of the GSK ELLIPTA relative to two other inhalers, a GSK DISKUS and the Boehringer Ingelheim HandiHaler shall be assessed. Placebo inhalers are used to remove any bias due to treatment effect, avoid the need for wash-in/wash-out periods, and to avoid the need to withhold or discontinue current COPD medications, which may affect the participant's clinical status (improvement or decline) and perceptions.

2. SCHEDULE OF ACTIVITIES (SOA)

Procedures	Visit 0 Screening (Can occur on same day as V1)	Visit 1 Randomization (Can occur on the same day as V0)	Visit 2 Assessment/ Cross-over	Visit 3 Last Visit/ End of Study/Early Withdrawal
Study Day		**1**	**28 (±2)**	**56 (±2)**
Screening/safety assessments				
Written informed consent [1]	**X**			
Participant demography	**X**			
Medical/disease history including chronic obstructive pulmonary disease (COPD) history	**X**			
Therapy history	**X**			
Inclusion/exclusion criteria	**X**			
Concomitant medication	**X**		**X**	**X**
Physical examination[2]		**X**		
Vital signs[2]		**X**		
Adverse events (AEs)/ Serious adverse event (SAEs)[3]		**X**	**X**	**X**
Randomization [4]		**X**		
Study inhaler correct use and preference				
Participant reviews written instructions on the correct use of the newly dispensed inhaler(s)		**X**	**X**	
Assess participant's ability to correctly use the newly dispensed inhaler (s) (following participant reading patient instruction leaflet (PIL) then demonstrating correct use)[5]		**X**	**X**	
Assess participant's ability to correctly use the returned inhaler(s) without instruction[6]			**X**	**X**

Procedures	**Visit 0 Screening (Can occur on same day as V1)**	**Visit 1 Randomization (Can occur on the same day as V0)**	**Visit 2 Assessment/ Cross-over**	**Visit 3 Last Visit/ End of Study/Early Withdrawal**
Study Day		**1**	**28 (±2)**	**56 (±2)**
Assess compliance with the returned study inhaler(s) (based on the dose counter)			**X**	**X**
Preference Questionnaire				**X**[8]
Worksheets and medication				
Dispense study inhaler(s)		**X**	**X**	
Collect study inhaler(s)			**X**	**X**
Dispense Medical Problems/Medications Taken Worksheet [7]		**X**	**X**	
Collect and review Medical Problems/Medications Taken Worksheet [7]			**X**	**X**

1. Participants will be assigned a subject number at the time when the informed consent form (ICF) is signed at Visit 0 or Visit 1. The ICF must be signed before any study procedures are conducted.
2. Results are recorded in the source documents only.
3. Refer to protocol Section 9.2.1.1 for AE/SAE data collection period.
4. Randomisation conducted if the Participant meets all study screening criteria.
5. A health care professional trained on the inhalers will conduct the assessments at Visits 1 and 2, following dispensing of the appropriate inhaler (s) for the next dosing period.
6. A health care professional trained on the inhalers will conduct the assessments of the participant's ability to correctly use the returned inhaler (s) at Visits 2 and 3 following return of the inhaler (s) used for the previous dosing period. This should be completed at Early Withdrawal Visit if a participant has taken one or more doses of the inhaler at home.
7. Participants will record medical problems and medications taken on the Medical Problems/Medications Taken Worksheet between visits.
8. Safety assessments will be completed at the Early Withdrawal Visit: however, inhaler preference questionnaires will not be completed.

3. INTRODUCTION

3.1. Study Rationale

This study is designed to assess the benefits of delivering triple therapy using a single ELLIPTA™ Dry powder inhaler (DPI) (fixed-dose combination closed triple therapy) versus delivering triple therapy using two different types of inhalers (open triple therapy) to participants with Chronic Obstructive Pulmonary Disease (COPD). It will assess correct inhaler use when using a single ELLIPTA™ DPI versus using combinations of commercially available and commonly used DPIs: DISKUS™ used in combination with HandiHaler This study will also assess critical errors and preference attributes for a fixed-dose triple therapy as compared to the multiple inhalers to receive triple therapy.

The cross-over design is chosen to allow participants to serve as their own control in their ability to use both the ELLIPTA and the DISKUS + HandiHaler inhalers. Placebo inhalers will be used to remove any bias due to treatment effect. The comparison of the ELLIPTA to the DISKUS + HandiHaler combination was chosen as this combination of inhalers is the most commonly prescribed triple combination in the United States. The 28-day treatment period is consistent with other ELLIPTA correct use and critical errors studies. Correct use will be evaluated with reference to the steps outlined in the manufacturer's package insert for the inhalers.

3.2. Background

Chronic Obstructive Pulmonary Disease (COPD) is a progressive disease of the airways. Noxious particles or gases lead to a modification in patient'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, 2017]

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 anticholinergics) 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, patients 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 minimize the number of inhalers required would simplify treatment, improve adherence, reduce errors in inhaler use, and potentially lead to better outcomes [GOLD, 2017].

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]. Critical errors made when using inhalers, which significantly reduce or completely inhibit drug delivery, have been identified for various inhalation devices [Van Der Palen, 2016]. Between 36 and 49% of patients with COPD perform critical inhaler errors with currently used inhalers [Van Der Palen, 2016]. For any prescribed inhaler, the patient needs to follow all the steps in the patient information leaflet correctly in order to ensure optimal drug delivery. In this regard, the time needed for a primary care nurse, 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). A fixed-dose 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

This study involves the use of placebo inhalers (placebo ELLIPTA, placebo DISKUS, and placebo HandiHaler) that do not contain active treatments. The inhalers contain the excipients lactose and lactose blended with magnesium stearate. Participants with known hypersensitivity to any of these or severe milk protein allergy that could contraindicate study participation are to be excluded from the study. Participants who meet the inclusion/exclusion criteria will continue their COPD treatment as prescribed by their

healthcare provider during their participation in the study. Participants should continue to follow up with their regular physician for their COPD healthcare during the study.

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 participant'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 excipient lactose and lactose blended with magnesium stearate. There are known allergies to these ingredients.	Participants with a know 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 and other appropriate drugs used in allergic reactions (e.g. glucocorticosteroids, adrenalin) guided by the nature and severity of the allergic reaction. Investigators will be instructed to assess the participant's condition to determine their eligibility to continue in the study and the need for alternative therapy.

3.3.2. Benefit Assessment

As this is a placebo study, no benefit to the participant is expected. No active treatment is being administered. The participant 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, in that no COPD medication, in addition to their already prescribed therapy is provided to participants.

4. OBJECTIVES AND ENDPOINTS

This study will compare correct inhaler use along with critical errors and participant preference of inhalers for fixed-dosed combination triple therapy from a single ELLIPTA inhaler versus triple therapy received from DISKUS in combination with HandiHaler.

Objectives	Endpoints
Primary • To evaluate the relative proportions of COPD participants who correctly use an ELLIPTA inhaler compared to those who correctly use a DISKUS + HandiHaler combination to receive their COPD medications.	• Comparison of correct inhaler use as defined by the percentage of participants with zero errors after 28 days of use.
Secondary • To evaluate the overall correct use of an ELLIPTA inhaler compared to the DISKUS + HandiHaler combination in COPD participants.	• Number of errors by type for each inhaler after 28 days of use. • Number and change in errors per participant for each treatment group (V2 and V3) after 28 days of use. • Number and change in errors for each treatment group in participants with one or more errors after 28 days of use.
• To evaluate the relative proportions of critical errors for COPD	• Comparison of correct inhaler use as defined by the percentage of

Objectives	Endpoints
participants using an ELLIPTA inhaler compared to those using a DISKUS + HandiHaler combination to receive their COPD medications.	participants with zero critical errors after 28 days of use.
Other • To evaluate the impact of number of COPD maintenance inhalers on study inhaler errors (ELLIPTA and DISKUS + HandiHaler) after 28 days of use.	• Comparison of correct inhalers use as defined by the percentage of participants with zero errors after 28 days of use, including the number of prescribed maintenance inhalers as a covariate.
• To evaluate the number of overall errors made by COPD participants after a participant has read the Patient Instruction Leaflet (PIL(s)).	• The comparison of participants making zero errors after reading the PIL (s) at the start of each treatment period.
• To evaluate the participant's preference of these inhaler options based on how easy it was to tell how many doses were remaining.	• Inhaler preference based on how easy it was to tell how many doses remain.
• To evaluate inhaler preference of taking a regimen that was one inhaler, once a day versus multiple inhalers with a varied dosing regimen.	• Inhaler dosing regimen preference.
• To evaluate whether more participants with COPD prefer the ELLIPTA inhaler to the DISKUS + HandiHaler combination inhalers regimen based on the number of steps needed to take the medication.	• Inhaler regimen preference based on the number of steps needed to take the medication.

5. STUDY DESIGN

5.1. Overall Design

This study will be conducted as a randomized, multi-center, open-label, cross-over study comparing placebo ELLIPTA (GSK) with placebo DISKUS (GSK) + HandiHaler [Boehringer Ingelheim (BI)] to assess correct inhaler use.

This study has 3 visits and will be completed in approximately 56 days. COPD diagnosed participants will attend the clinic for the screening visit (V0) and subsequent assessment visit (V1). These visits may occur on the same day.

There is no active treatment and participants will continue to take their own prescribed COPD maintenance medication and rescue medications during the entire 56-day study period.

The treatment groups are the following:

- At Visit 1 (Day 1) half of the participants will be randomized to receive a placebo ELLIPTA (QD) inhaler for use during the first 28 day treatment period. The remaining half of the participants will receive a placebo DISKUS (BID) + placebo HandiHaler (QD) for use during the first 28 day treatment period.

- At Visit 2 (Day 28) participants previously receiving the placebo DISKUS + placebo HandiHaler inhalers at Visit 1 will receive a placebo ELLIPTA (QD) inhaler for the second 28 day treatment period. Those participants initially receiving a placebo ELLIPTA inhaler at Visit 1 will receive a placebo DISKUS (BID) inhaler + a placebo HandiHaler (QD) inhaler for the second 28 day treatment period.

- At Visit 3 (Day 56) after conducting their last correct inhaler use assessments, participants will answer either preference questionnaire 1 or preference questionnaire 2 depending on their randomization schedule.

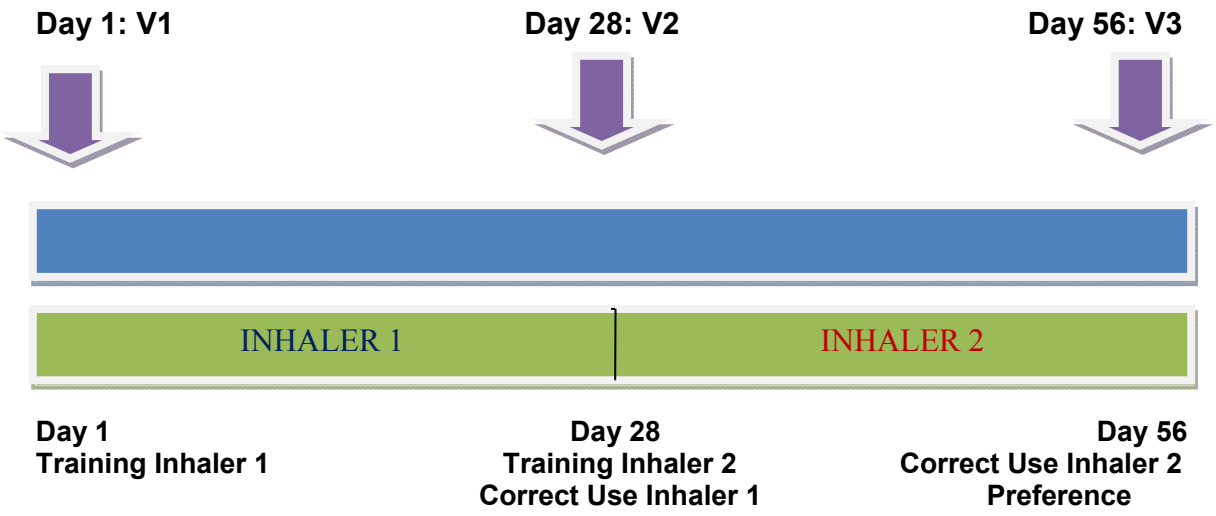
Randomization Group	Sequence of Using the Inhalers		Preference Questionnaire Version
	1st Period	2nd Period	
A	ELLIPTA	DISKUS + HandiHaler	1
B	ELLIPTA	DISKUS + HandiHaler	2
C	DISKUS + HandiHaler	ELLIPTA	1
D	DISKUS + HandiHaler	ELLIPTA	2

This study offers a design aimed at assessing the correct use and the number of errors made by the participant using each inhaler [after reading the instructions in the patient information leaflet (PIL) and after 28 days of use] and participant preference of the inhalers.

Assessment of errors will be conducted by health care professionals trained in the correct inhaler use of the three inhalers prior to the start of the study based on the checklist of errors. After randomization, participants will be asked to read the PIL of the first inhaler (s) and then asked to demonstrate correct inhaler use, if they do not demonstrate correct use they will be instructed verbally on correct use by the HCP. A baseline assessment will be conducted when the participant is initially dispensed the inhaler (s) and a second assessment will be conducted after each 28 day dosing period. After demonstrating correct use at Visit 1, the participant will be sent home with the inhaler and the PIL for the first 28 day treatment period. At Visit 2, two checklists shall be completed, the first checklist will be for the Day 28 assessment of the first inhaler (s) and the second checklist will be another baseline assessment for the second inhaler (s) dispensed.

A health care professional trained on the inhalers will assess the participant's ability to correctly use the returned inhalers. Either the ELLIPTA checklist or the DISKUS + HandiHaler combination checklist will be utilized after 28 days of treatment depending on the inhaler (s) returned. Individual checklist assessment of the DISKUS and the HandiHaler will not be assessed. Compliance with returned inhalers (based on the dose counter for the ELLIPTA and DISKUS and remaining capsules for the HandiHaler) will also be assessed by study staff at Visits 2 and 3. A Preference Questionnaire will also be administered and reviewed by study staff at Visit 3 or the last clinic visit.

Overall Design:



5.2. Number of Participants

Approximately 300 participants with COPD will be screened to achieve 240 randomized and 216 evaluable participants for an estimated total of 108 participants per device sequence (not accounting for questionnaires, see Section 10.2). Questionnaires will then be randomly assigned within each device sequence to give 54 per randomized treatment group.

For the purpose of this study an evaluable participant is defined as a randomized participant who completed error assessments for both randomized treatment groups.

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 study is designed to assess the benefits of delivering triple therapy using a single ELLIPTA DPI (fixed-dose combination triple therapy) versus delivering triple therapy using two different types of inhalers (open triple therapy) to participants with COPD. It will assess correct inhaler use when using a single ELLIPTA DPI versus using combinations of commercially available and commonly used DPIs: DISKUS used in combination with HandiHaler. This study will also assess critical errors (which significantly reduce or completely inhibit drug delivery), non-critical errors, and preference attributes for the fixed-dose combination triple therapy as compared to the open triple therapy.

The cross-over design is chosen to allow participants to serve as their own control in their ability to use both the ELLIPTA and the DISKUS + HandiHaler inhalers. Placebo inhalers are used to remove any bias due to treatment effect. The comparison of the ELLIPTA to the DISKUS + HandiHaler combination was chosen as this combination of inhalers is the most commonly prescribed triple combination in the United States. The 28-day treatment period is consistent with other ELLIPTA correct use and critical errors studies. Correct use will be evaluated with reference to the steps outlined in the manufacturer's package insert for the inhalers.

This study highlights the need for participants using a new inhaler device to have adequate training and assessment at the time when starting a new treatment, for periodic review of training, and also the need to ensure that the proper inhaler is selected for the participant.

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:

Informed Consent

1. Participants must be capable of giving signed informed consent as described in Appendix 3 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

Type of Participant and Diagnosis

2. Participants must have a diagnosis of COPD with a documented history of COPD for at least 12 months, in accordance with the definition by the American Thoracic Society/European Respiratory Society [Celli, 2004].

Age

3. Participants must be 40 years of age inclusive, at the time of signing the informed consent.

Gender

4. Males or Females. Females must not be pregnant or planning pregnancy during the study or not lactating (Appendix 4).

Disease Severity

5. Participants must have a documented post albuterol forced expiratory volume in one second (FEV_1)/ forced vital capacity (FVC) ratio <0.70 and $FEV_1 \leq 70\%$ of predicted obtained within two years of Visit 1.

Smoking History

6. Current or former (defined as participants who have quit smoking for at least 3 months prior to Screening/Visit 1) 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].

COPD Medications

7. All participants should be currently receiving maintenance treatment for COPD for at least 4 weeks prior to Randomization/Visit 1 and evaluated as unlikely to change COPD treatment within 4 weeks of Visit 1.

8. All participants should be able to stay on their prescribed maintenance COPD inhaler (s) without change throughout the entire treatment period.

Other

9. Participants must be able to read, comprehend, and record information in English.

6.2. Exclusion Criteria

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

Medical Conditions

1. Participants must not have a current diagnosis of asthma.

Prior/Concomitant COPD Therapy

2. Participants must not have used the ELLIPTA, DISKUS, or HandiHaler inhalers in the 12 months prior to Visit 1.

3. Participants must not be receiving their current COPD medications with the ELLIPTA, DISKUS, or HandiHaler inhalers.

4. Participants must not be receiving only inhaled short-acting beta-adrenergic agonists, i.e., albuterol as their daily COPD therapy (as needed [prn] or regularly scheduled).

Exacerbations

5. Participants must not have experienced more than 1 COPD exacerbation which required hospitalization in the 12 months prior to Visit 1.

Alcohol and Drug Abuse

6. Participants must not have a known or suspected history of alcohol or drug abuse within the last 2 years.

History of Hypersensitivity

7. Participants must not have a history of hypersensitivity to any component of the study inhalers (e.g. lactose, magnesium stearate). In addition, participants with a history of severe milk protein allergy that, in the opinion of the study physician, contraindicates participation will also be excluded.

Other Respiratory Disorders

8. Participants with other respiratory disorders, including active tuberculosis, active lung cancer, sarcoidosis, lung fibrosis, pulmonary hypertension, or pulmonary disease (including but not confined to asthma, bronchiectasis with the need for

treatment, cystic fibrosis, and bronchopulmonary dysplasia), interstitial lung diseases or other active pulmonary diseases.

Other Diseases/Abnormalities

Participants with:

9. 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 hematological abnormalities that are uncontrolled. Significant is defined as any disease that, in the opinion of the investigator, would put the safety of the participant at risk through participation, or which would affect the analysis if the disease/condition exacerbated during the study.

10. History of psychiatric disease, intellectual impairment, poor motivation or other conditions that will limit the validity of informed consent to participate in the study.

Compliance

11. Participants at risk of non-compliance, or unable to comply with the study procedures, or unable to continue their current medications.

Investigational Product

12. Participants who have received an investigational drug and/or medical device/inhaler within 30 days of entry into this study (Screening/Visit 1), or within five drug half-lives of the investigational drug, whichever is longer.

Affiliation with Investigator's Site

13. Participants 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.

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. 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).

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.

GSK Clinical Trials Supplies will provide the placebo inhalers for use in this study together with placebo capsules where appropriate.

7.1. Treatments Administered

This study does not involve the administration of any new treatments. It assesses the ability of the participants to use the placebo inhalers listed in the table below.

Study Treatment Name:	**ELLIPTA placebo DPI**	**DISKUS placebo DPI**	**HandiHaler DPI and placebo Capsules**
Dosage formulation:	Placebo DPI with two strips with 30 blisters per strip. First strip containing lactose monohydrate and a second strip containing lactose monohydrate blended with magnesium stearate.	Placebo DPI with one blister strip containing lactose monohydrate.	DPI with placebo capsules containing lactose monohydrate.
Unit dose strength(s)/Dosage level(s):	NA	NA	NA
Route of Administration	Oral inhalation (Inhalation Powder).	Oral inhalation (Inhalation Powder).	Oral inhalation (Inhalation Powder).
Dosing instructions:	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.
Manufacturer	GSK	GSK	Boehringer Ingelheim (HandiHaler); GSK/Catalent (placebo capsules)

7.1.1. Medical Devices

There are no medical devices utilized in this study.

7.2. Dose Modification

There are no dose modifications.

7.3. 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 and directions for the IWRS will be provided to each site.

Participants will be assigned in equal numbers to one of the following sequences. The possible sequences are shown below:

Randomization Group	Sequence of Using the Inhalers		Preference Questionnaire Version
	1st Period	2nd Period	
A	ELLIPTA	DISKUS + HandiHaler	1
B	ELLIPTA	DISKUS + HandiHaler	2
C	DISKUS + HandiHaler	ELLIPTA	1
D	DISKUS + HandiHaler	ELLIPTA	2

Study treatments will be dispensed at the study visit summarized in the SoA.

7.4. 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 randomizing the order of treatment and the preference questionnaire version answered by the participants.

7.5. 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.
- Only participants enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and 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.

7.6. Treatment Compliance

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

Compliance will be calculated from the dose counter on returned ELLIPTA and DISKUS inhalers after each 28 day treatment period. HandiHaler compliance will be calculated from the number of capsules supplied and returned after 28 days of use. For compliance calculations, study staff should document the number of remaining doses for each inhaler prior to the participant leaving the clinic.

7.7. 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 12 months from Visit 1, should be recorded in order to determine the participant's inclusion in the study.

Participants should continue to take their usual COPD and other medication through the conduct of the study.

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

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

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

7.8. Treatment after the End of the Study

There is no active treatment, placebo only, and participants will not receive any specific post study treatments.

8. DISCONTINUATION CRITERIA

8.1. Discontinuation of Study Treatment

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

8.1.1. Liver Chemistry Stopping Criteria

Not applicable as there is no active treatment; all participants will receive placebo treatment only.

8.1.2. QTc Stopping Criteria

Not applicable as there is no active treatment; all participants will receive placebo treatment only.

8.1.3. Temporary Discontinuation

Not applicable as there is no active treatment; all participants will receive placebo treatment only.

8.2. Withdrawal/Stopping Criteria

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

A participant will also be withdrawn from the study if they experience any of the following:

- 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).
- 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, DISKUS or HandiHaler inhalers (excluding placebo inhalers).
- Participant reports becoming pregnant during the study.

If a participant is prematurely discontinued from the study, the investigator must make every effort to perform the assessments as specified in the SoA at an early withdrawal (EW) visit as soon as possible and then discontinue the participant 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, participants will be discharged from the study.

8.3. Lost to Follow Up

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

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

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

9. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are 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 the diagnosis of COPD) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and was performed within the time frame defined in the SoA.
- Prior to randomization at Visit 1, all assessments to confirm inclusion into the study will be completed. The details of these assessments are defined in the SoA.

9.1. Efficacy Assessments

9.1.1. Primary Endpoint

The aim of the study is to evaluate the percentage of participants which correctly use the ELLIPTA DPI compared to the DISKUS + HandiHaler DPIs after a 28 day treatment period. "Correct Use" is defined as the percentage of participants with zero errors after 28 days of use.

A checklist for correct use of each of the study medications has been developed based on the steps identified in the Patient Instruction Leaflets (PIL's). Following removal of the inhaler from the packaging, an eligible participant, after reading the PIL, will be guided by a trained health care provider (HCP) to demonstrate correct use of the inhaler they have been assigned. A baseline assessment will be conducted when the participant is initially dispensed the inhaler and a second assessment will be conducted after each 28 day dosing period. A trained HCP will complete the appropriate Correct Use Checklist(s) at each visit. At visit 2, two checklists shall be completed, the first checklist will be for the Day 28 assessment of the first inhaler (s) and afterwards the second checklist will be another baseline assessment for the second inhaler (s) which has been dispensed.

9.1.2. Secondary Endpoints

A number of additional secondary endpoints shall be evaluated based on the information collected in the Correct Use Checklists. These include:

- Number of errors by type for each inhaler after 28 days of use.
- Number and change in errors per participant for each treatment group (V2, V3) after 28 days of use.
- Number and change in errors for each treatment group in participants with one or more errors after 28 days of use.
- Comparison of correct inhaler use as defined by the percentage of participants with zero critical errors after 28 days of use.

9.1.3. Other Endpoints

A number of additional other endpoints shall be evaluated based on the information collected in the Correct Use Checklists. These include:

- Comparison of correct inhaler use as defined by the percentage of participants with zero errors after 28 days of use, including the number of prescribed maintenance inhalers as a covariant.
- The comparison of participants making zero errors after reading the PIL (s) at the start of each treatment period.
- Inhaler preference based on how easy it was to tell how many doses remain.
- Inhaler dosing regimen preference.
- Inhaler regimen preference based on the number of steps needed to take the medication.

9.1.4. Assessment of Preference

After completing the correct use assessment for all treatments, the HCP will have the participant complete the assigned preference questionnaire. This assessment should occur at Visit 3 (Last Visit/End of Study) (Day 56) after the participant has demonstrated their inhaler use.

9.2. Safety Assessments

9.2.1. Adverse Events

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

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study treatment or the study, or that caused the participant to discontinue the study.

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

- All SAEs will be collected from the signing of the ICF until the time points specified in the SoA (Section 2).
- All AEs will be collected from randomization until the time points 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 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.
- Investigators are not obligated to actively seek AEs or SAEs in former study 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 3.

9.2.1.2. 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.

9.2.1.3. 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 (as defined in Section 8.3). Further information on follow-up procedures is given in Appendix 3

9.2.1.4. 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 e.g., summary or listing of SAE) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

9.2.2. Cardiovascular and Death Events

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

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

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

9.2.3. 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.

Participants 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 participant 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 participant should be withdrawn from the study.

If a participant 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 participants.

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

Signs and symptoms of COPD will not be considered AEs and will not be recorded in the eCRF.

9.2.4. Pregnancy

- Details of all pregnancies in female participants will be collected after the start of study treatment.
- If a pregnancy is reported, the investigator should inform GSK within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAE.

NOTE: Incidents fulfilling the definition of an AE/SAE will also follow the processes outlined in Appendix 4.

9.2.5. Treatment of Overdose

There is no active treatment in this study, placebo only.

9.2.6. Physical Examination

The following will be assessed at Visit 1 and recorded in the source documents:

- A brief physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

9.2.7. Vital Signs

The following will be assessed at Visit 1 and recorded in the source documents:

- Temperature, pulse rate, respiratory rate, and blood pressure will be assessed.
- Blood pressure and pulse measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (e.g., television, cell phones).
- Vital signs will be measured in a semi-supine position after 5 minutes rest and will include temperature, systolic and diastolic blood pressure, and pulse rate.

9.2.8. Electrocardiograms

Electrocardiograms will not be conducted during the study.

9.2.9. Clinical Safety Laboratory Assessments

Clinical safety laboratory assessments will not be conducted during the study.

9.3. Pharmacokinetics

PK parameters are not evaluated in this study.

9.4. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

9.5. Genetics

Genetics are not evaluated in this study.

9.6. Biomarkers

Biomarkers are not evaluated in this study.

9.7. 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 errors made by COPD participants, for the ELLIPTA inhaler or DISKUS + HandiHaler inhalers combined after 28 days use. This is a superiority study.

The primary endpoint is the percentage of participants making zero errors on the ELLIPTA inhaler compared with the DISKUS + HandiHaler inhalers.

The null hypothesis is that there is no difference in the proportion of participants making zero errors on the ELLIPTA inhaler compared to the DISKUS + HandiHaler inhalers.

H_0: $P_E - P_{D+H} = 0$

The alternative hypothesis is there is a difference in the proportion of participants making zero errors on the ELLIPTA inhaler compared to the DISKUS + HandiHaler inhalers.

H_1: $P_E - P_{D+H} \neq 0$

10.2. Sample Size Determination

The sample size calculations for this study have been based on the primary endpoint, which is the percentage of participants making zero errors in each treatment group (ELLIPTA or DISKUS + HandiHaler) after 28 days use.

The estimates of inhaler errors were taken from the overall errors reported in the 200301 study for each individual inhaler (ELLIPTA, DISKUS and HandiHaler) separately. Although this study is only assessing combined errors in the DISKUS + HandiHaler treatment group, individual inhaler errors were used to estimate the combined error rate in order to provide a conservative estimate. By doing this it assumes that participants, who made no errors on the DISKUS inhaler, would not make any errors of the HandiHaler inhaler and vice-versa.

As the 200301 study only had a single visit, no estimates were available for error rates over 28 days, however the study did provided estimates of participant errors after reading the PIL and after being instructed on correct use by a HCP up to three times. As participants will have the PIL for 28 days, and can be instructed by a HCP at the inhaler dispensing visit if necessary, both estimates of error rates along with a sensitivity analysis examining some of the potential error rates between were used to inform sample size calculations.

Using 10,000 simulations, a total of 216 participant (54 per treatment sequence) provide at least 90% power to show a statistically significance difference between the overall error rate of the ELLIPTA inhaler versus DISKUS + HandiHaler inhalers, for all of the paired treatment error rates shown in Table 1.

Table 1 Error rates of ELLIPTA vs. DISKUS + HandiHaler achievable with 90% power, 5 % Type 1 error using a total of 216 participants

ELLIPTA Error Rate	DISKUS + HandiHaler Error Rate
33%	>=50%
30%	>=47%
20%	>=35%
10%	>=23%
5%	>=15%

Conditional logistic regression and a two-sided 5% significance level were used as the analysis method for all simulations performed. As it is expected that some participants would drop out or change inhalers during the study, with 10% withdrawal it would be

necessary to enrol 240 participants (60 per treatment sequence) to ensure there were 216 participants with evaluable data at the end of the study.

For the purpose of this study an evaluable participant is defined as a randomized participant who completed error assessments for both randomized treatment groups.

10.3. Populations for Analyses

For purposes of analysis, the following populations are defined:

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 participant who was not screened but experienced a SAE between signing the informed consent and screening.
Intent-to-Treat (ITT)	All randomised participants, excluding those who were randomised in error, and did not have at least one error assessment at Visit 1. A participant who is recorded as a screen failure or run-in failure and also randomised will be considered to be randomised in error. Any other participant who receives a randomisation number will be considered to have been randomised. This population will be analysed according to the treatment sequence the participants were randomised to, and not the treatment sequence they actually received.
Safety	This population will be the same as the Intent-to-Treat population.

10.4. Statistical Analyses

10.4.1. Efficacy Analyses

Endpoint	Statistical Analysis Methods
Primary	The primary endpoint is the percentage of participants making at least zero errors after 28 days use. This endpoint will be analysed using conditional logistic regression with participant as fixed strata, and treatment option and period as fixed effects. The odds ratio, 95% confidence interval (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 percentage of participants making at least one critical error after 28 days use will be analysed using the same model as the primary

Endpoint	Statistical Analysis Methods
	endpoint. The impact of number of COPD maintenance inhalers will be analysed using the same model as the primary endpoint, but with number of maintenance inhalers as an additional covariate. The following secondary endpoints will be summarised only: • Number of errors by type for each treatment group after 28 days of use. • Number and change in errors per participant for each treatment group (V2 and V3) after 28 days of use. • Number and change in errors for each inhaler in participants with one or more errors after 28 days of use.
Other	Analysis of the following other endpoints will be defined in the Reporting and Analysis Plan: • Comparison of correct inhalers use as defined by the percentage of participants with zero errors after 28 days of use, including the number of prescribed maintenance inhalers as a covariate. • The percentage of participants making at least one overall error after reading the PIL (s) at the start of each treatment period. • Inhaler preference based on how easy it was to tell how many doses remain. • Inhaler and dosing regimen preference. • Inhaler regimen preference based on the number of steps needed to take the medication.

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 participants experiencing at least one AE of any type, AEs within each body system and AEs within each preferred term will be presented for each treatment group. Separate summaries will be provided for all AEs, drug related AEs, fatal 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 analysis will be documented in the Report and Analysis Plan.

10.4.4. Interim Analyses

There will be no interim analyses with this study.

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12. APPENDICES

12.1. Appendix 1: Abbreviations and Trademarks

Abbreviations

AE	Adverse Event
ASE	All Subjects Enrolled
BI	Boehringer Ingelheim
BID	Twice Daily
CI	Confidence Interval
CONSORT	Consolidated Standards of Reporting Trials
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
CSR	Clinical Study Report
CV	Cardiovascular
DPI	Dry Powder Inhaler
EW	Early Withdrawal
FEV_1	Forced Expiratory Volume in one Second
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GSK	GlaxoSmithKline
HCP	Healthcare Professional
ICF	Informed Consent Form
ICH	International Conference On Harmonisation
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
QD	Once Daily
SAE	Serious Adverse Event
SoA	Schedule of Activities
SUSAR	Suspected Unexpected Serious Adverse Reactions

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
ANORO ELLIPTA
BREO ELLIPTA
DISKUS
INCRUSE ELLIPTA

Trademarks not owned by the GlaxoSmithKline group of companies
HandiHaler

12.2. Appendix 2: Study Governance Considerations

Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with:
    - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
    - Applicable ICH Good Clinical Practice (GCP) Guidelines
    - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IEC/IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study 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 SAEs 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 center.
- 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.

Committees Structure

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

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 (e.g., 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 from the issue of the final Clinical Study Report (CSR)/ equivalent summary unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in the Study Reference Manual.

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

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

Definition of AE

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

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

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

assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of SAE

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

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

a. Results in death

b. Is life-threatening

The term 'life-threatening' in the definition of 'serious' refers to an event in which the 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 fulfils any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

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

d. Results in persistent disability/incapacity

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

and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Other situations: • Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the 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.

Definition of Cardiovascular Events

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

Recording AE and SAE

AE and SAE Recording
• When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) related to the event. • The investigator will then record all relevant AE/SAE information in the CRF.

- It is **not** acceptable for the investigator to send photocopies of the 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 sufficient 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.
- The investigator or medically-qualified sub-investigator must show evidence within the eCRF (e.g., check review box, signature, etc.) of review and verification of the relationship of each SAE to IP/study participation (causality) within 72 hours of SAE entry into the eCRF.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see

next Section) or to the medical monitor/SAE coordinator by telephone.

- Contacts for SAE reporting can be found in Study Reference Manual.

SAE Reporting to GSK via Paper CRF

- Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the **medical monitor or the SAE coordinator**.
- 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 Study Reference Manual.

12.4. Appendix 4: Collection of Pregnancy Information

Collection of Pregnancy Information

Female Participants who become pregnant

- Investigator will collect pregnancy information on any female participant, who becomes pregnant while participating in this study.
- Information will be recorded on the appropriate form and submitted to GSK within 24 hours of learning of a participant's pregnancy.
- Participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow up information on participant and neonate, which will be forwarded to GSK Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.
- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the investigator, will be reported to GSK as described in Appendix 3. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Any female participant who becomes pregnant while participating

- Will be withdrawn from the study.

12.5. Appendix 5: Protocol Amendment History

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

Protocol Title: A randomized, open-label, cross-over, placebo inhaler study to evaluate the correct use of ELLIPTA™ dry powder inhaler (DPI) compared to DISKUS™ DPI used in combination with HandiHaler™ DPI in participants with Chronic Obstructive Pulmonary Disease (COPD)

Protocol Number: 206901

Short Title: A clinical study evaluating the correct use of the placebo ELLIPTA dry powder inhaler, in comparison to combinations of placebo dry powder inhalers used to provide fixed-dose combination triple therapy, in participants with COPD.

Compound Number: GSK2834425 (GW685698+ GSK573719+GW642444)

Sponsor Name and Legal Registered Address:

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

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

Regulatory Agency Identifying Number(s): IND No. 114873

Approval Date: 27-FEB-2017

SPONSOR SIGNATORY:

PPD

Steven Pascoe,
Vice President, Respiratory Head Unit Physician

27th Feb 2017
Date

PPD

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1. SYNOPSIS

Protocol Title: A randomized, open-label, cross-over, placebo inhaler study to evaluate the correct use of ELLIPTA dry powder inhaler (DPI) compared to DISKUS DPI used in combination with HandiHaler DPI in participants with Chronic Obstructive Pulmonary Disease (COPD).

Short Title: A clinical study evaluating the correct use of the placebo ELLIPTA dry powder inhaler, in comparison to combinations of placebo dry powder inhalers used to provide fixed-dose combination triple therapy, in participants with COPD.

Rationale: This study is designed to assess the benefits of delivering triple therapy using a single ELLIPTA™ DPI (fixed-dose combination triple therapy) versus delivering triple therapy using two different types of inhalers (open triple therapy) to participants with Chronic Obstructive Pulmonary Disease (COPD). It will assess correct inhaler use when using a single ELLIPTA™ DPI versus using combinations of commercially available and commonly used DPIs: DISKUS™ used in combination with HandiHaler. This study will also assess critical errors and preference attributes for fixed-dose combination triple therapy as compared to the open triple therapy.

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

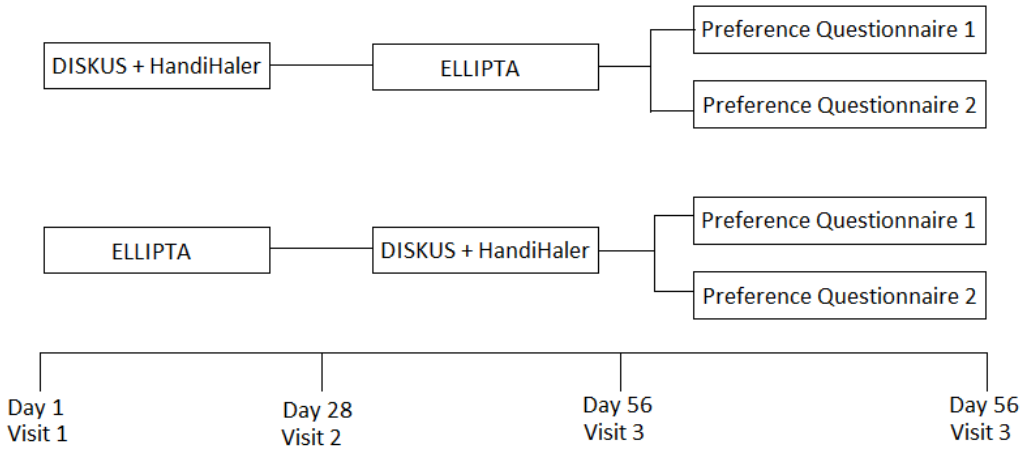
Objective	Endpoint
Primary	
• To evaluate the relative proportions of COPD participants who correctly use an ELLIPTA inhaler compared to those who correctly use a DISKUS + HandiHaler combination to receive their COPD medications.	• Comparison of the correct inhaler use as defined by the percentage of participants with zero errors after 28 days of use.
Secondary	
• To evaluate the overall correct use of an ELLIPTA inhaler compared to the DISKUS + HandiHaler combination in COPD participants.	• Number of errors by type for each inhaler after 28 days of use. • Number and change in errors per participant for each treatment group (V2 and V3) after 28 days of use. • Number and change in errors for each treatment group in participants with one or more errors after 28 days of use.

Objective	Endpoint
• To evaluate the relative proportions of critical errors for COPD participants using an ELLIPTA inhaler compared to those using a DISKUS and HandiHaler to receive their COPD medications.	• Comparison of correct inhaler use as defined by the percentage of participants with zero critical errors after 28 days of use.
Other	
• To evaluate the impact of number of COPD maintenance inhalers on study inhaler errors (ELLIPTA and DISKUS + HandiHaler) after 28 days of use.	• Comparison of correct inhalers use as defined by the percentage of participants with zero errors after 28 days of use, including the number of prescribed maintenance inhalers as a covariate.
• To evaluate the number of overall errors made by COPD participants after a participant has read the Patient Instruction Leaflet (PIL(s)).	• The comparison of participants making zero errors after reading the PIL (s) at the start of each treatment period.
• To evaluate the participant's preference of these inhaler options based on how easy it was to tell how many doses were remaining.	• Inhaler preference based on how easy it was to tell how many doses remain.
• To evaluate inhaler preference of taking a regimen that was one inhaler, once a day versus multiple inhalers with a varied dosing regimen.	• Inhaler dosing regimen preference.

Overall Design: This study will be conducted as a randomized, multi-center, open-label, cross-over study comparing placebo ELLIPTA (GSK) with placebo DISKUS (GSK) + HandiHaler [Boehringer Ingelheim (BI)] to assess correct inhaler use. A sufficient number of participants with COPD will be randomized such that 216 participants complete the study. Participants will continue taking their usual COPD maintenance treatment and rescue medications during the entire 56-day study period.

This study has 3 visits and will be completed in approximately 56 days.

Study Schematic:



Number of Participants: Approximately 300 participants with COPD will be screened to ensure approximately 240 participants will be randomized, such that approximately 216 evaluable participants complete the study.

Treatment Groups and Duration: Duration is 3 clinical visits over approximately 56 days.

There is no active treatment and participants will continue to take their own prescribed COPD maintenance and rescue medication during the entire 56-day study period.

The treatment groups are the following:

- At Visit 1 (Day 1) approximately half of the participants will be randomized to receive a placebo ELLIPTA (QD) inhaler for use during the first 28 day treatment period. The remaining half of the participants will receive a placebo DISKUS (BID) + placebo HandiHaler (QD) for use during the first 28 day treatment period.

- At Visit 2 (Day 28) participants previously receiving the placebo DISKUS + placebo HandiHaler inhalers at Visit 1 will receive a placebo ELLIPTA (QD) inhaler for the second 28 day treatment period. Those participants initially receiving a placebo ELLIPTA inhaler at Visit 1 will receive a placebo DISKUS (BID) inhaler + a placebo HandiHaler (QD) inhaler for the second 28 day treatment period.

- At Visit 3 (Day 56) after conducting their last correct inhaler use assessments, the participants will answer either preference questionnaire 1 or preference questionnaire 2 depending on their randomization schedule.

Randomization Group	Sequence of Using the Inhalers		Preference Questionnaire Version
	1st Period	2nd Period	
A	ELLIPTA	DISKUS + HandiHaler	1
B	ELLIPTA	DISKUS + HandiHaler	2
C	DISKUS + HandiHaler	ELLIPTA	1
D	DISKUS + HandiHaler	ELLIPTA	2

Participants will use the assigned placebo inhaler, in each period to match the dose in the prescribing information for the medication that they match. ELLIPTA DPI and HandiHaler DPI will both be taken as one inhalation, once daily. DISKUS DPI will be taken as one inhalation, twice daily.

Study endpoints will be based on evaluation of participant's correct use and preference questionnaires.

The aim of this study is to further evaluate the participant handling errors on ELLIPTA relative to a subset of other available inhalers. The overall correct use of the GSK ELLIPTA relative to two other inhalers, a GSK DISKUS and the Boehringer Ingelheim HandiHaler shall be assessed. Placebo inhalers are used to remove any bias due to treatment effect, avoid the need for wash-in/wash-out periods, and to avoid the need to withhold or discontinue current COPD medications, which may affect the participant's clinical status (improvement or decline) and perceptions.

2. SCHEDULE OF ACTIVITIES (SOA)

Procedures	Visit 0 Screening (Can occur on same day as V1)	Visit 1 Randomization (Can occur on the same day as V0)	Visit 2 Assessment/ Cross-over	Visit 3 Last Visit/ End of Study/Early Withdrawal
Study Day		**1**	**28 (±2)**	**56 (±2)**
Screening/safety assessments				
Written informed consent [1]	**X**			
Participant demography	**X**			
Medical/disease history including chronic obstructive pulmonary disease (COPD) history	**X**			
Therapy history	**X**			
Inclusion/exclusion criteria	**X**			
Concomitant medication	**X**		**X**	**X**
Physical examination[2]		**X**		
Vital signs[2]		**X**		
Adverse events (AEs)/ Serious adverse event (SAEs)[3]		**X**	**X**	**X**
Randomization [4]		**X**		
Study inhaler correct use and preference				
Participant reviews written instructions on the correct use of the newly dispensed inhaler(s)		**X**	**X**	
Assess participant's ability to correctly use the newly dispensed inhaler (following participant reading patient instruction leaflet (PIL) then demonstrating correct use)[5]		**X**	**X**	
Assess participant's ability to correctly use the returned inhaler(s) without instruction[6]			**X**	**X**

Procedures	**Visit 0 Screening (Can occur on same day as V1)**	**Visit 1 Randomization (Can occur on the same day as V0)**	**Visit 2 Assessment/ Cross-over**	**Visit 3 Last Visit/ End of Study/Early Withdrawal**
Study Day		**1**	**28 (±2)**	**56 (±2)**
Assess compliance with the returned study inhaler(s) (based on the dose counter)			**X**	**X**
Preference Questionnaire				**X**
Worksheets and medication				
Dispense study inhaler(s)		**X**	**X**	
Collect study inhaler(s)			**X**	**X**
Dispense Medical Problems/Medications Taken Worksheet [7]		**X**	**X**	
Collect and review Medical Problems/Medications Taken Worksheet [7]			**X**	**X**

1. Participants will be assigned a subject number at the time when the informed consent form (ICF) is signed at Visit 0 or Visit 1. The ICF must be signed before any study procedures are conducted.
2. Results are recorded in the source documents only.
3. Refer to protocol Section 9.2.1.1 for AE/SAE data collection period.
4. Randomisation conducted if the Participant meets all study screening criteria.
5. A health care professional trained on the inhalers will conduct the assessments at Visits 1 and 2, following dispensing of the appropriate inhaler (s) for the next dosing period.
6. A health care professional trained on the inhalers will conduct the assessments of the participant's ability to correctly use the returned inhaler (s) at Visits 2 and 3 following return of the inhaler (s) used for the previous dosing period. This should be completed at Early Withdrawal Visit if a participant has taken one or more doses of the inhaler at home.
7. Participants will record medical problems and medications taken on the Medical Problems/Medications Taken Worksheet between visits.

3. INTRODUCTION

3.1. Study Rationale

This study is designed to assess the benefits of delivering triple therapy using a single ELLIPTA™ Dry powder inhaler (DPI) (fixed-dose combination closed triple therapy) versus delivering triple therapy using two different types of inhalers (open triple therapy) to participants with Chronic Obstructive Pulmonary Disease (COPD). It will assess correct inhaler use when using a single ELLIPTA™ DPI versus using combinations of commercially available and commonly used DPIs: DISKUS™ used in combination with HandiHaler. This study will also assess critical errors and preference attributes for a fixed-dose triple therapy as compared to the multiple inhalers to receive triple therapy.

The cross-over design is chosen to allow participants to serve as their own control in their ability to use both the ELLIPTA and the DISKUS + HandiHaler inhalers. Placebo inhalers will be used to remove any bias due to treatment effect. The comparison of the ELLIPTA to the DISKUS + HandiHaler combination was chosen as this combination of inhalers is the most commonly prescribed triple combination in the United States. The 28-day treatment period is consistent with other ELLIPTA correct use and critical errors studies. Correct use will be evaluated with reference to the steps outlined in the manufacturer's package insert for the inhalers.

3.2. Background

Chronic Obstructive Pulmonary Disease (COPD) is a progressive disease of the airways. Noxious particles or gases lead to a modification in patient'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, 2017]

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 anticholinergics) 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, patients 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 minimize the number of inhalers required would simplify treatment, improve adherence, reduce errors in inhaler use, and potentially lead to better outcomes [GOLD, 2017].

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]. Critical errors made when using inhalers, which significantly reduce or completely inhibit drug delivery, have been identified for various inhalation devices [Van Der Palen, 2016]. Between 36 and 49% of patients with COPD perform critical inhaler errors with currently used inhalers [Van Der Palen, 2016]. For any prescribed inhaler, the patient needs to follow all the steps in the patient information leaflet correctly in order to ensure optimal drug delivery. In this regard, the time needed for a primary care nurse, 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). A fixed-dose 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

This study involves the use of placebo inhalers (placebo ELLIPTA, placebo DISKUS, and placebo HandiHaler) that do not contain active treatments. The inhalers contain the excipients lactose and lactose blended with magnesium stearate. Participants with known hypersensitivity to any of these or severe milk protein allergy that could contraindicate study participation are to be excluded from the study. Participants who meet the inclusion/exclusion criteria will continue their COPD treatment as prescribed by their

healthcare provider during their participation in the study. Participants should continue to follow up with their regular physician for their COPD healthcare during the study.

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 participants'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 excipient lactose and lactose blended with magnesium stearate. There are known allergies to these ingredients.	Participants with a know 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 and other appropriate drugs used in allergic reactions (e.g. glucocorticosteroids, adrenalin) guided by the nature and severity of the allergic reaction. Investigators will be instructed to assess the participant's condition to determine their eligibility to continue in the study and the need for alternative therapy.

3.3.2. Benefit Assessment

As this is a placebo study, no benefit to the participant is expected. No active treatment is being administered. The participant 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, in that no COPD medication, in addition to their already prescribed therapy is provided to participants.

4. OBJECTIVES AND ENDPOINTS

This study will compare correct inhaler use along with critical errors and participant preference of inhalers for fixed-dosed combination triple therapy from a single ELLIPTA inhaler versus triple therapy received from DISKUS in combination with HandiHaler.

Objectives	Endpoints
Primary • To evaluate the relative proportions of COPD participants who correctly use an ELLIPTA inhaler compared to those who correctly use a DISKUS + HandiHaler combination to receive their COPD medications.	• Comparison of correct inhaler use as defined by the percentage of participants with zero errors after 28 days of use.
Secondary • To evaluate the overall correct use of an ELLIPTA inhaler compared to the DISKUS + HandiHaler combination in COPD participants.	• Number of errors by type for each inhaler after 28 days of use. • Number and change in errors per participant for each treatment group (V2 and V3) after 28 days of use. • Number and change in errors for each treatment group in participants with one or more errors after 28 days of use.
• To evaluate the relative proportions of critical errors for COPD	• Comparison of correct inhaler use as defined by the percentage of

Objectives	Endpoints
participants using an ELLIPTA inhaler compared to those using a DISKUS and HandiHaler to receive their COPD medications.	participants with zero critical errors after 28 days of use.
Other • To evaluate the impact of number of COPD maintenance inhalers on study inhaler errors (ELLIPTA and DISKUS + HandiHaler) after 28 days of use.	• Comparison of correct inhalers use as defined by the percentage of participants with zero errors after 28 days of use, including the number of prescribed maintenance inhalers as a covariate.
• To evaluate the number of overall errors made by COPD participants after a participant has read the Patient Instruction Leaflet (PIL(s)).	• The comparison of participants making zero errors after reading the PIL (s) at the start of each treatment period.
• To evaluate the participant's preference of these inhaler options based on how easy it was to tell how many doses were remaining.	• Inhaler preference based on how easy it was to tell how many doses remain.
• To evaluate inhaler preference of taking a regimen that was one inhaler, once a day versus multiple inhalers with a varied dosing regimen.	• Inhaler dosing regimen preference.

5. STUDY DESIGN

5.1. Overall Design

This study will be conducted as a randomized, multi-center, open-label, cross-over study comparing placebo ELLIPTA (GSK) with placebo DISKUS (GSK) + HandiHaler [Boehringer Ingelheim (BI)] to assess correct inhaler use.

This study has 3 visits and will be completed in approximately 56 days. COPD diagnosed participants will attend the clinic for the screening visit (V0) and subsequent assessment visit (V1). These visits may occur on the same day.

There is no active treatment and participants will continue to take their own prescribed COPD maintenance medication and rescue medications during the entire 56-day study period.

The treatment groups are the following:

- At Visit 1 (Day 1) half of the participants will be randomized to receive a placebo ELLIPTA (QD) inhaler for use during the first 28 day treatment period. The remaining half of the participants will receive a placebo DISKUS (BID) + placebo HandiHaler (QD) for use during the first 28 day treatment period.

- At Visit 2 (Day 28) participants previously receiving the placebo DISKUS + placebo HandiHaler inhalers at Visit 1 will receive a placebo ELLIPTA (QD) inhaler for the second 28 day treatment period. Those participants initially receiving a placebo ELLIPTA inhaler at Visit 1 will receive a placebo DISKUS (BID) inhaler + a placebo HandiHaler (QD) inhaler for the second 28 day treatment period.

- At Visit 3 (Day 56) after conducting their last correct inhaler use assessments, participants will answer either preference questionnaire 1 or preference questionnaire 2 depending on their randomization schedule.

Randomization Group	Sequence of Using the Inhalers		Preference Questionnaire Version
	1st Period	2nd Period	
A	ELLIPTA	DISKUS + HandiHaler	1
B	ELLIPTA	DISKUS + HandiHaler	2
C	DISKUS + HandiHaler	ELLIPTA	1
D	DISKUS + HandiHaler	ELLIPTA	2

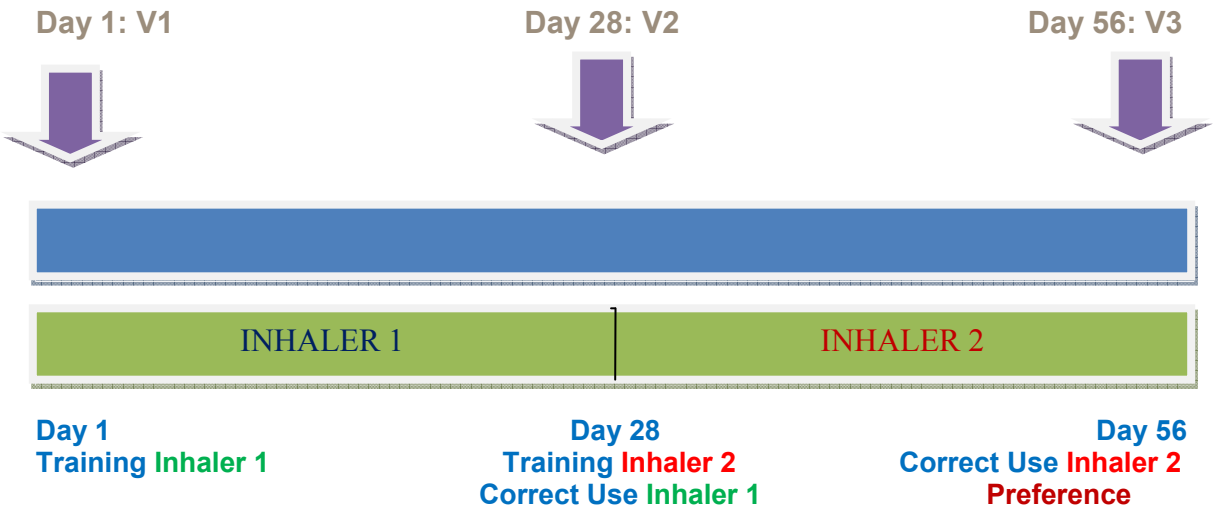
This study offers a design aimed at assessing the correct use and the number of errors made by the participant using each inhaler [after reading the instructions in the patient information leaflet and after healthcare professional (HCP) instruction] and participant preference of the inhalers.

Assessment of errors will be conducted by health care professionals trained in the correct inhaler use of three inhalers prior to the start of the study by face-to-face and

videotaped instruction training based on the checklist of errors. After randomization, participants will be asked to read the PIL of the first inhaler and then asked to demonstrate correct inhaler use, if they do not demonstrate correct use they will be instructed on correct use by the HCP. A baseline assessment will be conducted when the participant is initially dispensed the inhaler and a second assessment will be conducted after each 28 day dosing period. After demonstrating correct use at Visit 1, the participant will be sent home with the inhaler for the first 28 day treatment period. At Visit 2, two checklists shall be completed, the first checklist will be for the Day 28 assessment of the first inhaler and the second checklist will be another baseline assessment for the second inhaler which has been dispensed.

A health care professional trained on the inhalers will assess the participant's ability to correctly use the returned inhalers. Either the ELLIPTA checklist or the DISKUS + HandiHaler combination checklist will be utilized after 28 days of treatment depending on the inhalers returned. Individual checklist assessment of the DISKUS and the HandiHaler will not be assessed. Compliance with returned inhalers (based on the dose counter and remaining capsules) will also be assessed by study staff at Visits 2 and 3. A Preference Questionnaire will also be administered and reviewed by study staff at Visit 3 or the last clinic visit.

Overall Design:



5.2. Number of Participants

Approximately 300 participants with COPD will be screened to achieve 240 randomized and 216 evaluable participants for an estimated total of 108 participants per device sequence (not accounting for questionnaires, see Section 10.2). Questionnaires will then be randomly assigned within each device sequence to give 54 per randomized treatment group.

For the purpose of this study an evaluable participant is defined as a randomized participant who completed error assessments for both randomized treatment groups.

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 study is designed to assess the benefits of delivering triple therapy using a single ELLIPTA DPI (fixed-dose combination triple therapy) versus delivering triple therapy using two different types of inhalers (open triple therapy) to participants with COPD. It will assess correct inhaler use when using a single ELLIPTA DPI versus using combinations of commercially available and commonly used DPIs: DISKUS used in combination with HandiHaler. This study will also assess critical errors (which significantly reduce or completely inhibit drug delivery), non-critical errors, and preference attributes for the fixed-dose combination triple therapy as compared to the open triple therapy.

The cross-over design is chosen to allow participants to serve as their own control in their ability to use both the ELLIPTA and the DISKUS + HandiHaler inhalers. Placebo inhalers are used to remove any bias due to treatment effect. The comparison of the ELLIPTA to the DISKUS + HandiHaler combination was chosen as this combination of inhalers is the most commonly prescribed triple combination in the United States. The 28-day treatment period is consistent with other ELLIPTA correct use and critical errors studies. Correct use will be evaluated with reference to the steps outlined in the manufacturer's package insert for the inhalers.

This study highlights the need for participants using a new inhaler device to have adequate training and assessment at the time when starting a new treatment, for periodic review of training, and also the need to ensure that the proper inhaler is selected for the participant.

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:

Informed Consent

- Participants must be capable of giving signed informed consent as described in Appendix 3 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

Type of Participant and Diagnosis

- Participants must have a diagnosis 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].

Age

- Participants must be 40 years of age inclusive, at the time of signing the informed consent.

Gender

- Males or Females. Females must not be pregnant or planning pregnancy during the study or not lactating (Appendix 4).

Disease Severity

- Participants must have a documented post albuterol forced expiratory volume in one second (FEV_1)/ forced vital capacity (FVC) ratio <0.70 and $FEV_1 \leq 70\%$ of predicted obtained within two years of Visit 1.

Smoking History

- Current or former (defined as participants who have quit smoking for at least 3 months prior to Screening/Visit 1) 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].

COPD Medications

- All participants should be currently receiving maintenance treatment for COPD for at least 4 weeks prior to Randomization/Visit 1 and evaluated as unlikely to change COPD treatment within 4 weeks of Visit 1.

- All participants should be able to stay on their prescribed maintenance COPD treatment without change throughout the entire treatment period.

Other

- Participants must be able to read, comprehend, and record information in English.

6.2. Exclusion Criteria

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

Medical Conditions

- Participants must not have a current diagnosis of asthma.

Prior/Concomitant COPD Therapy

- Participants must not have used the ELLIPTA, DISKUS, or HandiHaler inhalers in the 6 months prior to Visit 1.

- Participants must not be receiving their current COPD medications with the ELLIPTA, DISKUS, or HandiHaler inhalers.

Exacerbations

- Participants must not have experienced more than 1 COPD exacerbation which required hospitalization in the 12 months prior to Visit 1.

Alcohol and Drug Abuse

- Participants must not have a known or suspected history of alcohol or drug abuse within the last 2 years.

History of Hypersensitivity

- Participants must not have a history of hypersensitivity to any component of the study inhalers (e.g. lactose, magnesium stearate). In addition, participants with a history of severe milk protein allergy that, in the opinion of the study physician, contraindicates participation will also be excluded.

Other Respiratory Disorders

- Participants with other respiratory disorders, including active tuberculosis, active lung cancer, sarcoidosis, lung fibrosis, pulmonary hypertension, or pulmonary disease (including but not confined to asthma, bronchiectasis with the need for treatment, cystic fibrosis, and bronchopulmonary dysplasia), interstitial lung diseases or other active pulmonary diseases.

Other Diseases/Abnormalities

Participants with:

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

- History of psychiatric disease, intellectual impairment, poor motivation or other conditions that will limit the validity of informed consent to participate in the study.

Compliance

- Participants at risk of non-compliance, or unable to comply with the study procedures, or unable to continue their current medications.

Investigational Product

- Participants who have received an investigational drug and/or medical device/inhaler within 30 days of entry into this study (Screening/Visit 1), or within five drug half-lives of the investigational drug, whichever is longer.

Affiliation with Investigator's Site

- Participants 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.

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. 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).

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.

GSK Clinical Trials Supplies will provide the placebo inhalers for use in this study together with placebo capsules where appropriate.

7.1. Treatments Administered

This study does not involve the administration of any new treatments. It assesses the ability of the participants to use the placebo inhalers listed in the table below.

Study Treatment Name:	**ELLIPTA placebo DPI**	**DISKUS placebo DPI**	**HandiHaler DPI and placebo Capsules**
Dosage formulation:	Placebo DPI with two strips with 30 blisters per strip. First strip containing lactose monohydrate and a second strip containing lactose monohydrate blended with magnesium stearate.	Placebo DPI with one blister strip containing lactose monohydrate.	DPI with placebo capsules containing lactose monohydrate.
Unit dose strength(s)/Dosage level(s):	NA	NA	NA
Route of Administration	Oral inhalation (Inhalation Powder).	Oral inhalation (Inhalation Powder).	Oral inhalation (Inhalation Powder).
Dosing instructions:	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.
Manufacturer	GSK	GSK	Boehringer Ingelheim (HandiHaler); GSK/Catalent (placebo capsules)

7.1.1. Medical Devices

There are no medical devices utilized in this study.

7.2. Dose Modification

There are no dose modifications.

7.3. 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 and directions for the IWRS will be provided to each site.

Participants will be assigned in equal numbers to one of the following sequences. The possible sequences are shown below:

Randomization Group	Sequence of Using the Inhalers		Preference Questionnaire Version
	1st Period	2nd Period	
A	ELLIPTA	DISKUS + HandiHaler	1
B	ELLIPTA	DISKUS + HandiHaler	2
C	DISKUS + HandiHaler	ELLIPTA	1
D	DISKUS + HandiHaler	ELLIPTA	2

Study treatments will be dispensed at the study visit summarized in the SoA.

7.4. 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 randomizing the order of treatment and the preference questionnaire version answered by the participants.

7.5. 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.
- Only participants enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and 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.

7.6. Treatment Compliance

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

Compliance will be calculated from the dose counter on returned ELLIPTA and DISKUS inhalers after each 28 day treatment period. HandiHaler compliance will be calculated from the number of capsules supplied and returned after 28 days of use. For compliance calculations, study staff should document the number of remaining doses for each inhaler prior to the participant leaving the clinic.

7.7. 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 6 months from Visit 1, should be recorded in order to determine the participant's inclusion in the study.

Participants should continue to take their usual COPD and other medication through the conduct of the study.

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

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

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

7.8. Treatment after the End of the Study

There is no active treatment, placebo only, and participants will not receive any specific post study treatments.

8. DISCONTINUATION CRITERIA

8.1. Discontinuation of Study Treatment

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

8.1.1. Liver Chemistry Stopping Criteria

Not applicable as there is no active treatment; all participants will receive placebo treatment only.

8.1.2. QTc Stopping Criteria

Not applicable as there is no active treatment; all participants will receive placebo treatment only.

8.1.3. Temporary Discontinuation

Not applicable as there is no active treatment; all participants will receive placebo treatment only.

8.2. Withdrawal/Stopping Criteria

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

A participant will also be withdrawn from the study if they experience any of the following:

- Participant is not able to demonstrate correct use of the inhalers within two 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).
- 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, DISKUS or HandiHaler inhalers (excluding placebo inhalers).
- Participant reports becoming pregnant during the study.

If a participant is prematurely discontinued from the study, the investigator must make every effort to perform the assessments as specified in the SoA at an early withdrawal (EW) visit as soon as possible and then discontinue the participant 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, participants will be discharged from the study.

8.3. Lost to Follow Up

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

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

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

9. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are 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 the diagnosis of COPD) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and was performed within the time frame defined in the SoA.
- Prior to randomization at Visit 1, all assessments to confirm inclusion into the study will be completed. The details of these assessments are defined in the SoA.

9.1. Efficacy Assessments

9.1.1. Primary Endpoint

The aim of the study is to evaluate the percentage of participants which correctly use the ELLIPTA DPI compared to the DISKUS + HandiHaler DPIs after a 28 day treatment period. "Correct Use" is defined as the percentage of participants with zero errors after 28 days of use.

A checklist for correct use of each of the study medications has been developed based on the steps identified in the Patient Instruction Leaflets (PIL's). Following removal of the inhaler from the packaging, an eligible participant, after reading the PIL, will be guided by a trained health care provider (HCP) to demonstrate correct use of the inhaler they have been assigned. A baseline assessment will be conducted when the participant is initially dispensed the inhaler and a second assessment will be conducted after each 28 day dosing period. A trained HCP will complete the appropriate Correct Use Checklist(s) at each visit. At visit 2, two checklists shall be completed, the first checklist will be for the Day 28 assessment of the first inhaler and afterwards the second checklist will be another baseline assessment for the second inhaler which has been dispensed.

9.1.2. Secondary Endpoints

A number of additional secondary endpoints shall be evaluated based on the information collected in the Correct Use Checklists. These include:

- Number of errors by type for each inhaler after 28 days of use.
- Number and change in errors per participant for each treatment group (V2, V3) after 28 days of use.
- Number and change in errors for each treatment group in participants with one or more errors after 28 days of use.
- Comparison of correct inhaler use as defined by the percentage of participants with zero critical errors after 28 days of use.

9.1.3. Other Endpoints

A number of additional other endpoints shall be evaluated based on the information collected in the Correct Use Checklists. These include:

- Comparison of correct inhaler use as defined by the percentage of participants with zero errors after 28 days of use, including the number of prescribed maintenance inhalers as a covariant.
- The comparison of participants making zero errors after reading the PIL (s) at the start of each treatment period.
- Inhaler preference based on how easy it was to tell how many doses remain.
- Inhaler dosing regimen preference.

9.1.4. Assessment of Preference

After completing the correct use assessment for all treatments, the HCP will have the participant complete the assigned preference questionnaire. This assessment should occur at Visit 3 (Last Visit/End of Study) (Day 56) after the participant has demonstrated their inhaler use.

9.2. Safety Assessments

9.2.1. Adverse Events

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

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study treatment or the study, or that caused the participant to discontinue the study.

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

- All SAEs will be collected from the signing of the ICF until the time points specified in the SoA (Section 2).
- All AEs will be collected from randomization until the time points 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 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

- Investigators are not obligated to actively seek AEs or SAEs in former study 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 3.

9.2.1.2. 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.

9.2.1.3. 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 (as defined in Section 8.3). Further information on follow-up procedures is given in Appendix 3

9.2.1.4. 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 e.g., summary or listing of SAE) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

9.2.2. Cardiovascular and Death Events

For any cardiovascular events detailed in Appendix 3 and all deaths, whether or not they are considered SAEs, specific Cardiovascular (CV) and Death sections of the CRF will

be required to be completed. These sections include questions regarding cardiovascular (including sudden cardiac death) and non-cardiovascular death.

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

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

9.2.3. 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.

Participants 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 participant 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 participant should be withdrawn from the study.

If a participant 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 participants.

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

Signs and symptoms of COPD will not be considered AEs and will not be recorded in the eCRF.

9.2.4. Pregnancy

- Details of all pregnancies in female participants will be collected after the start of study treatment.
- If a pregnancy is reported, the investigator should inform GSK within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4.

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

NOTE: Incidents fulfilling the definition of an AE/SAE will also follow the processes outlined in Appendix 4.

9.2.5. Treatment of Overdose

There is no active treatment in this study, placebo only.

9.2.6. Physical Examination

The following will be assessed at Visit 1 and recorded in the source documents:

- A brief physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

9.2.7. Vital Signs

The following will be assessed at Visit 1 and recorded in the source documents:

- Temperature, pulse rate, respiratory rate, and blood pressure will be assessed.
- Blood pressure and pulse measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (e.g., television, cell phones).
- Vital signs will be measured in a semi-supine position after 5 minutes rest and will include temperature, systolic and diastolic blood pressure, and pulse rate.

9.2.8. Electrocardiograms

Electrocardiograms will not be conducted during the study.

9.2.9. Clinical Safety Laboratory Assessments

Clinical safety laboratory assessments will not be conducted during the study.

9.3. Pharmacokinetics

PK parameters are not evaluated in this study.

9.4. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

9.5. Genetics

Genetics are not evaluated in this study.

9.6. Biomarkers

Biomarkers are not evaluated in this study.

9.7. 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 errors made by COPD participants, for the ELLIPTA inhaler or DISKUS + HandiHaler inhalers combined after 28 days use. This is a superiority study.

The primary endpoint is the percentage of participants making zero errors on the ELLIPTA inhaler compared with the DISKUS + HandiHaler inhalers.

The null hypothesis is that there is no difference in the proportion of participants making zero errors on the ELLIPTA inhaler compared to the DISKUS + HandiHaler inhalers.

H_0: $P_E - P_{D+H} = 0$

The alternative hypothesis is there is a difference in the proportion of participants making zero errors on the ELLIPTA inhaler compared to the DISKUS + HandiHaler inhalers.

H_1: $P_E - P_{D+H} \neq 0$

10.2. Sample Size Determination

The sample size calculations for this study have been based on the primary endpoint, which is the percentage of participants making zero errors in each treatment group (ELLIPTA or DISKUS + HandiHaler) after 28 days use.

The estimates of inhaler errors were taken from the overall errors reported in the 200301 study for each individual inhaler (ELLIPTA, DISKUS and HandiHaler) separately. Although this study is only assessing combined errors in the DISKUS + HandiHaler treatment group, individual inhaler errors were used to estimate the combined error rate in order to provide a conservative estimate. By doing this it assumes that participants,

who made no errors on the DISKUS inhaler, would not make any errors of the HandiHaler inhaler and vice-versa.

As the 200301 study only had a single visit, no estimates were available for error rates over 28 days, however the study did provided estimates of participant errors after reading the PIL and after being instructed on correct use by a HCP up to three times. As participants will have the PIL for 28 days, and can be instructed by a HCP at the inhaler dispensing visit if necessary, both estimates of error rates along with a sensitivity analysis examining some of the potential error rates between were used to inform sample size calculations.

Using 10,000 simulations, a total of 216 participant (54 per treatment sequence) provide at least 90% power to show a statistically significance difference between the overall error rate of the ELLIPTA inhaler versus DISKUS + HandiHaler inhalers, for all of the paired treatment error rates shown in Table 1.

Table 1 Error rates of ELLIPTA vs. DISKUS + HandiHaler achievable with 90% power, 5 % Type 1 error using a total of 216 participants

ELLIPTA Error Rate	DISKUS + HandiHaler Error Rate
33%	>=50%
30%	>=47%
20%	>=35%
10%	>=23%
5%	>=15%

Conditional logistic regression and a two-sided 5% significance level were used as the analysis method for all simulations performed. As it is expected that some participants would drop out or change inhalers during the study, with 10% withdrawal it would be necessary to enrol 240 participants (60 per treatment sequence) to ensure there were 216 participants with evaluable data at the end of the study.

For the purpose of this study an evaluable participant is defined as a randomized participant who completed error assessments for both randomized treatment groups.

10.3. Populations for Analyses

For purposes of analysis, the following populations are defined:

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 participant who was not screened but experienced an SAE between the date of informed consent and the planned date of the Screening visit.
Intent-to-Treat (ITT)	All randomised participants, excluding those who were randomised in error, and did not have at least one error assessment at Visit 1. A participant who is recorded as a screen failure or run-in failure and also randomised will be considered to be randomised in error. Any other participant who receives a randomisation number will be considered to have been randomised. This population will be analysed according to the treatment sequence the participants were randomised to, and not the treatment sequence they actually received.
Safety	This population will be the same as the Intent-to-Treat population.

10.4. Statistical Analyses

10.4.1. Efficacy Analyses

Endpoint	Statistical Analysis Methods
Primary	The primary endpoint is the percentage of participants making at least zero errors after 28 days use. This endpoint will be analysed using conditional logistic regression with participant as fixed strata, and treatment option and period as fixed effects. The odds ratio, 95% confidence interval (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 percentage of participants making at least one critical error after 28 days use will be analysed using the same model as the primary endpoint. The impact of number of COPD maintenance inhalers will be analysed using the same model as the primary endpoint, but with number of maintenance inhalers as an additional covariate. The following secondary endpoints will be summarised only: • Number of errors by type for each treatment group after 28

Endpoint	Statistical Analysis Methods
	days of use. • Number and change in errors per participant for each treatment group (V2 and V3) after 28 days of use. • Number and change in errors for each inhaler in participants with one or more errors after 28 days of use.
Other	Analysis of the following other endpoints will be defined in the Reporting and Analysis Plan: • Comparison of correct inhalers use as defined by the percentage of participants with zero errors after 28 days of use, including the number of prescribed maintenance inhalers as a covariate. • The percentage of participants making at least one overall error after reading the PIL (s) at the start of each treatment period. • Inhaler preference based on how easy it was to tell how many doses remain. • Inhaler and dosing regimen preference.

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 participants experiencing at least one AE of any type, AEs within each body system and AEs within each preferred term will be presented for each treatment group. Separate summaries will be provided for all AEs, drug related AEs, fatal 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 analysis will be documented in the Report and Analysis Plan.

10.4.4. Interim Analyses

There will be no interim analyses with this study.

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12. APPENDICES

12.1. Appendix 1: Abbreviations and Trademarks

Abbreviations

AE	Adverse Event
ASE	All Subjects Enrolled
BI	Boehringer Ingelheim
BID	Twice Daily
CI	Confidence Interval
CONSORT	Consolidated Standards of Reporting Trials
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
CSR	Clinical Study Report
CV	Cardiovascular
DPI	Dry Powder Inhaler
EW	Early Withdrawal
FEV_1	Forced Expiratory Volume in one Second
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GSK	GlaxoSmithKline
HCP	Healthcare Professional
ICF	Informed Consent Form
ICH	International Conference On Harmonisation
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
QD	Once Daily
SAE	Serious Adverse Event
SoA	Schedule of Activities
SUSAR	Suspected Unexpected Serious Adverse Reactions

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
ANORO ELLIPTA
BREO ELLIPTA
DISKUS
INCRUSE ELLIPTA

Trademarks not owned by the GlaxoSmithKline group of companies
HandiHaler

12.2. Appendix 2: Study Governance Considerations

Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with:
    - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
    - Applicable ICH Good Clinical Practice (GCP) Guidelines
    - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IEC/IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study 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 SAEs 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 center.
- 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.

Committees Structure

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

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 (e.g., 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 from the issue of the final Clinical Study Report (CSR)/ equivalent summary unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in the Study Reference Manual.

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

12.3. Appendix 3: 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 (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE. • The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE. Also, "lack of efficacy" or "failure of expected pharmacological action" constitutes an AE or SAE.

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

assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the 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 (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of SAE

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

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

a. Results in death

b. Is life-threatening

The term 'life-threatening' in the definition of 'serious' refers to an event in which the 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 fulfils any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

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

d. Results in persistent disability/incapacity

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

and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Other situations: • Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the 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.

Definition of Cardiovascular Events

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

Recording AE and SAE

AE and SAE Recording
• When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) related to the event. • The investigator will then record all relevant AE/SAE information in the CRF.

- It is **not** acceptable for the investigator to send photocopies of the 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 sufficient 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.
- The investigator or medically-qualified sub-investigator must show evidence within the eCRF (e.g., check review box, signature, etc.) of review and verification of the relationship of each SAE to IP/study participation (causality) within 72 hours of SAE entry into the eCRF.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see

next Section) or to the medical monitor/SAE coordinator by telephone.

- Contacts for SAE reporting can be found in Study Reference Manual.

SAE Reporting to GSK via Paper CRF

- Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the **medical monitor or the SAE coordinator**.
- 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 Study Reference Manual.

12.4. Appendix 4: Collection of Pregnancy Information

Collection of Pregnancy Information

Female Participants who become pregnant

- Investigator will collect pregnancy information on any female participant, who becomes pregnant while participating in this study.
- Information will be recorded on the appropriate form and submitted to GSK within 24 hours of learning of a participant's pregnancy.
- Participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow up information on participant and neonate, which will be forwarded to GSK Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.
- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the investigator, will be reported to GSK as described in Appendix 3. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Any female participant who becomes pregnant while participating

- Will be withdrawn from the study.