TITLE PAGE

Protocol Title: A randomized, multi-center, open-label, cross-over study comparing critical errors, overall errors, training/teaching time, and preference attributes of the ELLIPTA dry powder inhaler versus the BREEZHALER dry powder inhaler, in adult participants with mild to moderate asthma.

Protocol Number: 213306

Compound Number or Name: GSK2285997

Brief Title: A comparison of critical errors, overall errors, training/teaching time, and preference attributes of the ELLIPTA versus BREEZHALER dry powder inhalers in adult participants with asthma.

Study Phase: IV

Sponsor Name and Legal Registered Address:

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Manufacturer: Placebo **BREEZHALER,**

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Approval Date: 05-JAN-2021

SPONSOR SIGNATORY:

Protocol Title: A randomized, multi-center, open-label, cross-over study comparing critical errors, overall errors, training/teaching time, and preference attributes of the ELLIPTA dry powder inhaler versus the BREEZHALER dry powder inhaler, in adult participants with mild to moderate asthma.

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1. PROTOCOL SUMMARY

1.1. Synopsis

A randomized, multi-center, open-label, cross-over study comparing critical errors, overall errors, training/teaching time, and preference attributes of the ELLIPTA dry powder inhaler versus the BREEZHALER dry powder inhalers, in adult participants with mild to moderate asthma.

Brief Title: A comparison of critical errors, overall errors, training/ teaching time, and preference attributes of the ELLIPTA versus BREEZHALER dry powder inhalers in adult participants with asthma

Rationale: Previous evidence has demonstrated that participants with chronic obstructive pulmonary disease (COPD) had significantly fewer critical errors (defined as an error that is most likely to result in no or significantly reduced medication being inhaled) with the ELLIPTA dry powder inhaler (DPI) than with the BREEZHALER DPI after only reading the patient information leaflet (PIL); however, the performance of the ELLIPTA DPI compared to the BREEZHALER DPI remains untested in asthma patients. As many as 25% of asthma patients have never received instruction on inhaler technique from a health-care professional (HCP) and therefore it is considered important that patients be prescribed an inhaler that is least prone to patient errors after the only instruction on technique received is via the reading of the patient information leaflet. This study is designed therefore to provide data in asthma participants to assist HCPs in assessing the various attributes of the ELLIPTA and BREEZHALER DPIs, by comparing the incidence of critical and overall errors, patient preference, willingness to continue with the inhaler and time to correct use.

Objectives and Endpoints:

Primary objective	**Endpoint**
To compare the proportion of participants who make at least one critical error after reading the section on inhaler use in the patient information leaflets (PILs) for ELLIPTA and BREEZHALER inhalers	Participants who make at least one critical error after reading the section on inhaler use in the patient information leaflets (PILs).
Secondary Objectives	**Endpoints**
To compare the proportion of participants who still make at least one critical error after receiving further instruction from the Healthcare Professional (HCP) for ELLIPTA and BREEZHALER inhalers	Participants who still make at least one critical error after receiving further instruction (up to 3) from the HCP.

To compare the proportion of overall errors made by the participants after reading the PIL, and if necessary, with additional instruction from the HCP for ELLIPTA and BREEZHALER inhalers	• Participants who make at least one overall error after reading the PIL. • Participants who still make at least one overall error after receiving further instruction (up to 3) from the HCP.
To summarize the number of errors (critical and overall) made on each inhaler, with or without further HCP instruction.	Number of errors made after reading the PIL(s), and, if necessary, after receiving further instruction from the HCP.
To compare the proportion of participants that require further instruction from the HCP to demonstrate correct inhaler use for ELLIPTA and BREEZHALER inhalers	Requiring further instruction from the HCP to demonstrate correct inhaler use.
To compare the Training/Teaching Time required to demonstrate correct inhaler use for ELLIPTA and BREEZHALER inhalers-	• The amount of time taken to demonstrate inhaler use without HCP intervention (T1). • The amount of time taken to be given instruction by the HCP (up to 3 times) on use of the inhaler and to demonstrate inhaler use (T2). • The total amount of time taken to demonstrate inhaler use (T1+T2).
To compare ease-of-use for ELLIPTA and BREEZHALER inhalers	Ease-of-use from questionnaire. This will be grouped as easy ([redacted] or difficult [redacted]. The variables will include: • Ease of use rating • Telling how many doses are left in inhaler • Learning how to use the inhaler • Handling the inhaler • Preparing the inhaler • Holding the inhaler while using it
To summarize ease-of-use for ELLIPTA and BREEZHALER inhalers	Ease-of-use from questionnaire [redacted]. The variables will include the: • Ease of use rating • Telling how many doses are left in inhaler • Learning how to use the inhaler

	• Handling the inhaler • Preparing the inhaler • Holding the inhaler while using it
To compare the willingness to continue with the ELLIPTA and/or BREEZHALER inhaler	Willingness to continue with the inhaler using a visual analogue scale (VAS) between 0 CCI [redacted] to 100 CCI [redacted]
To compare preference attributes for ELLIPTA and BREEZHALER inhalers	Inhaler preference from questionnaire (ELLIPTA, BREEZHALER or no preference). The variables will include: • Preferred inhaler, overall. • Number of steps to take the medication • Time needed to take the medication • How easy the inhaler is to use • Size of the inhaler • Comfort of the mouthpiece • Ease of opening the inhaler
Safety	
To evaluate the safety of the ELLIPTA device and the BREEZHALER device	Incidence of adverse device effects (ADEs)/serious adverse events (SAEs)/serious adverse device effects (SADEs).

The primary estimand is the odds ratio between the ELLIPTA inhaler and the BREEZHALER inhaler in participants with mild to moderate asthma who make at least one critical error while demonstrating use of the inhaler after reading the PIL(s) based on participants who were able to attempt to demonstrate the use of both inhalers.

The primary estimand consists of the following attributes:

- *Inhaler comparison*: ELLIPTA or BREEZHALER inhaler.
- *Population:* participants with mild to moderate asthma diagnosis who attempt demonstration of both inhalers.
- *Variable:* participants who make at least one critical error after reading the section on inhaler use in the PIL (without further instruction).
- *Population-summary measure*: The odds ratio between the ELLIPTA and BREEZHALER inhalers.
- *Intercurrent event:* Not attempting demonstration of the inhaler (ELLIPTA or BREEZHALER). This is addressed in the population attribute (principal stratum strategy).

A principal stratum strategy will be used to address the intercurrent event for participants who do not attempt demonstration of the inhaler (ELLIPTA or BREEZHALER). This means all participants randomized will fall into exactly one of the following four strata:

1. S_{00}: Stratum of randomized participants who attempt inhaler demonstration (ELLIPTA and BREEZHALER) independent of period.
2. S_{01}: Stratum of randomized participants who attempt the demonstration of the BREEZHALER inhaler and do not attempt demonstration of the ELLIPTA inhaler independent of period.
3. S_{10}: Stratum of randomized participants who attempt the demonstration of the ELLIPTA inhaler and do not complete demonstration of the BREEZHALER inhaler independent of period.
4. S_{11}: Stratum of randomized participants who do not attempt inhaler demonstration (ELLIPTA and BREEZHALER) independent of period.

Comparisons made between the ELLIPTA and BREEZHALER inhaler will be based on those who fall in the S_{00} stratum.

All secondary estimands will use the same population, inhaler comparison and strategy for the intercurrent event as for the primary estimand. Secondary estimands for the proportion of participants who still make at least one critical error after receiving further HCP instruction, the proportion of participants who make at least one overall error after reading the PIL(s) and the proportion of participants who make at least one overall error after receiving further HCP instruction will use the same summary measure as for the primary estimand. Training/teaching time will be summarized using median time for each inhaler.

Overall Design:

The study will be a randomized, multi-center, open label, placebo inhaler-handling study with a 2x2 complete block crossover design. The study involves two visits which can be completed on the same day: Visit 0 (V0) is for screening and informed consent while V1 is for the inhaler assessment (V1). Visit 1 must be completed no later than 30 days after the initial consent at Visit 0. Eligible participants will be randomized to test either the ELLIPTA DPI followed by BREEZHALER DPI or BREEZHALER DPI followed by ELLIPTA DPI. After the critical and overall errors assessment has been completed for each inhaler, participants will complete the inhaler ease-of-use questionnaire and then be asked to complete a visual analogue scale (VAS) on their willingness to continue with the inhaler. Once participants have completed assessments for both inhalers, they will complete one of the two versions of the preference questionnaire in each of the two-blocks

The population to be studied is participants aged 18 years and older with mild to moderate asthma who have been prescribed to use maintenance therapy with inhaled corticosteroids (ICS) or ICS/long acting β2-Agonist (LABA) for at least 12 weeks prior to study and naïve to both ELLIPTA and BREEZHALER DPI inhalers. Main exclusion criteria is concurrent diagnosis of COPD.

Number of Participants: This study will randomly assign 114 adult participants with mild to moderate asthma

Brief Summary:

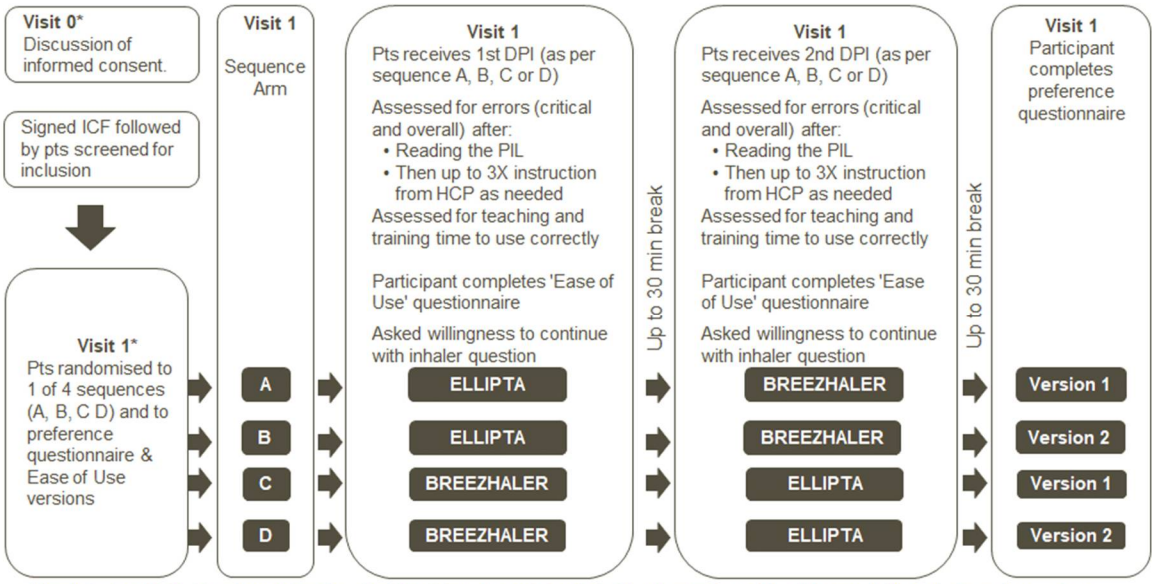
This is a randomized, multi-centre, open label, placebo inhaler-handling study with a 2x2 complete block crossover design to study critical errors, overall errors, training/teaching time, ease-of-use and willingness to continue and preference attributes of two dry powder inhalers: ELLIPTA and BREEZHALER. This study will randomly assign 114 adult asthma participants aged ≥18 years with mild to moderate asthma, naïve to both the DPI inhalers (ELLIPTA and BREEZHALER). Each participant will be randomized to one of the four groups: ELLIPTA followed by BREEZHALER or BREEZHALER followed by ELLIPTA and further refined by assignment of the preference questionnaire version. The study involves two visits which can be completed on the same day.

Intervention Groups and Duration:

The eligible participants will be randomized to receive either the ELLIPTA DPI followed by BREEZHALER DPI or BREEZHALER DPI followed by ELLIPTA DPI. As this is an inhaler use study, placebo inhalers will be utilised.

Data Monitoring/ Other Committee: No

1.2. Schema



*V0 ample time is provided for informed consent discussions. If participant is happy to proceed, they sign the informed consent form and then will be screened. V0 can take place on the same day as V1 where participants are randomised to one of 4 treatment sequences. V1 should be completed no later than 30 days after V0

1.3. Schedule of Activities (SoA)

Visit Number	**V0**	**V1**	**Notes**
Study Day	**1**	**1 (or 2*)**	*V0 can take place on the same day as V1. V1 should be completed no later than 30 days after V0.
Procedure:			
Screening Assessments			Completed prior to randomization
Written informed consent	X		Participants must be randomized within 30 days of providing written informed consent[a].
Participant demography	X		Age, year of birth, sex, ethnicity and geographic ancestry will be recorded
Medical/disease history including Asthma	X		Participant will have a medical history of asthma, confirmed by HCP
Concomitant asthma medication history	X		Current asthma concomitant medication will be recorded.
Inclusion/exclusion criteria	X[b]		All criteria must be met prior to randomization at V1
Study Assessments			Completed once participants are confirmed as eligible
Randomization		X	Randomized to inhaler order and preference questionnaires
Assess the number of inhaler errors (critical and overall)[c] on each inhaler after reading the relevant section of the PIL for Inhaler tested		X	No instruction is provided by the HCP for this assessment.
Assess the number of inhaler errors (overall and critical)[c] on each inhaler after each of 3 attempts following instruction by HCP		X	If a participant cannot show correct use after reading the inhaler use sections of the PIL (Attempt 1), then the HCP has up to 3 attempts to instruct the participant to attain this (Attempts 2-4).

Visit Number	V0	V1	Notes
Teaching-Training Time for each inhaler.		X	The HCP will record • Start and end time of participant reading the PIL (T0) • Start and end time of first demonstration following PIL reading (T1). • Start time from the first HCP instruction to participant demonstrating correct use (up to 3 attempts) (T2).
Ease-of-use questionnaire[d]		X	Participant will complete ease-of-use Questionnaire for that inhaler
Willingness to continue VAS[e]		X	At the end of the assessment for each inhaler, participant will be asked to indicate their willingness to continue with the device using a VAS between 0 CCI [redacted] CCI to 100 CCI [redacted]
Preference questionnaire[f]		X	Participant will complete version of preference questionnaire to which they have been randomized.
SAE/AE assessment		X	Collected until completion of final study assessment at V1.

a) Participants could start the reconsent, screening and randomization procedures once more if they miss the 30-day window
b) If Visit 1 is a separate day to the screening visit (Visit 0), the investigator should confirm that the participant has not used one of the inhalers of interest (i.e. ELLIPTA or BREEZHALER) in the time between V0 and V1 prior to randomization. If an inhaler has been used, then this would be a screen fail.
c) Overall and critical errors for each inhaler are defined in Appendix 3
d) Ease of use questionnaire is included in Appendix 4
e) Willingness to continue VAS is in Appendix 5
f) Preference questionnaire is included in Appendix 6

- The Competent Authority (CA) and ethics committee (EC) will be informed of any safety issues that constitute a substantial amendment and require alteration of the safety monitoring scheme or amendment of the informed consent form (ICF). The changes will be approved by the CA and the EC before implementation

2. INTRODUCTION

Inhaled medications (i.e., inhaled corticosteroids [ICSs], short-acting and long-acting β_2-adrenergic agonists [SABAs and LABAs, respectively] and long-acting anti-muscarinic antagonists [LAMA] are the cornerstone of asthma management [GINA, 2020]. Short-acting bronchodilators (e.g. SABAs and short-acting muscarinic antagonists) are given as quick-relief medications to alleviate acute attacks, while ICS, and ICS/LABA ± LAMA combinations, which target the underlying inflammatory pathology of the disease and bronchoconstriction are given as regular maintenance therapy to control symptoms and reduce the risk of exacerbations [GINA, 2020].

In terms of inhalers, GINA advises to choose the most appropriate inhaler for patients and if there are several inhalers to choose from, to involve the patient in this choice [GINA, 2020]. GINA also recommends checking inhaler technique at every opportunity and to identify and correct any errors by demonstration of inhaler use before escalating the therapy. Assessing and understanding inhaler handling errors by patients is therefore key to maximising the therapeutic benefit of the medication and ensuring as good a control of their disease can be achieved.

2.1. Study Rationale

Previous evidence has demonstrated that participants with COPD had significantly fewer critical errors with ELLIPTA than with the BREEZHALER [van der Palen, 2016] when reading the patient information leaflet (PIL). However, its performance against BREEZHALER remains untested in asthma patients. As many as 25% patients have never received verbal inhaler technique instruction [Lavorini, 2008] and therefore it is important that patients should be prescribed an inhaler that is least prone to errors after only reading the patient information leaflet. This study is designed therefore to provide data in asthma participants to assist health-care professionals (HCPs) in assessing the various attributes of both inhalers, including critical and overall errors, time to correct use, ease-of-use questionnaire, willingness to continue with the inhaler and patient preference.

2.2. Background

The importance of correct use of inhalers is emphasised by GINA for asthma patients [GINA, 2020] and by GOLD for patients with chronic obstructive pulmonary disease (COPD) [GOLD, 2020] by ensuring selection of the appropriate inhaler, demonstration of the inhaler and assessment of inhaler use is reviewed prior to escalating therapy. Errors made by the patient can affect the amount of medication received and disease control so it is essential to ensure good inhaler technique.

Comparison of inhaler techniques between asthma and COPD patients suggests inconsistencies with some observational studies demonstrating similar error rates [Arora, 2014; Chorão, 2014; Takaku, 2017; Ocakli, 2018] and other studies demonstrating higher rates in COPD patients [Khassawneh, 2008; Melani, 2011] but when adjusting for age, inhaler and level of instruction, this difference disappeared [Melani, 2011]. Study designs often observational, in usual practice with patients being familiar with their

inhalers, in different geographical and socio-economic areas may account for the inconsistent effects. Old age [Arora, 2014; Chorão, 2014], lower socio-economic [Arora, 2014] and educational levels [Arora, 2014; Chorão, 2014] and female gender [Chorão, 2014] were risk factors for greater errors in inhaler handling.

The ELLIPTA DPI was developed to deliver various inhaled maintenance medications, including mono, dual and triple therapies, for the treatment of asthma and COPD. Participants with asthma or COPD make fewer critical errors (defined as an error that is most likely to result in no or significantly reduced medication being inhaled) and overall errors (any error in inhaler technique) with the ELLIPTA DPI than with other DPIs [van der Palen, 2016]. Furthermore, participant preference for the ELLIPTA DPI has been demonstrated previously versus other DPIs for many attributes, including ease of use and time to train [van der Palen, 2016]. The BREEZHALER DPI is also approved for use with a variety of inhaled mono- or combination-medications although has not yet been widely used by asthma patients.

The present study involves the use of ELLIPTA and BREEZHALER DPI inhalers that contain placebo and not active treatments. Participants will continue to take their own prescribed asthma medication and other concomitant medication during the study. Participants should also follow-up with their regular physician for their asthma healthcare during the study.

The placebo inhaler for ELLIPTA and the placebo capsules for BREEZHALER contain the excipients lactose. Participants with a known hypersensitivity to these or severe milk protein allergy are excluded from the study (Section 5.2)

2.3. Benefit/Risk Assessment

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention(s)		
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 from FF/VI, 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.
Allergic reaction due to hypersensitivity to placebo excipients.	The placebo inhalers and placebo capsules (for BREEZHALER) contain the excipient lactose. There are known allergies to this ingredient.	Participants with a known hypersensitivity to this, or severe milk protein allergy that could contraindicate study participation are excluded from the study (Section 5.2). If an allergic reaction occurs, it should be treated immediately with a fast and short acting inhaled bronchodilator. Investigators will be instructed to assess the participant's condition to determine their eligibility to continue in the study.

2.3.2. Benefit Assessment

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

2.3.3. Overall Benefit: Risk Conclusion

The overall potential risk identified is considered minimal due to the placebo nature of the study and the 1-day duration of inhaler assessments at Visit 1.

3. OBJECTIVES AND ENDPOINTS AND ESTIMANDS

Primary objective	**Endpoint**
To compare the proportion of participants who make at least one critical error after reading the section on inhaler use in the patient information leaflets (PILs) for ELLIPTA and BREEZHALER inhalers.	Participants who make at least one critical error after reading the section on inhaler use in the patient information leaflets (PILs).
Secondary Objectives	**Endpoints**
To compare the proportion of participants who still make at least one critical error after receiving further instruction from the Healthcare Professional (HCP) for ELLIPTA and BREEZHALER inhalers.	Participants who still make at least one critical error after receiving further instruction (up to 3) from the HCP.
To compare the proportion of overall errors made by the participants after reading the PIL, and if necessary, with additional instruction from the HCP for ELLIPTA and BREEZHALER inhalers.	• Participants who make at least one overall error after reading the PIL(s). • Participants who still make at least one overall error after receiving further instruction (up to 3) from the HCP.
To summarize the number of errors (critical and overall) made on each inhaler, with or without further HCP instruction.	Number of errors made after reading the PIL(s), and, if necessary, after receiving further instruction from the HCP.
To compare the proportion of participants that require further instruction from the HCP to demonstrate correct inhaler use for ELLIPTA and BREEZHALER inhalers.	Requiring further instruction from the HCP to demonstrate correct inhaler use.

To compare the Training/Teaching Time required to demonstrate correct inhaler use for ELLIPTA and BREEZHALER inhalers.	• The amount of time taken to demonstrate inhaler use without HCP intervention (T1). • The amount of time taken to be given instruction by the HCP (up to 3 times) on use of the inhaler and to demonstrate inhaler use (T2). • The total amount of time taken to demonstrate inhaler use (T1+T2).
To compare ease-of-use for ELLIPTA and BREEZHALER inhalers.	Ease-of-use from questionnaire. This will be grouped as easy CCI [redacted] or difficult CCI [redacted] The variables will include: • Ease of use rating • Telling how many doses are left in inhaler • Learning how to use the inhaler • Handling the inhaler • Preparing the inhaler • Holding the inhaler while using it.
To summarize ease-of-use for ELLIPTA and BREEZHALER inhalers.	Ease-of-use from questionnaire CCI [redacted] The variables will include the: • Ease of use rating • Telling how many doses are left in Inhaler • Learning how to use the inhaler • Handling the inhaler • Preparing the inhaler • Holding the inhaler while using it.
To compare the willingness to continue with the ELLIPTA and/or BREEZHALER inhaler.	Willingness to continue with the inhaler using a visual analogue scale (VAS) between 0 CCI [redacted] to 100 CCI [redacted] CCI [redacted]
To compare preference attributes for ELLIPTA and BREEZHALER inhalers.	Inhaler preference from questionnaire (ELLIPTA, BREEZHALER or no preference). The variables will include: • Preferred inhaler, overall. • Number of steps to take the medication

	• Time needed to take the medication • How easy the inhaler is to use • Size of the inhaler • Comfort of the mouthpiece • Ease of opening the inhaler.
Safety	
To evaluate the safety of the ELLIPTA device and the BREEZHALER device.	Incidence of adverse device effects (ADEs)/serious adverse events (SAEs)/serious adverse device effects (SADEs).

The primary estimand is the odds ratio between the ELLIPTA inhaler and the BREEZHALER inhaler in participants with mild to moderate asthma who make at least one critical error while demonstrating use of the inhaler after reading the PIL(s) based on participants who were able to attempt to demonstrate the use of both inhalers.

The primary estimand consists of the following attributes:

- *Inhaler comparison*: ELLIPTA or BREEZHALER inhaler.

- *Population:* participants with mild to moderate asthma diagnosis who attempt demonstration of both inhalers.

- *Variable:* participants who make at least one critical error after reading the section on inhaler use in the PIL (without further instruction).

- *Population-summary measure*: The odds ratio between the ELLIPTA and BREEZHALER inhalers.

- *Intercurrent event:* Not attempting demonstration of the inhaler (ELLIPTA or BREEZHALER). This is addressed in the population attribute (principal stratum strategy).

A principal stratum strategy will be used to address the intercurrent event for participants who do not attempt demonstration of the inhaler (ELLIPTA or BREEZHALER). This means all participants randomized will fall into exactly one of the following four strata:

1. S_{00}: Stratum of randomized participants who attempt inhaler demonstration (ELLIPTA and BREEZHALER) independent of period.
2. S_{01}: Stratum of randomized participants who attempt the demonstration of the BREEZHALER inhaler and do not attempt demonstration of the ELLIPTA inhaler independent of period.
3. S_{10}: Stratum of randomized participants who attempt the demonstration of the ELLIPTA inhaler and do not complete demonstration of the BREEZHALER inhaler independent of period.

4. S_{11}: Stratum of randomized participants who do not attempt inhaler demonstration (ELLIPTA and BREEZHALER) independent of period.

Comparisons made between the ELLIPTA and BREEZHALER inhaler will be based on those who fall in the S_{00} stratum.

All secondary estimands will use the same population, inhaler comparison and strategy for the intercurrent event as for the primary estimand. Secondary estimands for the proportion of participants who still make at least one critical error after receiving further HCP instruction, the proportion of participants who make at least one overall error after reading the PIL(s) and the proportion of participants who make at least one overall error after receiving further HCP instruction will use the same summary measure as for the primary estimand. Training/teaching time will be summarized using median time for each inhaler.

4. STUDY DESIGN

4.1. Overall Design

The study will be a randomized, multi-center, open label, placebo study with a 2x2 complete block crossover design. The study will have one visit (although there could be two visits with up to 30 days between the informed consent visit (V0) and the study intervention visit (V1).

Eligible participants with mild to moderate asthma will be randomized to test either the ELLIPTA DPI (containing placebo) followed by BREEZHALER DPI (with placebo capsules), or vice versa in each of the two blocks for the crossover study. Only participants who are naïve to both ELLIPTA and BREEZHALER inhaler will be included.

Participants will demonstrate inhaler use for the first inhaler after reading the relevant sections of the PIL (Attempt 1). If the participant makes any errors, the investigator demonstrates the correct use of the inhaler by conducting a full demonstration as described in the relevant section of the PIL, and the participant will try inhaler use again (Attempt 2). If after the first demonstration by the investigator the participant continues to make errors, the investigator will demonstrate correct inhaler use to the participant up to two additional times (Attempts 3 & 4).

Following each attempted use of the inhaler by the participant, the trained investigator will assess for and document any critical errors (i.e. defined as an error that is most likely to result in no or significantly reduced medication being inhaled) (See Appendix 3) and non-critical errors made by the participant. This process of error assessment will be used to assess for critical and non-critical errors made by the participant for both inhalers being tested.

At the end of the assessment of the first inhaler, participants will be asked to. complete the ease-of-use questionnaire for this device (Appendix 4) followed by

participant completion of the visual analogue scale (VAS) on their willingness to continue with this inhaler (Appendix 5).

Participants will be permitted up to a 30-minute break (if required) between completing the assessment of the first inhaler and commencing error assessments for the second inhaler. The second inhaler critical errors assessment follows the same sequence of testing as the first – (Attempts 1 is with no HCP instruction and Attempts 2-4 are with HCP instruction as required).

Once the error assessment of the second inhaler has been completed the participant will complete the ease-of-use questionnaire for this device (Appendix 4) followed by participant completion of the VAS on their willingness to continue with this inhaler (Appendix 5).

If required, another period of up to 30 min for a break would be allowed followed by the participant completing one of the two versions of the preference questionnaire (Appendix 6), as per randomization sequence.

Two versions of the inhaler preference questionnaire (See Appendix 6) are provided to minimize any potential bias introduced from the order in which the inhalers are taken in relation to the order the inhalers are assessed by the participant in each questionnaire. The version of each questionnaire to be completed by each participant is determined by the sequence arm they are randomly assigned to at Visit 1 (see Table 1).

Further details are available in the study schematic in Section 1.2 and the assessments to be performed are detailed in the schedule of activities (SOA) in Section 1.3 and in study assessments Section 8.

4.2. Scientific Rationale for Study Design

- Assessment of critical errors from inhaler handling studies has been used in previous GSK studies using an open-label, cross-over, placebo treatment design [van der Palen, 2016 van der Palen, 2018].
- In common with these previous studies, a cross-over design has been chosen for the present study. No carry-over effects were demonstrated when using this design previously [van der Palen, 2013]. This design also allows participants to act as their own control in assessing their ability to use both inhalers, as well as allowing for the screening visit (V_0) and the Visit 1 to occur on the same day, thereby reducing the inconvenience to participants of multiple study site visits. Breaks of up to 30-minutes have been included in the design to allow a degree of flexibility for the participant.
- The study will use placebo inhalers for all study assessments. This aims to remove bias from any perceived benefit a participant may have for a particular active treatment. There is also no need for participants to withhold any treatments they are receiving, and there will be no need for a washout period between the inhaler used in each Assessment Period.

4.2.1. Participant Input into Design

There was no participant engagement into the design.

4.3. Justification for Dose

This is a placebo inhaler study so there is no active medication.

4.4. End of Study Definition

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

A participant is considered to have completed the study if he/she has completed the critical and overall error assessment for both inhalers, willingness to continue with inhaler question and both the questionnaires (preference and ease of use) in the study including the last scheduled procedure shown in the SoA (Section 1.3)

5. STUDY POPULATION

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

5.1. Inclusion Criteria

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

Age

1. Participant must be aged 18 years or older at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2. Participants who have a confirmed mild or moderate asthma diagnosis as per GINA, 2020.
3. Participants must be on asthma maintenance therapy (ICS or ICS/LABA) for at least 12 weeks prior to study participation.
4. Participants must be naïve to both the ELLIPTA and BREEZHALER inhalers

   If Visit 1 is a separate day from the screening visit (Visit 0), the investigator should confirm that the participant has not used one of the inhalers of interest (i.e. ELLIPTA or BREEZHALER) in the time between V0 and V1 prior to randomization. If an inhaler has been used, then this would be a screen fail.

*V0 can take place on the same day as V1. V1 should be completed no later than 30 days after consent. Participants could start the reconsent, screening and randomization procedures **once** more if they miss the 30-day window.*

5. Male or female who are not pregnant or not planning a pregnancy during the study or not Lactating

Informed Consent

6. Capable of giving signed informed consent as described in Section 10.1.3 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

5.2. Exclusion Criteria

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

Medical Conditions

1. Concurrent diagnosis of COPD or other respiratory disorders including active tuberculosis, lung cancer, bronchiectasis, sarcoidosis, lung fibrosis, pulmonary hypertension, interstitial lung diseases or other active pulmonary diseases.
2. History of hypersensitivity to any components of the study inhaler (e.g., lactose). 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.
3. Historical or current evidence of clinically significant or rapidly progressing or unstable 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.

Other Exclusions

4. Drug/alcohol abuse: Participants with a known or suspected alcohol or drug abuse, which in the opinion of the investigator could interfere with the participant's proper completion of the protocol requirement.
5. A participant 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, as well as employees of GSK or Novartis.
6. Inability to Read: In the opinion of the investigator, any participant who is unable to read and/or would not be able to complete a questionnaire and understand verbal instructions.
7. Medical and physical conditions that in the opinion of the investigator could impact the ability of the participant to manipulate the inhaler.

5.3. Lifestyle Considerations

There are no lifestyle restrictions.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomized/entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, any protocol deviations and any serious adverse events (SAEs).

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened one further time at the discretion of the investigator. Rescreened participants must be assigned a new participant number for every screening/rescreening event.

5.5. Criteria for Temporarily Delaying Enrollment/Randomization/Administration of Study Intervention Administration

The study involves two visits (V0 and V1), which can be completed on the same day. The assessments are completed on V1, which is when participants are randomized so this section is not applicable.

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

6.1. Study Intervention(s) Administered

ARM Name	ELLIPTA Arm	BREEZHALER Arm
Intervention Name	Placebo ELLIPTA	Placebo BREEZHALER
Type	Dry Powder Inhaler	Dry Powder Inhaler
Dose Formulation	Placebo composed of lactose	Placebo
Unit Dose Strength(s)	N/A	N/A
Dosage Level(s)	Placebo	Placebo
Route of Administration	For Oral Inhalation	For Oral Inhalation

IMP and NIMP	NIMP	NIMP
Sourcing	GSK	Novartis
Packaging and Labelling	To be labelled in accordance to Regulatory Requirements	To be labelled in accordance to Regulatory Requirements

6.1.1. Medical Devices

- The GSK manufactured medical devices provided for use in this study is the ELLIPTA.
- The other medical device (not manufactured by or for GSK provided for use in this study is the BREEZHALER (Novartis).
- GSK medical device deficiencies, (including malfunction, use error and inadequate labelling) shall be documented, and reported by the investigator throughout the clinical investigation (see Section 8.3.8) and appropriately managed by the sponsor.

6.2. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study interventions 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.
3. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
4. Further guidance and information for the final disposition of unused study intervention are provided in the study Reference Manual.
    - Under normal conditions of handling and administration, study intervention is not expected to pose significant safety risks to site staff.
    - A Material Safety Data Sheet (MSDS)/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from GSK.

6.3. Measures to Minimize Bias: Randomization and Blinding

This is an open-label study; however, the specific intervention to be taken by a participant will be assigned using an IVRS/IWRS. The site will contact the IVRS/IWRS prior to the start of study intervention administration for each participant. The site will record the intervention assignment on the applicable electronic case report form (eCRF), if required. Potential bias will be reduced by the following steps: by randomizing the order of intervention and the preference questionnaire versions that will be answered by the participants as per Table 1.

Table 1 Randomization Schedule

Sequence Arm	Part 1	Part 2	Preference Questionnaire (versions)
A	ELLIPTA	BREEZHALER	1
B	ELLIPTA	BREEZHALER	2
C	BREEZHALER	ELLIPTA	1
D	BREEZHALER	ELLIPTA	2

6.4. Study Intervention Compliance

- The participant must use the inhaler under supervision of the investigator or designee, who will assess if there are any errors in the use of the inhaler. The intervention follows sequential hierarchical use of the inhaler
    - First Inhaler
        - First use after reading inhaler use section of PIL (Attempt 1)
        - If Failed – Second use after first instruction by HCP (Attempt 2)
        - If Failed – Third use after second instruction by HCP (Attempt 3)
        - If Failed – fourth use after third instruction by HCP (Attempt 4)
        - If Failed – Recorded and no further intention with first inhaler
    - Second Inhaler
        - First use after reading inhaler use section of PIL (Attempt 1)
        - If Failed – Second use after first instruction by HCP (Attempt 2)
        - If Failed – Third use after second instruction by HCP (Attempt 3)
        - If Failed – fourth use after third instruction by HCP (Attempt 4)
        - If Failed – Recorded and no further intention

6.5. Dose Modification

This section is not applicable.

6.6. Continued Access to Study Intervention after the End of the Study

This section is not applicable as no active treatments are being administered in the study.

6.7. Treatment of Overdose

This section is not applicable as all participants will receive the placebo only.

6.8. Concomitant Therapy

Any medication that the participant is receiving at the time of enrolment or receives during the study must be recorded along with:

- reason for use
- dosage information including dose and frequency

In case, the participants visit the site within the 30 days interval between the Visit 0 and Visit 1 for enrolment, the participants can continue to take their concomitant medications as per their routine therapy except the use of ELLIPTA and BREEZHALER inhalers. The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

This section is not applicable since discontinuation of study intervention corresponds to withdrawal from the study since each inhaler is only available on a single day.

7.2. Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioural, or compliance reasons. This is expected to be uncommon.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws during the interval between screening (V0) and Visit 1, there are no assessments that would need to be completed following withdrawal. A participant can also withdraw following randomization. In such cases, the

participant may be asked to provide the reason for discontinuation which needs to be documented.

7.3. Lost to Follow Up

This section is not applicable as the assessment visit (V1) occurs on a single day

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA (Section 1.3).
- 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 intervention.
- Adherence to the study design requirements, including those specified in the SoA (Section 1.3), is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management and obtained before signing of ICF may be 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 (Section 1.3).
- Prior to randomization, at V1, all assessments to confirm inclusion at V0 will be completed. The details of these assessment are provided in the SoA (Section 1.3)

8.1. Efficacy Assessments

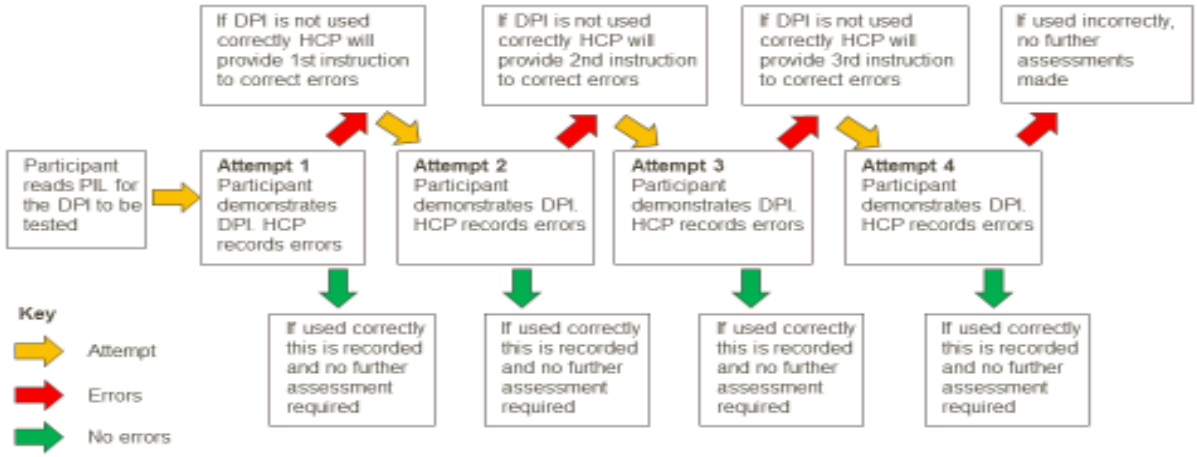
8.1.1. Assessment of errors in use of inhalers

- Participants will be randomized to the order of inhaler as detailed in Table 1 and the sequence of questionnaire completion is indicated in the study Schema in Section 1.2. Participants will be provided with the relevant sections of the PIL, explaining the correct use for both inhalers. The critical and overall errors per inhaler and how these have been defined are outlined in Section 10.3 Appendix 3
- The errors listed will be aligned with the correct use information from the respective PILs, in a checklist for each inhaler which will be provided to the HCPs for scoring errors during the study conduct. The checklists to be completed by the investigator will be provided.

  The steps required to assess participant errors in using the inhalers is illustrated in Figure 1 and summarized below:

- Participants will demonstrate inhaler use after reading the use sections of the PIL which is provided to them by the investigator (Attempt 1).
- If the participant makes any errors according to the error checklists in Appendix 3, the investigator demonstrates the correct use of the inhaler, and the participant will try inhaler use again (Attempt 2). If after the first demonstration the participant continues to make errors, the investigator will again demonstrate correct inhaler use to the participant prior to the participant trying again (Attempt 3). If the participant has still not demonstrated correct use, the HCP will again demonstrate correct use for the final time, followed by the final attempt for the participant to demonstrate use of the inhaler (Attempt 4).
- Following each attempted use of the inhaler by the participant, the trained investigator will assess for, and document, any critical errors (i.e., defined as an error that is most likely to result in no or significantly reduced medication being inhaled) and non-critical errors made by the participant.
- This process of error assessment will be used to assess for critical and non-critical errors made by the participant for both inhalers being tested.
- Participants will be permitted up to a 30-minute break between completing the assessment of the first inhaler and commencing error assessments for the second inhaler.

Figure 1 Assessment of errors for each inhaler



8.1.2. Time taken to demonstrate correct use of the inhaler

Time taken to correctly use the inhaler will be recorded as follows:

- T0: the time taken from when the participant starts to read the relevant sections of the PIL until they complete the reading and are ready to start demonstration of the inhaler
- T1: the time from when the participant starts the demonstration of the inhaler after reading the PIL until they have completed demonstration of inhaler use
- T2: the time from when the investigator starts to instruct the participant until correct use is demonstrated (up to max. 3 attempts)
    - T2 includes the time used by the investigator for re-instructing the participants throughout.
- T1 + T2: the time from when the participant starts the demonstration until correct use is demonstrated (4 attempts - once after the reading the PIL and following instruction from investigator up to 3 times).

8.1.3. Assessment of ease-of-use

Once the error assessment of each inhaler has been completed the participant will complete the ease of use questionnaire for that device (Appendix 4). This is a series of 6 questions which the participant is asked to rate their ease of use experience with the device. This is completed for the first device before moving to the critical errors assessment of the second device.

8.1.4. Willingness to continue with the inhaler

After completion of the critical errors assessment for each inhaler and the ease of use questionnaire for that inhaler, the participant will also be asked the following question using a visual analogue scale (Appendix 5): 'On a scale of 0 CCI to 100 CCI would you be willing to continue with this inhaler?'

8.1.5. Preference questionnaire

After completing the errors in use assessment for both devices, the participants will complete the assigned preference questionnaires (Appendix 6).

8.2. Safety Assessments

There are no safety assessments within this study except collection of adverse device events, serious adverse device events and serious adverse events arising from the use of the inhaler. These will be dealt with as per Section 8.3.

8.2.1. Pregnancy Testing

Pregnancy testing is not required during the study.

8.3. Serious Adverse Events (SAEs) and Other Safety Reporting

The definitions of adverse events (AE) or serious adverse events (SAEs) can be found in Section 10.2. **In this study, only AEs which meet the seriousness criteria will be collected**. The method of recording, evaluating, and assessing causality of SAEs and the procedures for completing and transmitting SAE reports are provided in Section 10.2.

All device-related safety events (adverse device effects [ADEs] and serious adverse device effects [SADEs]) will be collected in this study. Definitions of ADEs and SADEs, can be found in Section 10.7. Device deficiencies are covered in Section 10.7.

SAEs, ADEs and SADEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and reporting events that meet the definition of an SAE, ADE and SADE and remain responsible for following up all SAEs and SADEs only.

8.3.1. Time Period and Frequency for Collecting SAE, ADE, and SADE Information

- All SAEs, ADEs, and SADEs will be collected from consent until the time points specified in the SoA (Section 1.3).
- Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded as Medical History/Current Medical Conditions.
- All SAEs and SADEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 2. The investigator will submit any updated SAE/SADE data to the sponsor within 24 hours of it being available.
- Investigators are not obligated to actively seek information on SAEs and SADEs after the conclusion of the study participation. However, if the investigator learns of any SAE/SADE, 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 intervention or study participation, the investigator must promptly notify the sponsor.

8.3.2. Method of Detecting SAEs, ADEs, and SADEs

- Care will be taken not to introduce bias when detecting SAEs, ADEs, and/or SADEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about SAE/ADE/SADE occurrence.

8.3.3. Follow-up of SAEs and SADEs

All SAEs/SADEs, will be followed until the event is resolved, stabilized, otherwise explained. Further information on follow-up procedures is given in Appendix 2.

8.3.4. Regulatory Reporting Requirements for SAEs/SADEs

- Prompt notification by the investigator to the sponsor of an SAE/SADE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention 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 intervention 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.
- An investigator who receives an investigator safety report describing an SAE/SADE or other specific safety information (e.g., summary or listing of SAEs/SADEs) from the sponsor will review Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.
- 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.
- The complaint including labelling failure must be logged, processed and reported under the requirements of the Regulation (EU) 2017/745 Medical Device Regulation (MDR) Article 80(2) and GSK Medical Device Complaint Management System in accordance with ISO 13485 procedural requirements for ELLIPTA Device. While for BREEZHALER, the data must be reported under the requirements of the Regulation (EU) 2017/745 Medical Device Regulation (MDR) Article 80(2). Further details on reporting are included in the study reference manual.

8.3.5. Cardiovascular and Death Events

For any cardiovascular events detailed in Section 10.2.3 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.

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

This section is not applicable

8.3.7. Adverse Events of Special Interest

This section is not applicable

8.3.8. Medical Device Deficiencies

Medical devices are being provided for use in this study. To fulfil regulatory reporting obligations worldwide, the investigator is responsible for the detection and documentation of events meeting the definitions of device deficiency that occur during the study with such devices.

The definition of a Medical Device Deficiency can be found in Section 10.7 Appendix 7 of the protocol.

8.3.8.1. Time Period for Detecting Medical Device Deficiencies

- Medical device deficiencies that result in an incident will be detected, documented, and reported during all periods of the study in which the medical device is used.
- If the investigator learns of any device deficiency at any time after a participant has been discharged from the study, and such device deficiency is considered reasonably related to a medical device provided for the study, the investigator will promptly notify the sponsor.
- The method of documenting Medical Device Incidents is provided in Section 10.6 Appendix 6 .

8.3.8.2. Follow-up of Medical Device Deficiencies

- Follow-up applies to all participants, including those who discontinue study intervention or the study.
- The investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the deficiency.
- New or updated information will be recorded on the originally completed form with all changes signed and dated by the investigator.

8.3.8.3. Prompt Reporting of Medical Device Deficiencies to Sponsor

- Device deficiencies will be reported to the sponsor within 24 hours after the investigator determines that the event meets the protocol definition of a device deficiency.
- The Medical Device Deficiency Report Form will be sent to the sponsor electronically. If electronic is unavailable, then paper reporting should be utilized.
- The sponsor will be the contact for the receipt of device deficiency reports.

8.3.8.4. Regulatory Reporting Requirements for Medical Device Incidents

- The investigator will promptly report all deficiencies occurring with any medical device provided for use in the study in order for the sponsor to fulfil the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.
- The investigator, or responsible person according to local requirements (e.g., the head of the medical institution), will comply with the applicable local regulatory requirements relating to the reporting of device deficiencies to the IRB/IEC.

8.4. Pharmacokinetics

Pharmacokinetic parameters are not being evaluated in this study.

8.5. Genetics and/or Pharmacogenomics

Genetics are not being evaluated in this study.

8.6. Biomarkers

Biomarkers will not be evaluated in this study.

8.7. Immunogenicity Assessments

Immunogenicity assessments will not be performed

8.8. Health Economics OR Medical Resource Utilization and Health Economics

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

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

The primary purpose of this study is to assess the number of critical errors (defined as an error that is most likely to result in no or significantly reduced medication being inhaled) made by asthma participants, after they have read the patient information leaflet(s) (PIL) for each inhaler. This is a superiority study.

The primary estimand is the odds ratio between the ELLIPTA and BREEZHALER inhaler in participants with mild to moderate asthma who make at least one critical error while demonstrating use of the inhaler after reading the PIL(s) based on participants who were able to attempt to demonstrate the use of both inhalers.

The null hypothesis is that there is no difference in the proportion of participants who make at least one critical error on the ELLIPTA inhaler compared with the BREEZHALER inhaler:

H0: $P_{ELLIPTA}=P_{BREEZHALER}$

The alternative hypothesis is that there is a difference in the proportion of participants who make at least one critical error on the ELLIPTA inhaler compared with the BREEZHALER inhaler:

H1: $P_{ELLIPTA}\neq P_{BREEZHALER}$

This comparison will be tested at the two-sided 5% significance level.

9.2. Sample Size Determination

A total of 114 participants will be randomly assigned to study intervention such that approximately 114 evaluable participants complete the study.

The sample size for a 2x2 crossover study is based on the formula presented by Chow, 2008 and Kung-Jong, 2016. To calculate the conditional odds ratio (via McNemar's) the proportion of participants who have discordant pairs (those who had at least one critical error in one inhaler but not the other) was determined based on expert advice. A panel of 5 experts was convened to consider the evidence from previous studies of similar design [van der Palen, 2016;van der Palen, 2018] and with consideration given to observational studies in the literature [Khassawneh, 2008; Melani, 2011; Arora, 2014; Chorão, 2014; Takaku, 2017; Ocakli, 2018]. A consensus view of the likely error rates that would be observed with the ELLIPTA and BREEZHALER devices was subsequently reached.

A consensus was reached that the proportion of participants who make a critical error in the ELLIPTA inhaler and not on the BREEZHALER inhaler would be 6% and the proportion of patients who make a critical error in the BREEZHALER inhaler and not on the ELLIPTA inhaler would be 20%.

Based on the discordant proportions, an odds ratio of 0.3 was calculated and a standard deviation on the log odds ratio scale of 2.785 was calculated based on GSK study 200301 [van der Palen, 2016. Based on these estimates and a two-sided Type I error rate of 5%, a total of 114 participants are required to provide 90% power. No withdrawals are expected based on previous similarly designed studies. No correlation between periods is assumed and no carry over effect is assumed based on previous evidence [van der Palen, 2013]. Moreover, both inhalers will contain placebo and participants may have up to a 30-minute break after demonstrating the first inhaler.

9.3. Analysis Sets

For the purposes of analysis, the following analysis data sets are defined:

Participant Analysis Set	**Description**
Screened	All participants screened and Signed ICF
Randomized	All participants randomized
Performance Evaluable	All participants who complete reading of the PIL(s) and attempt demonstration on both inhalers.
Safety	All randomized participants who complete (whether successful or unsuccessful) at least one inhalation with any study inhaler

9.4. Statistical Analyses

The statistical analysis plan will be finalized prior to data base lock (DBL) and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.4.1. Primary Endpoint

Objectives	**Statistical Analysis Methods**
Primary	**Primary estimand** The proportion of participants who make at least one critical error in each inhaler (ELLIPTA or BREEZHALER) after reading the section on inhaler use in the PIL(s) assessed on the Day/Visit 1. The primary treatment effect to be estimated will be the comparison of the ELLIPTA inhaler to the BREEZHALER inhaler. The population will be participants with mild to moderate asthma who attempt demonstration of both inhalers. The population-summary measure is an odds ratio. The intercurrent event is participants who do not attempt demonstration of the inhaler (ELLIPTA or BREEZHALER). A principal stratum strategy will be used to address the intercurrent event. Participants will fall into exactly one of the following four strata: 1. S_{00}: Stratum of randomized participants who attempt inhaler demonstration (ELLIPTA and BREEZHALER) independent of period.

Objectives	Statistical Analysis Methods
	2. S_{01}: Stratum of randomized participants who attempt the demonstration of the BREEZHALER inhaler and do not attempt demonstration of the ELLIPTA inhaler independent of period. 3. S_{10}: Stratum of randomized participants who attempt the demonstration of the ELLIPTA inhaler and do not complete demonstration of the BREEZHALER inhaler independent of period. 4. S_{11}: Stratum of randomized participants who do not attempt inhaler demonstration (ELLIPTA and BREEZHALER) independent of period. The estimated treatment effect will be based on participants who fall in the S_{00} strata. The comparison of ELLIPTA with BREEZHALER will be summarized by an odds ratio. The proportion of participants who make at least one critical error in each inhaler will be analysed using an exact conditional logistic regression model with participant as fixed strata with inhaler, and period as fixed effects. The odds ratio of ELLIPTA relative to BREEZHALER together with the 95% confidence interval and two-sided p-value will also be presented. Superiority will be declared based on a significance level at the two-sided 5% level. **Sensitivity analysis** A sensitivity analysis will be performed using a generalised mixed effects model with a binomial family and log link with a random effect for participant ID and inhaler, period, age and sex as fixed effects. An unstructured variance-covariance matrix will be used.

9.4.2. Secondary Endpoint(s)

Estimands for the secondary variables will use the same inhaler comparison, population and strategy for the intercurrent event as for the primary estimand. This means the estimated treatment effect comparing the ELLIPTA inhaler to the BREEZHALER inhaler will be based on the stratum of participants who were able to attempt demonstration on both inhalers. All comparisons will be made at the two-sided 5% significance level.

Objectives	Statistical analysis methods
To compare the proportion of participants who still make at least one critical error after	Participants who still make at least one critical error after receiving further instruction (up to 3) from the HCP. Participants receive further instruction if an error was made after reading the PIL.

Objectives	**Statistical analysis methods**
receiving further instruction from the Healthcare Professional (HCP) for ELLIPTA and BREEZHALER inhalers	• *Variable:* participants making at least one critical error after the a) first instruction from the HCP (attempt 2), b) the second instruction from HCP (attempt 3) and c) third instruction from the HCP (attempt 4). • *Population-summary measure*: The odds ratio of participants making at least one critical error between the ELLIPTA and BREEZHALER inhalers. a) The denominator will include all participants who fall in the S_{00} stratum. Participants who do not receive the first HCP instruction are assumed to have zero critical errors. b) The denominator for those that require a second further instruction will include all participants who fall in the S_{00} stratum. Participants who do not receive the second HCP instruction are assumed to have zero critical errors. c) The denominator for those that require a third further instruction will include all participants who fall in the S_{00} stratum. Participants who do not receive the third HCP instruction are assumed to have zero critical errors. The analysis method will be the same as for the primary endpoint. Note: This model will only be fitted if there is sufficient data, otherwise summary statistics will be presented.
To compare the proportion of overall errors made by participants after reading the inhaler use sections of the PIL, and if necessary, with additional instruction from the HCP for ELLIPTA and BREEZHALER inhalers	• Participants who make at least one overall error after reading the PIL(s) (Attempt 1). • *Variable:* participants who make at least one overall error after reading the PIL. • *Population-summary measure*: The odds ratio between the ELLIPTA and BREEZHALER inhalers. The analysis method will be the same as for the primary endpoint. This will be repeated for the participants who still make at least one overall error after receiving further instruction (up to 3) from the HCP. Participants receive further instruction if an error was made after reading the PIL.

Objectives	**Statistical analysis methods**
	• *Variable:* participants who make at least one overall error after the a) first instruction from the HCP (attempt 2), b) the second instruction from HCP (attempt 3) and c) third instruction from the HCP (attempt 4). • *Population-summary measure*: The odds ratio of participants making at least one overall error. a) The denominator will include all participants who fall in the S_{00} stratum. Participants who do not receive the first instruction by the HCP are assumed to have zero overall errors. b) The denominator for those that require a second further instruction will include all participants who fall in the S_{00} stratum. Participants who do not receive the second HCP instruction are assumed to have zero overall errors. c) The denominator for those that require a third further instruction will include all participants who fall in the S_{00} stratum. Participants who do not receive the third HCP instruction are assumed to have zero overall errors. Note: the model will only be fitted for the endpoints where further instruction is required provided there is sufficient data, otherwise summary statistics will be presented.
To summarize the number of errors (critical and overall) made on each inhaler, with or without further HCP instruction.	Number of errors (critical and overall) made after reading the PIL(s), and, if necessary, after receiving further instruction from the HCP. • Variable: Critical and overall errors made with or without further HCP instruction. • Population-summary measure: The number of critical errors and overall errors made will be presented for each inhaler by instruction (0, 1, 2, 3).
To compare the proportion of participants that require further instruction from the HCP to demonstrate correct inhaler use for ELLIPTA and BREEZHALER inhalers	Requiring further instruction from the HCP to demonstrate correct inhaler use: • *Variable:* participants who do or do not require further instruction from the HCP. • *Population-summary measure:* The number and percentage of participants who require further instruction from the HCP will be summarized. A McNemar's test will be performed comparing the proportion of requiring further instruction on the ELLIPTA

Objectives	Statistical analysis methods
	inhaler vs. requiring further instruction on the BREEZHALER inhaler.
To compare the Training/Teaching Time required to demonstrate correct inhaler use for ELLIPTA and BREEZHALER inhalers	The amount of time taken to demonstrate inhaler use without HCP intervention (T1). • *Variable:* time taken to demonstrate inhaler use without HCP intervention (T1). • *Population-summary measure:* Median time to demonstrate inhaler use. The median time will be taken from the Kaplan-Meier model. Additionally, the mean (SD), median, minimum and maximum will also be presented for participants who demonstrate correct inhaler use. Participants who fail to demonstrate the correct use will be censored at the end of T1. The amount of time taken to be given instruction by the HCP (up to 3 times) on use of the inhaler and to demonstrate inhaler use (T2). • *Variable:* time taken to be given instruction by the HCP (up to 3 times) on use of the inhaler and demonstrate inhaler use (T2). • *Population-summary measure:* Median time to demonstrate inhaler use. The median time will be taken from the Kaplan-Meier model. Additionally, the mean (SD), median, minimum and maximum will also be presented for participants who demonstrate correct inhaler use. • Those who demonstrate correct use after reading the PIL (and therefore do not require further instruction) will be considered as demonstrating correct use at T2 and time taken to demonstrate correct use will equal to 0 minutes. The total amount of time taken to demonstrate correct inhaler use until correct demonstration is observed (T1+T2). *Variable:* total time taken to demonstrate inhaler use (T1+T2). • *Population-summary measure:* Median time and to demonstrate inhaler use. The median time will be taken from the Kaplan-Meier model. Additionally, the mean (SD), median, minimum and maximum will also be presented for participants who demonstrate correct inhaler use.
To compare ease-of-use for ELLIPTA and	• Ease-of-use preference from questionnaire. This will be grouped as easy CCI [redacted] or difficult CCI [redacted]

Objectives	**Statistical analysis methods**
BREEZHALER inhalers	CCI [redacted], that is, how the ease of use is rated by the participant. ○ *Variable:* ease of use rating. ○ *Population-summary measure:* The number and percentage of participants who rate the inhaler easy to use. To test whether the ease of use was easy or difficult, a McNemar's test will be performed. The population-measure summary defined above will be the same way for the following variables as indicated by participants' ease of use: • Telling how many doses are left in inhaler • Learning how to use the inhaler • Handling the inhaler • Preparing the inhaler • Holding the inhaler while using it
To summarise ease-of-use for ELLIPTA and BREEZHALER inhalers	• Ease-of-use preference from questionnaire, that is, how the ease of use is rated CCI [redacted] CCI [redacted] ○ *Variable:* ease of use rating. ○ *Population-summary measure:* The number and percentage of participants who rate the inhaler for each category. The population-measure summary defined above will be the same way for the following variables as indicated by participants' ease of use: • Telling how many doses are left in inhaler • Learning how to use the inhaler • Handling the inhaler • Preparing the inhaler • Holding the inhaler while using it
To compare the willingness to continue with the ELLIPTA and/or BREEZHALER inhaler	Willingness to continue with the inhaler using a VAS between 0 CCI [redacted] to 100 CCI [redacted] • *Variable:* Willingness to continue with the inhaler. • *Population summary measure:* The mean and standard deviation for willingness to continue with the inhaler will be presented for each inhaler and a comparison made between the inhalers (ELLIPTA vs. BREEZHALER). The mean (SD), minimum and maximum will be presented. A paired t-test will be performed comparing the mean

Objectives	Statistical analysis methods
	willingness to continue with the ELLIPTA inhaler vs. the mean willingness to continue with the BREEZHALER inhaler.
To compare preference attributes for ELLIPTA and BREEZHALER inhalers	Participants who expressed a preference on attributes from the preference questionnaire. • *Variable:* preferred inhaler, overall. • *Population-summary measure:* The number and percentage of participants who prefer the respective inhaler overall (ELLIPTA, BREEZHALER or no preference). A comparison will be made between the inhalers (ELLIPTA vs. BREEZHALER) using Prescott's test, where participants who select "no preference" included as uninformative. The population-summary measure defined above will be the same for the following variables as indicated by the participant's preference: • Preference based on the number of steps to take the medication. • Preference based on the time needed to take the medication. • Preference based on how easy the inhaler is to use. • Preference based on the size of the inhaler. • Preference based on the comfort of the mouthpiece. • Preference based on the ease of opening the inhaler.

9.4.3. Safety Analysis

All safety analyses will be performed on the safety analysis set. All ADEs will be summarized by each inhaler. Listings will be presented for SAEs and SADEs.

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

9.5. Interim Analysis

No interim analyses are planned for this study.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. 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 and ISO 14155 2020 guidelines
    - Applicable laws and regulations
- The protocol, protocol amendments, ICF, IB 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.
- Protocols and any substantial amendments to the protocol will require Central Ethics Committee (CEC) approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
    - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC
    - Notifying the IRB/IEC of SAE or other significant safety findings as required by IRB/IEC procedures
    - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable),), European Medical Device Regulation 2017/745 for clinical device research, and all other applicable local regulations

10.1.2. 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.

10.1.3. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant and answer all questions regarding the study.
  - Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, ISO 14155 Health Insurance Portability and Accountability Act (HIPAA), GDPR 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

A participant who is rescreened is not required to sign another ICF if the rescreening occurs within (30) days from the previous ICF signature date.

GSK (alone or working with others) may use participant's coded study data and other information to carry out this study; understand the results of this study; learn more about the study disease; publish the results of these research efforts

10.1.4. 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 who will be required to give consent for their data to be used as described in the informed consent.
- 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.

- Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.
- GSK will also provide all investigators who participated in the study with a summary of the study results and will tell the investigators what treatment their patients' received. The investigators are encouraged to share the summary results with the study participants, as appropriate.
- Under the framework of the SHARE initiative, GSK intends to make anonymized participant-level data from this trial available to external researchers for scientific analyses or to conduct further research that can help advance medical science or improve patient care. This helps ensure the data provided by trial participants are used to maximum effect in the creation of knowledge and understanding. Requests for access may be made through www.clinicalstudydatarequest.com.
- The procedures and timing for public disclosure of the protocol and results summary and for development of a manuscript for publication for this study will be in accordance with GSK Policy.
- GSK intends to make anonymized patient-level data from this trial available to external researchers for scientific analyses or to conduct further research that can help advance medical science or improve patient care. This helps ensure the data provided by trial participants are used to maximum effect in the creation of knowledge and understanding

10.1.5. 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.
- Guidance on completion of CRFs will be provided in eCRF completion guidelines.
- Quality tolerance limits (QTLs) will be pre-defined in the QTL plan to identify systematic issues that can impact participant safety and/or reliability of study results. These pre-defined parameters will be monitored during and at the end of the study and all deviations from the QTLs and remedial actions taken will be summarized in the clinical study report.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy including definition of study critical data items and processes (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of

noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.

- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (e.g., Contract Research Organizations).
- 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.

10.1.6. 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 and its origin can be found in [Source Data Acknowledgment].
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- 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.

10.1.7. Study and Site Start and Closure

First Act of Recruitment

The study start date is the date on which the clinical study will be open for recruitment of participants.

Study/Site Termination

GSK or 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:

For study termination:

- Discontinuation of further study intervention development

For site termination:

- 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 or no recruitment of participants (evaluated after a reasonable amount of time) by the investigator
- If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up

10.1.8. 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.

10.2. Appendix 2: AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.2.1. Definition of AE

AE Definition
• AEs are defined below, however only AEs which meet the seriousness criteria (see Section 10.2.2) will be collected in this study: • An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of a study intervention, whether or not considered related to the study intervention. • 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 intervention.

10.2.2. Definition of SAE

An SAE is defined as any serious adverse event 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 admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AE. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. • Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d. Results in persistent or significant 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. Is a suspected transmission of any infectious agent via an authorised medicinal product
g. Other situations: • Possible Hy's Law case: ALT≥3xULN AND total bilirubin ≥2xULN (>35% direct bilirubin) or international normalized ratio (INR) >1.5 must be reported as SAE • Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that 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. o Examples of such events include invasive or malignant cancers, intensive treatment for allergic bronchospasm, blood dyscrasias, convulsions, or development of intervention dependency or intervention abuse.

10.2.3. Definition of Cardiovascular Events

Cardiovascular Events (CV) Definition:
Investigators will be required to fill out the specific CV event page of the CRF for the following 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

10.2.4. Recording and Follow-Up of SAE

SAE Recording

- When an 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 SAE information.
- 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 required form.
- 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 SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each 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 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 intervention and each occurrence of each 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 intervention 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 SAE, the investigator **must** document in the medical notes that he/she has reviewed the 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 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 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 submitted documents.
- The investigator will submit any updated SAE data to GSK within 24 hours of receipt of the information.

10.2.5. 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, then the site will use the paper SAE data collection tool (see next section) to report the event within 24 hours.
- 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 the study reference manual .

SAE Reporting to GSK via Paper Data Collection Tool

- Facsimile transmission of the SAE paper data collection tool 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 data collection tool within the designated reporting time frames.
- Contacts for SAE reporting can be found in the study reference manual.

10.3. Appendix 3 CRITICAL ERROR CHECKLISTS

A critical error is defined as an error that is most likely to result in no or significantly reduced medication being inhaled. These errors will be captured in a checklist provided for HCP assessment of DPI use.

Please note, the critical error checklists are designed to record any errors that are made by the participant based on the patient information leaflet for each device. Any inadequacies of the medical devices that that fall under the definition of a device deficiency (as defined in Section 10.7 Appendix 7) , must be reported separately as per Regulation (EU) 2017/745 Medical Device Regulation (MDR) Article 80(2).

10.3.1. ELLIPTA Critical Error Checklist

Protocol Identifier	Participant Identifier	ELLIPTA Checklist
213306	☐☐☐☐☐☐	Visit 1

Date of Assessment:	☐☐ DAY	☐☐☐ MONTH	☐☐ YEAR	
Attempt Number:	☐ PIL (1)	☐ HCP (2)	☐ HCP (3)	☐ HCP(4)

PIL Step	PIL Wording	Error (Underlined text indicates a critical error)	Step Performed correctly	Step Performed Incorrectly
1	**Prepare a dose** Wait to open the cover until you are ready to take your dose. Do not shake the inhaler. • Slide the cover down until you hear a “click”.	Failed to open cover until click is heard	☐	☐
		Intentionally shook the inhaler after dose preparation	☐	☐
2	**Inhale your medicine** • While holding the inhaler away from your mouth, breathe out as far as is comfortable. Do not breathe out into the inhaler.	No exhalation before an inhalation	☐	☐
		Exhaled directly into mouthpiece	☐	☐

	• Put the mouthpiece between your lips and close your lips firmly around it. Do not block the air vent with your fingers. • Take one long, steady, deep breath in. Hold this breath for as long as possible (at least 3-4 seconds). • Remove the inhaler from your mouth. • Breathe out slowly and gently.	No seal created by lips around the mouthpiece during the inhalation	☐	☐
		Inhalation manoeuvre was **NOT**: - long - steady - deep	☐	☐
		Blocked air inlet during inhalation manoeuvre	☐	☐
		Did not hold breath	☐	☐
3	Close the inhaler and rinse your mouth.	Did not close the inhaler (Note: this is an error but one which does not affect the medication that is inhaled)	☐	☐
		Did not rinse mouth out with water (Note: this is an error but one which does not affect the medication that is inhaled)	☐	☐
Other comments:				

10.3.2. BREEZHALER Critical Error Checklist

Protocol Identifier **213306**	**Participant Identifier** ☐☐☐☐☐☐	**BREEZHALER checklist** **Visit #**
Date of Assessment: ☐☐ ☐☐☐ ☐☐		
Attempt Number: ☐☐☐☐		

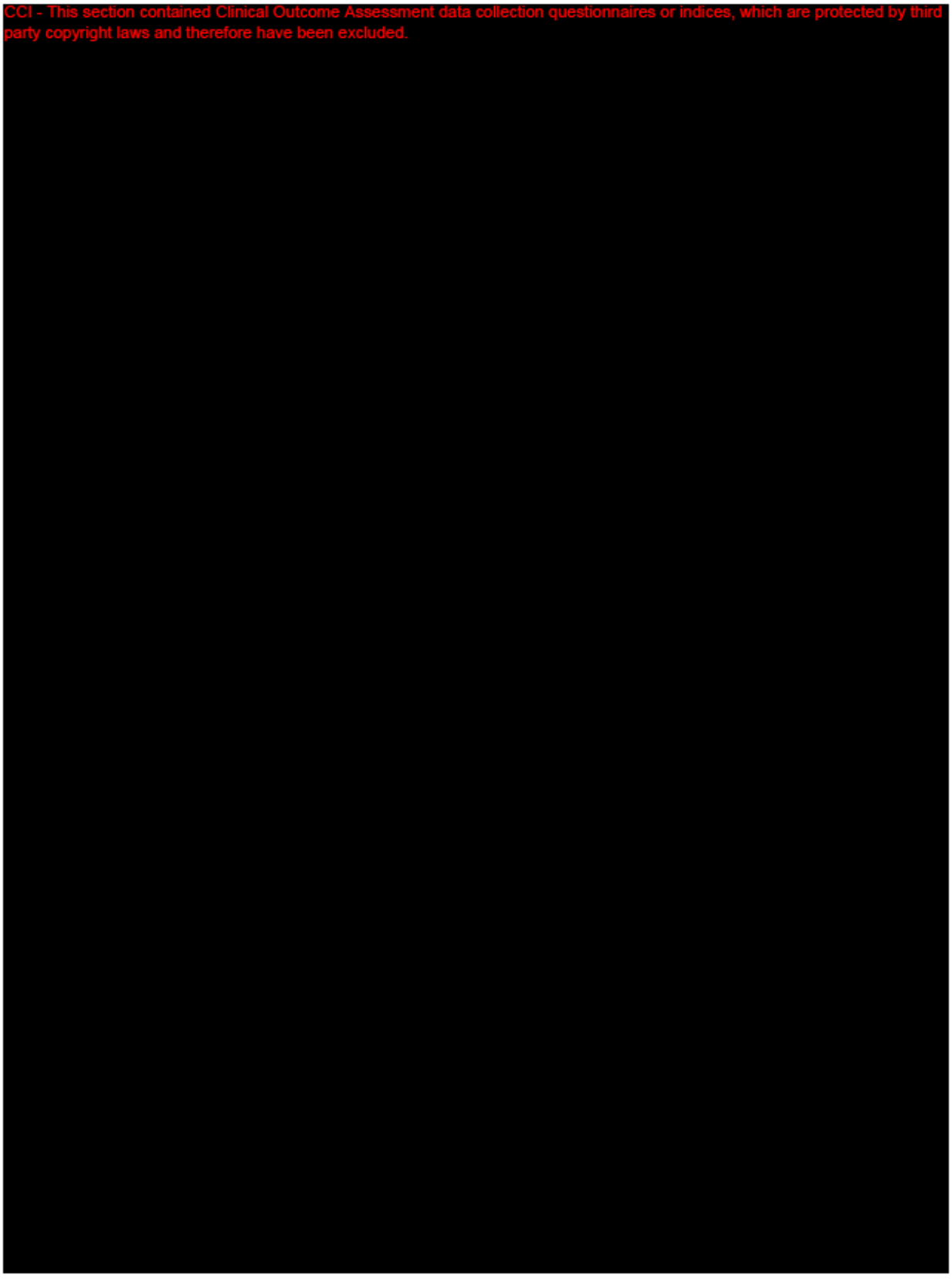
PIL Step	**PIL Wording**	**Error** **(Underlined text indicates a critical error)**	**Completed Correctly**	**Not Completed Correctly**
1	**Prepare a dose** Pull off cap.	Failed to pull off cap	☐	☐
2	**Open inhaler** Tilt the mouthpiece to open the inhaler	Failed to open inhaler	☐	☐
3	**Remove a capsule** Remove capsule from blister pack.	Failed to remove capsule from blister pack	☐	☐
4	**Insert capsule** Place the capsule into the capsule chamber.	Failed to insert capsule into the chamber	☐	☐
5	**Close the Inhaler** Close the inhaler until you hear a "**click**".	Failed to close the inhaler (heard 'click' when satisfactory)	☐	☐
6	**Pierce the capsule:** Pierce the capsule with the mouthpiece pointing up and firmly pressing together both sides until you hear a "click" and release the side buttons fully	Failed to pierce capsule and failed to release the piercing buttons	☐	☐
		Intentionally shook the inhaler after preparation	☐	☐

HCP (4)

7	**Breathe out fully** While holding the inhaler away from your mouth, breathe out as far as is comfortable. Do not breathe out into the Inhaler.	No exhalation before inhalation	☐	☐
		Exhaled directly into mouthpiece	☐	☐
8	**Inhale medicine deeply** Put the mouthpiece between your lips, and close your lips firmly around it. Do not press the side buttons • Take in one rapid and deep breath, sufficient to hear or feel the capsule.	No seal created by the lips round the mouthpiece during inhalation Pressed the side buttons while inhaling through the mouthpiece	☐	☐
		Inhalation maneuver **was not**: -Rapid -Deep	☐	☐
9	As you breathe, the capsule should make a whirring noise • If there is no whirring noise, loosen the capsule by tapping the base of inhaler and repeat step 7 and 8.	Capsule did not whirr	☐	☐
10	Hold this breath for up to 5 secs • Remove the inhaler from your mouth.	Failed to hold breath	☐	☐
11	Check capsule chamber is empty Open the capsule to check it is empty If powder remains in capsule, close the inhaler and repeat steps 7-12	Did not check the capsule chamber	☐	☐
		Failed to repeat inhalation when powder remained in the capsule	☐	☐
12	Close the inhaler and replace the cap	Did not close the inhaler and close the cap		
Other comments:				

10.4. Appendix 4: Ease of Use Questionnaires

ELLIPTA



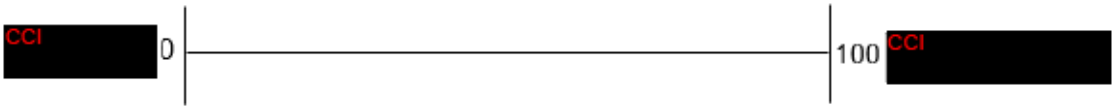
CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.

CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.

10.5. Appendix 5. Willingness to continue with inhaler

The investigator will ask you the following question:

On a scale of 0 [redacted] to 100 [redacted] would you be to continue with this inhaler. Please mark on the line how willing you would be to continue with this inhaler.



10.6. Appendix 6: Preference Questionnaires

Version 1 - Sequence A (ELLIPTA BREEZHALER) and Sequence C (BREEZHALER ELLIPTA)

ELLIPTA BREEZHALER

CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.

Version 2 - Sequence B (ELLIPTA BREEZHALER) and Sequence D (BREEZHALER ELLIPTA)

BREEZHALER

ELLIPTA

CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.

10.7. Appendix 7: ADEs, SADEs, and Device Deficiencies: Definition and Procedures for Recording, Evaluating, Follow-up, and Reporting in Medical Device Studies

- The definitions and procedures detailed in this appendix are in accordance with ISO 14155 and European Medical Device Regulation (MDR) 2017/745 for clinical device research (if applicable).
- Both the investigator and the sponsor will comply with all local medical device reporting requirements for medical devices.
- The detection and documentation procedures described in this protocol apply to all GSK medical devices provided for use in the study (see Section 6.1.1 for the list of GSK medical devices).

10.7.1. Definition of ADE

ADE Definition
• An adverse device effect (ADE) is an AE related to the use of an investigational medical device. This definition includes any AE resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device as well as any event resulting from use error or from intentional misuse of the investigational medical device.

10.7.2. Definition of SADE

A SADE is any serious ADE **that:**
a. Led to death
b. Led to serious deterioration in the health of the participant, that either resulted in: • A life-threatening illness or injury. 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. • A permanent impairment of a body structure or a body function. • Inpatient or prolonged hospitalization. Planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered an SADE. • Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function
c. Led to fetal distress, fetal death or a congenital abnormality or birth defect
d. Is a suspected transmission of any infectious agent via a medicinal product

Definition
• A SADE is defined as an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event. • Any device deficiency that might have led to an SAE/SADE if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate.

10.7.3. Definition of Device Deficiency

Device Deficiency Definition
• A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. Device deficiencies include malfunctions, use errors, and information supplied by the manufacturer.

10.7.4. Recording and Follow-Up of ADE, SADEs, and Device Deficiencies

ADE, SADE, and Device Deficiency Recording
• When an ADE/SADE/device deficiency occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event. • The investigator will then record all relevant ADE/SADE device deficiency information in the participant's medical records, in accordance with the investigator's normal clinical practice, and on the appropriate form. • It is not acceptable for the investigator to send photocopies of the participant's medical records to the medical monitor or SAE coordinator in lieu of completion of the ADE/SADE/device deficiency form. • There may be instances when copies of medical records for certain cases are requested by the medical monitor. 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 the medical monitor. • 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 ADE/ SADE. • For device deficiencies, it is very important that the investigator describes any corrective or remedial actions taken to prevent recurrence of the deficiency. o A remedial action is any action other than routine maintenance or servicing of a medical device where such action is necessary to prevent recurrence of a

device deficiency. This includes any amendment to the device design to prevent recurrence.
Assessment of Intensity
• The investigator will make an assessment of intensity for each ADE/ SADE/ device deficiency reported during the study and assign it to one 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 ADE that is assessed as severe should not be confused with an SADE. Severe is a category used for rating the intensity of an event; both ADEs and SADEs 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 SADE, not when it is rated as severe.

Assessment of Causality
• The investigator is obligated to assess the relationship between study intervention and each occurrence of each ADE/SADE/device deficiency • 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 intervention administration will be considered and investigated. • The investigator will also consult the Investigator's Brochure (IB), in his/her assessment. • For each ADE/SADE/device deficiency, the investigator **must** document in the medical notes that he/she has reviewed the ADE/SADE/device deficiency and has provided an assessment of causality. • There may be situations in which an SADE 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 SADE data to GSK. • The investigator may change his/her opinion of causality in light of follow-up information and send an SADE 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 SADE/device deficiency

- 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 SADE/ device deficiency 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 SADE data to GSK within 24 hours of receipt of the information.

10.7.5. Reporting of SADEs

SADE Reporting to GSK via an Electronic Data Collection Tool

- The primary mechanism for reporting an SADE to GSK will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SADE data collection tool (see next table) in order to report the event within 24 hours.
- The site will enter the SADE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken offline to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SADE from a study participant or receives updated data on a previously reported SADE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SADE form (see next section) or to the GSK medical monitor/SAE coordinator by telephone.
- Contacts for SADE reporting can be found in the study reference manual.

SADE Reporting to GSK via Paper Data CollectionTool

- Facsimile transmission of the SADE data collection tool is the preferred method to transmit this information to the GSK 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 SADE paper 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 SADE paper data collection tool within the designated reporting time frames.
- Contacts for SADE reporting can be found in the study reference manual.

10.7.6. Reporting of Device Deficiencies

- **Device Deficiency Reporting to GSK**

- NOTE: There are additional reporting obligations for medical device deficiencies that are potentially related to SAEs/SADEs that must fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.
- Any device deficiency that is associated with an SAE/SADE must be reported to GSK within 24 hours after the investigator determines that the event meets the definition of a device deficiency.
- GSK will review all device deficiencies and determine and document in writing whether they could have led to an SAE/SADE. These device deficiencies will be reported to the regulatory authorities and IRBs/IECs as required by national regulations.
- Contacts for SAE/SADE reporting can be found in the study reference manual.

10.8. Appendix 8: Abbreviations and Definitions and Trademarks

ADE	Adverse Device Effects
AE	Adverse Event
CONSORT	Consolidated Standards of Reporting trials
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
DPI	Dry Powder Inhaler
GINA	Global Initiative for Asthma
HCP	Healthcare professional
ICS	Inhaled Corticosteroids
IEC	Independent Ethics Committees
IRB	Institutional Review Boards
LABA	Long Acting β_2-Agonist
LAMA	Long Acting Anticholinergic
MedDRA	Medical Dictionary of Regulatory Activities
PIL	Patient instruction Leaflet
QTL	Quality Tolerance Limits
SABA	Short Acting α_2-Adrenergic Agonist
SADE	Serious Adverse Device Effects
SAE	Serious Adverse Events
SAMA	Short Acting Muscarinic Antagonist
SoA	Schedule of Activities
SRM	Study Reference Manual

SUSAR	Suspected Unexpected Serious Adverse Reactions

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11. REFERENCES

Arora P, Kumar L, Vohra V, Sarin R, Jaiswal A, Puri MM et al. Evaluating the technique of using inhalation device in COPD and bronchial asthma patients. Respir Med 2014; 108 (7):992-998

Chorão P, Pereira AM, Fonseca JA. Inhaler devices in asthma and COPD – An assessment of inhaler technique and patient preferences. Resp Med 2014; 108 (7): 968-975.

Chow, S.C., Shao, J., and Wang, H. Sample Size Calculations in Clinical Research, 2nd edition . Chapman and Hall/CRC , New York , 2008

Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention, 2020. Available from: www.ginasthma.org. Accessed 12 Dec 2020.

Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global Strategy for the Diagnosis, Management and Prevention of Chronic Obstructive Pulmonary Disease, 2020. Available from www.goldcopd.org. Accessed 17 Sep 2020

Khassawneh BY, Al-Ali MK, Alzoubi KH,Batarseh MZ, Al-Safi SA, Sharara AM et al. Handling of inhaler devices in actual pulmonary practice: metered dose inhaler versus dry powder inhalers. Respir Care 2008; 53 (3):324-328

Kung-Jong Lui. 2016. Crossover Designs: Testing, Estimation, and Sample Size. John Wiley & Sons Ltd. Chichester, West Sussex, England

Lavorini F, Magnan A, Dubus JC, Voshaar Thomas, Corbetta Lorenzo, Broeders M et al. Effect of incorrect use of dry powder inhalers on management of patients with asthma and COPD. Respir Med 2008;102 (4):593–604:

Melani AS, Bonavia M, Cilenti V , Cinti C, Lodi M, Martucci P et al. Inhaler mishandling remains common in real life and is associated with reduced disease control. Respir Med 2011; 105 (6): 930-938

Ocakli B, Ozmen O, Tuncay EA, Gungor S, Altinoz H, Adiguzel N et al. A comparative analysis of errors in inhaler technique among COPD versus asthma patients. Int J COPD 2018; 13: 2941-2947

Takaku Y, Kurashima K, Ohta C, Ishiguro T, Kagiyama N, Yanagisawa T et al. How many instructions are required to correct inhalation errors in patients with asthma and chronic obstructive pulmonary disease. Respir Med 2017; 123: 110-11

van der Palen J, Moeskops-van Beurden W, Dawson CM, James Wai-Yee, Preece A et al. A randomized, open-label, single-visit, crossover study simulating triple-drug delivery with Ellipta compared with dual inhaler combinations in patients with COPD. *Int J Chron Obstruct Pulmon Dis*. 2018;13:2515-2523.

van der Palen J, Thomas M, Chrystyn H, Sharma RK, van der Valk PD, Goosens M, et al. A randomized open-label cross-over study of inhaler errors, preference and time to achieve correct inhaler use in patients with COPD or asthma: comparison of ELLIPTA with other inhaler devices. NPJ Prim Care Respir Med 2016;26:16079.

van der Palen J, van der Valk P, Goosens M, Groothuis-Oudshoorn, Brusse-Keizer M. A randomised cross-over trial investigating the ease of use and preference of two dry powder inhaler in patients with asthma or chronic obstructive pulmonary disease. Expert Opinion on Drug Delivery 2013; 10: 1171-1178