Statistical Analysis Plan

Study ID: 213306

Official Title of Study: 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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Title Page

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Short Title: PH4, ELLIPTA vs BREEZHALER DPI, comparison of critical errors, overall errors, training/teaching time and preference attributes in pts with asthma.

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TABLE OF CONTENTS

PAGE

Version history

Table 1 SAP Version History Summary

SAP Version	Document Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
1	12-04-2021	Protocol Version 1 (05-JAN-2020)	Not Applicable	Original version
2	24-05-2021	Protocol Version 1 (05-JAN-2020)	Inclusion of Safety analysis set.	ADEs and SADEs to be summarised according to the intervention actually received instead of randomised intervention.
			Inclusion of analysis tables required for Safety analyses.	Summary tables required for SAEs and SADEs have been included where only listings had previously been specified.

1. INTRODUCTION

The aim of Study 213306 is to assess critical errors, overall errors, training/teaching time, ease-of-use, willingness to continue and preference attributes of the ELLIPTA dry powder inhaler compared with the BREEZHALER dry powder inhalers, in adult participants with mild to moderate asthma.

The purpose of this SAP is to describe the planned analyses to be included in the Clinical Study Report (CSR) for Study 213306. Details of the planned final analysis are provided.

Descriptive study population analyses such as summary of demography and baseline characteristics and additional detail with regards to data handling conventions and the specification of data displays will be provided in the Output and Programming Specification (OPS) document.

1.1. Objectives, Estimands and Endpoints

1.1.1. Objectives and Endpoints

Table 1 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(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] CCI [redacted] or difficult CCI [redacted] 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] 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]
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).

1.1.2. Estimands

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.

Each study primary and secondary objective is presented in Table 2 with additional information, including pre-specified estimands with related attributes.

Table 2 Estimands

The following two attributes apply to all estimands listed in the table below:

- Inhaler comparison: ELLIPTA inhaler vs BREEZHALER inhaler
- Population: participants with mild to moderate asthma diagnosis who attempt demonstration of both inhalers (principal stratum strategy).

Objective	**Estimand Category**	**Estimand Variable/ Endpoint**	**Intercurrent Event Strategy**	**Population Level Summary Measure**
Primary Objective: 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.	Primary	Participants who make at least one critical error after reading the section on inhaler use in the patient information leaflets (PILs).	Not attempting demonstration of the inhaler (ELLIPTA or BREEZHALER).	Odds ratio between ELLIPTA and BREEZHALER.
	Sensitivity		As for primary.	As for primary.
Secondary Objective: To compare the proportion of participants who still make at least one critical error after receiving further instruction from the	Secondary 1	Participants who still make at least one critical error after receiving further instruction (up to 3) from the HCP.	As for primary.	As for primary.

Objective	Estimand Category	Estimand Variable/ Endpoint	Intercurrent Event Strategy	Population Level Summary Measure
Healthcare Professional (HCP) for ELLIPTA and BREEZHALER inhalers				
Secondary Objective: 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.	Secondary 2	a) Participants who make at least one overall error after reading the PIL(s). b) Participants who still make at least one overall error after receiving further instruction (up to 3) from the HCP.	As for primary.	a) and b) will be summarised as for primary.
Secondary Objective: To summarize the number of errors (critical and overall) made on each inhaler, with or without further HCP instruction.	Secondary 3	Number of errors made after reading the PIL(s), and, if necessary, after receiving further instruction from the HCP.	As for primary.	The number of critical errors and overall errors made for each inhaler (ELLIPTA and BREEZHALER) by instruction (0, 1, 2, 3).

Objective	Estimand Category	Estimand Variable/ Endpoint	Intercurrent Event Strategy	Population Level Summary Measure
Secondary Objective: To compare the proportion of participants that require further instruction from the HCP to demonstrate correct inhaler use for ELLIPTA and BREEZHALER inhalers.	Secondary 4	Requiring further instruction from the HCP to demonstrate correct inhaler use.	As for primary.	The number and percentage of participants who require further instruction from the HCP will be summarized for each inhaler (ELLIPTA and BREEZHALER). A McNemar's test will be used to compare ELLIPTA vs. BREEZHALER.
Secondary Objective: To compare the Training/Teaching Time required to demonstrate correct inhaler use for ELLIPTA and BREEZHALER inhalers.	Secondary 5	a) The amount of time taken to demonstrate inhaler use without HCP intervention (T1). b) 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).	As for primary.	a) Median time to demonstrate inhaler use for each inhaler (ELLIPTA and BREEZHALER). b) and c) will be summarised as for a).

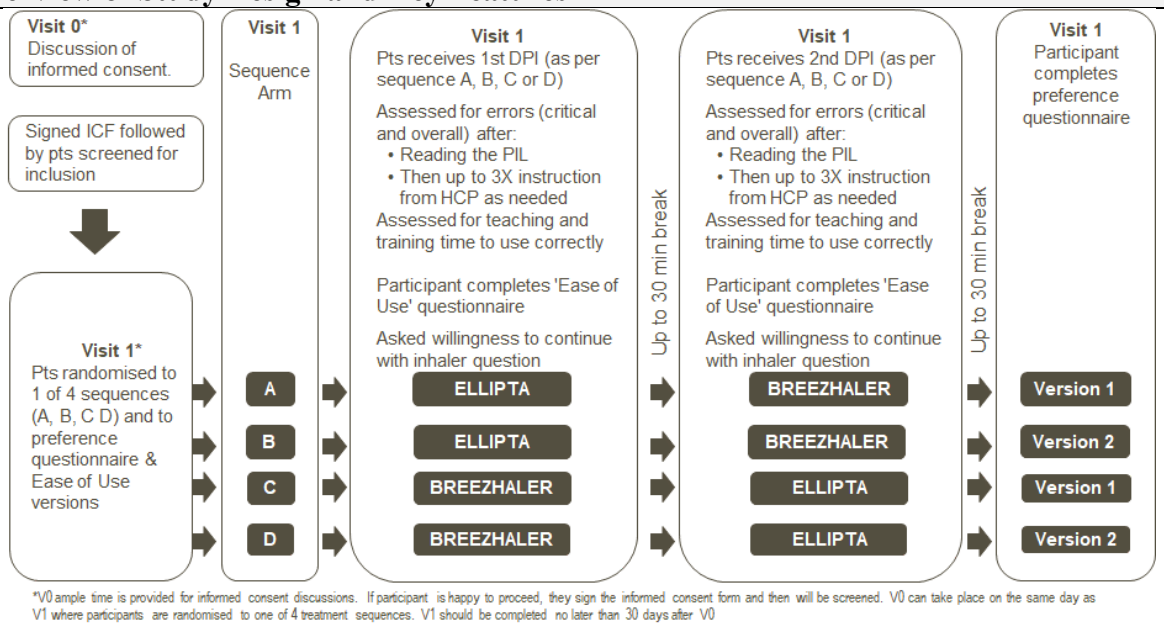
Objective	Estimand Category	Estimand Variable/ Endpoint	Intercurrent Event Strategy	Population Level Summary Measure
		c) The total amount of time taken to demonstrate inhaler use (T1+T2).		
Secondary Objective: To compare ease-of-use for ELLIPTA and BREEZHALER inhalers.	Secondary 6	Ease-of-use from questionnaire. This will be grouped as easy [redacted] or difficult [redacted] The variables will include: a) Ease of use rating b) Telling how many doses are left in inhaler c) Learning how to use the inhaler d) Handling the inhaler e) Preparing the inhaler f) Holding the inhaler while using it.	As for primary.	The number and percentage of participants who rate the inhaler easy to use summarised for each inhaler (ELLIPTA and BREEZHALER). A McNemar's test will be performed to compare ELLIPTA vs. BREEZHALER. This will be performed for variables a) to f).

Objective	Estimand Category	Estimand Variable/ Endpoint	Intercurrent Event Strategy	Population Level Summary Measure
To summarize ease-of-use for ELLIPTA and BREEZHALER inhalers	Secondary 7	Ease-of-use from questionnaire CCI [redacted] CCI [redacted] CCI [redacted] The variables will include the: a) Ease of use rating b) Telling how many doses are left in inhaler c) Learning how to use the inhaler d) Handling the inhaler e) Preparing the inhaler f) Holding the inhaler while using it.	As for primary.	The number and percentage of participants who rate the inhaler for each category for each inhaler (ELLIPTA and BREEZHALER). This will be performed for variables a) to f).
Secondary Objective: To compare the willingness to continue with the ELLIPTA and/or BREEZHALER inhaler.	Secondary 8	Willingness to continue with the inhaler using a visual analogue scale (VAS) between 0 CCI [redacted] CCI [redacted] to 100 CCI [redacted] CCI [redacted]	As for primary.	The mean and standard deviation for willingness to continue with the inhaler will be presented for each inhaler (ELLIPTA and BREEZHALER). A t-test will be performed

Objective	Estimand Category	Estimand Variable/ Endpoint	Intercurrent Event Strategy	Population Level Summary Measure
				to compare ELLIPTA vs. BREEZHALER.
Secondary Objective: To compare preference attributes for ELLIPTA and BREEZHALER inhalers.	Secondary 9	Inhaler preference from questionnaire (ELLIPTA, BREEZHALER or no preference). The variables will include: a) Preferred inhaler, overall. b) Number of steps to take the medication c) Time needed to take the medication d) How easy the inhaler is to use e) Size of the inhaler f) Comfort of the mouthpiece g) Ease of opening the inhaler.	As for primary.	The number and percentage of participants who prefer the respective inhaler overall (ELLIPTA, BREEZHALER or no preference). A Prescott's test will be performed to compare ELLIPTA vs. BREEZHALER. This will be performed for variables a) to g).

1.2. Study Design

Overview of Study Design and Key Features



*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

Design Features	• 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. • 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 (i.e. version 1 or 2). • The study involves two visits which can be completed on the same day. Visit 1 may be completed up to 30 days after visit 0. • A participant is considered to have completed study treatment if demonstration of both inhalers has been completed on Day 1 (Visit 1). • A participant is considered to have completed the study if all assessments have been completed on Day 1 (Visit 1). • Period 1 is complete once demonstration has been completed on the first inhaler after reading the PIL (or receiving up to 3 further HCP instructions), after completing the “Ease of Use” questionnaire and after completing the “Willingness to Continue” question. • Period 2 is complete once demonstration has been completed on the second inhaler after reading the PIL (or receiving up to 3 further HCP instructions), after completing the “Ease of Use” questionnaire and after completing the “Willingness to Continue” question. • Participants may take up to a 30-minute break between period 1 and period 2.

Overview of Study Design and Key Features	
	• Participants may take up to a 30-minute break after period 2 prior to completion of the preference questionnaire. • 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.
Study intervention	• This is a placebo inhaler device study. Participants will receive both inhalers (ELLIPTA and BREEZHALER) on day 1 (Visit 1). • Discontinuation of study intervention corresponds to withdrawal from the study since each inhaler is only available on a single day. • 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.
Study intervention Assignment	• This study will randomly assign 114 adult asthma participants aged ≥18 years with mild to moderate asthma, naïve to both DPI inhalers (ELLIPTA and BREEZHALER). Each participant will be randomized to inhaler sequence (ELLIPTA/BREEZHALER or BREEZHALER/ELLIPTA) and to the preference questionnaire (version 1 or version 2). There will be a total of four possible groups: o ELLIPTA/BREEZHALER/preference questionnaire version 1 o ELLIPTA/BREEZHALER/preference questionnaire version 2 o BREEZHALER/ELLIPTA/preference questionnaire version 1 o BREEZHALER/ELLIPTA/preference questionnaire version 2 • The randomisation schedule will be generated using the GSK validated randomisation software RandAll NG. Eligible participants will be assigned to study treatment randomly using RAMOS NG, an Interactive Web Response System (IWRS).
Interim Analysis	No interim analysis of data is planned for this study.

2. 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.

2.1. Multiplicity Adjustment

No multiplicity adjustments will be made for this study.

3. ANALYSIS SETS

Analysis Set	Definition / Criteria	Analyses Evaluated
Screened	• All participants who were screened for eligibility and signed the ICF.	• Screening status and reasons for screen failures
Enrolled	• All participants enrolled and for whom a record exists on the study database.	• Study population
Randomised	• All participants who were randomly assigned to study intervention in the study. • Any participant who receives a randomisation number will be considered to have been randomised.	• Study population
Full Analysis Set (FAS)	• All randomised participants who used at least one study inhaler. • Data will be reported according to the randomised study intervention.	• Study population • Safety
Safety	• All randomised participants who used at least one study inhaler. • Data will be reported according to the study intervention actually received.	• Safety
Modified intention-to-treat (mITT)	• All participants who were randomised to study intervention in the study, completed reading of the PIL and attempted demonstration of both inhalers. • Data will be reported according to the randomised study intervention.	• Efficacy

For CDISC purposes, the modified intention-to-treat (mITT) analysis set refers to the performance evaluable analysis set as defined within the protocol.

4. STATISTICAL ANALYSES

4.1. General Considerations

4.1.1. General Methodology

The full analysis set (FAS) will be used for all Study Population analyses and Safety analyses, the mITT analysis set will be used for all Efficacy analyses and the Safety analysis set will be used to summarise Adverse Device Effects and Serious Adverse Device Effects.

Confidence intervals will use 95% confidence levels unless otherwise specified.

Unless otherwise specified, continuous data will be summarized using descriptive statistics: n, mean, standard deviation (SD), median, minimum and maximum. Categorical data will be summarized as the number and percentage of participants in each category.

4.1.2. Baseline Definition

Baseline is defined as the latest non-missing measurement collected prior to demonstrating inhaler use on the first inhaler (i.e. before period 1). This will generally be on the beginning of the Day 1 (Visit 1) assessment.

Unless otherwise stated, if baseline data is missing no derivation will be performed and baseline will be set to missing.

4.1.2.1. Time taken to demonstrate correct use of the inhaler

Time taken to correctly use each inhaler within the respective period (1 and 2) 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 a maximum of 3 attempts).
    - T2 includes the time used by the investigator for re-instructing the participants throughout.
    - Note, where correct use of the inhaler is <u>not</u> demonstrated after the fourth attempt, T2 will be calculated from when the investigator starts to instruct the participant until the fourth attempt has been completed.
- T1 + T2: the time from when the participant starts the demonstration until correct use is demonstrated (a total of 4 attempts - once after the reading the PIL and following instruction from investigator up to 3 times).

4.2. Primary Endpoint Analyses

4.2.1. Definition of endpoint

The primary endpoint is participants who make at least one critical error after reading the section on inhaler use in the patient information leaflets (PILs).

4.2.2. Main analytical approach

Comparisons made between the ELLIPTA and BREEZHALER inhaler will be based on those who fall in the S_{00} stratum. For the full definition of the primary estimand, see section 1.1.

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. To account for very small or zero frequency counts, an exact test has been specified. In case of period effects, period has been included in the model as a fixed effect (Mehta, et al., 1995). 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.

Residual vs. Fitted plots will be generated to help assess the constant variance assumption. Deviance and Pearson goodness of fit statistics from the model will be examined to help assess the null hypothesis that the model is an adequate fit to the data.

4.2.3. Sensitivity analyses

The analysis for the primary estimand incorporates covariates that are time varying; a feature of a conditional logistic model. Therefore, a sensitivity analysis for the primary estimand will be performed including age and sex as additional baseline covariates.

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. Residual vs. Fitted plots will be generated to help assess the constant variance assumption.

4.3. Secondary Estimands Analyses

4.3.1. 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 (see section 1.1.2). 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 (S_{00}). All comparisons will be made at the two-sided 5% significance level.

4.3.1.1. Definition of endpoint(s)

The secondary endpoints for analysis are:

- Participants who still make at least one critical error after receiving further instruction (up to 3) from the HCP.
- 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.
- 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 correct inhaler use (T1+T2).
- Requiring further instruction from the HCP to demonstrate correct inhaler use.
- Ease-of-use from ease-of-use questionnaire (easy or difficult).
- Willingness to continue with the inhaler using a visual analogue scale (VAS) between 0 [redacted] to 100 [redacted]
- Inhaler preference from questionnaire (ELLIPTA, BREEZHALER or no preference).

4.3.1.2. Critical error after reading the PIL(s)

Participants may receive further instruction (maximum of 3) if any error was made after reading the PIL. For the endpoint of participants who still make at least one critical error after receiving further instruction (up to 3) from the HCP:

a) The variable for attempt 2 is participants making at least one critical error after receiving the first instruction from the HCP (attempt 2). 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 variable for attempt 3 is participants making at least one critical error after receiving the second instruction from the HCP (attempt 3). The denominator 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 variable for attempt 4 is participants making at least one critical error after receiving the third instruction from the HCP (attempt 4). The denominator 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 population-summary measure for a)-c) is the odds ratio of participants making at least one critical error between the ELLIPTA and BREEZHALER inhalers. 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.

4.3.1.3. Overall errors

For the endpoint of participants who make at least one overall error after reading the PIL (attempt 1), the population-summary measure will be the odds ratio between the ELLIPTA and BREEZHALER inhalers. The analysis method will be the same as for the primary endpoint.

The population-summary measure and analysis method defined above for participants who make at least one overall error after reading the PIL will be performed for the endpoint of participants who still make at least one overall error after receiving further instruction (up to 3) from the HCP. Participants may receive up to three further instructions if any error was made after reading the PIL.

a) For participants who make at least one overall error after receiving the first instruction from the HCP (attempt 2), 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) For participants who make at least one overall error after the second instruction from the HCP (attempt 3), 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) For participants who make at least one overall error after the third instruction from the HCP (attempt 4), 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 where further instruction is required provided there is sufficient data, otherwise summary statistics will be presented.

4.3.1.4. Requiring further instruction

For the endpoint of requiring further instruction from the HCP to demonstrate correct inhaler use, the variable is participants who do or do not require further instruction from the HCP. Participants who require ≥1 instructions from the HCP (maximum of 3) will be considered as requiring further instruction. The population-summary measure is the number and percentage of participants who do or do not require further instruction from the HCP. To compare the proportion of requiring further instruction on the ELLIPTA inhaler vs. requiring further instruction on the BREEZHALER inhaler, a McNemar's test will be performed.

4.3.1.5. Training/teaching time

The population-summary measure for teaching/training time is the 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.

a) T1: the amount of time taken to correctly demonstrate inhaler use without HCP intervention. Participants who fail to demonstrate the correct use will be censored at the end of T1, having completed demonstration of the first attempt.

b) T2: 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. Participants 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. Participants who fail to demonstrate the correct use will be censored at the end of T2, after completing the fourth attempt.

c) The total amount of time taken to demonstrate correct inhaler use until correct demonstration is observed is calculated by: T1+T2. Kaplan-Meier survivor functions of T1+T2 will be obtained for each inhaler group and plotted on the same figure.

4.3.1.6. Ease-of-use questionnaire (easy vs. difficult)

The ease-of-use rating from the ease-of-use questionnaire will be rated by participants as: CCI [redacted] These ratings will be grouped into easy CCI [redacted] or difficult CCI [redacted] and a McNemar's test will be performed to test whether the ease-of-use was easy or difficult. The population-summary measure is the number and percentage of participants who rate the inhaler easy to use.

The population-measure summary defined above for ease-of-use will be the same for the following variables as indicated by the ease-of-use questionnaire rated by participants:

a) Telling how many doses are left in inhaler.
b) Learning how to use the inhaler.
c) Handling the inhaler.
d) Preparing the inhaler.
e) Holding the inhaler while using it.

4.3.1.7. Willingness to continue with the inhaler

Willingness to continue with the inhaler will be measured on a VAS scale between 0 CCI [redacted] to 100 CCI [redacted] The difference in means between the ELLIPTA and BREEZHALER inhaler will be presented with 95% CIs and a comparison made between the inhalers (ELLIPTA vs. BREEZHALER) using a paired t-test. The mean, standard deviation, minimum and maximum will also be presented for each inhaler. Histograms and QQ plots will be generated to assess the normality assumption.

4.3.1.8. Preference questionnaire

For the endpoint of participants who expressed a preference on attributes from the preference questionnaire, the population summary measure is 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. This analysis will be performed for the following variables as indicated by the participant's preference:

a) Preferred inhaler, overall.
b) Preference based on the number of steps to take the medication.
c) Preference based on the time needed to take the medication.
d) Preference based on how easy the inhaler is to use.
e) Preference based on the size of the inhaler.
f) Preference based on the comfort of the mouthpiece.
g) Preference based on the ease of opening the inhaler.

4.3.2. Other Endpoint(s) Analyses

Other endpoints will be summarised descriptively and based on the mITT analysis set. Categorical data will be summarized as the number and percentage of participants in each inhaler group (ELLIPTA or BREEZHALER).

4.3.2.1. Definition of endpoint(s)

Other endpoints are:

- Number of errors (critical and overall) made after reading the PIL(s), and, if necessary, after receiving further instruction from the HCP.
- Ease-of-use from questionnaire CCI [redacted]

4.3.2.2. Number of errors made

The number and percentage of participants who make at least one critical error will be presented by sequence (ELLIPTA/BREEZHALER or BREEZHALER/ELLIPTA) within each period and overall for each inhaler (ELLIPTA and BREEZHALER), by instruction:

- 0: after reading the PIL,
- 1: following the first instruction,
- 2: following the second instruction,
- 3: following the third (and final) instruction.

The number and percentage of participants who make at least one overall error will be presented in the same way as those who make at least one critical error.

In addition, the total number of critical errors and overall errors made will also be presented by instruction for each inhaler.

4.3.2.3. Ease-of-use questionnaire

The number and percentage of participants who rate the ease of using the inhaler as CCI [redacted] CCI will be presented for each ease-of-use attribute within the questionnaire:

- Ease of using the inhaler
- 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

All model checking statistics will be assessed but not formally reported in a table, listing or figure.

4.4. Safety Analyses

The safety analyses will be based on the Safety Analysis Set for all Adverse Device Effects. As this is a placebo only inhaler study and no active drug is being prescribed, summaries and listings for all other safety analyses will be presented for all participants combined based on the Full Analysis Set.

4.4.1. Extent of Exposure

This is a one-day inhaler-handling study in which all participants will receive placebo.

4.4.2. Serious Adverse Events and Other Safety Reporting

Reporting of safety analyses includes the analysis of adverse device effects (ADEs), Serious AEs (SAEs), Serious ADEs (SADEs) and other significant ADEs will be based on GSK Core Data Standards.

Adverse events (AEs) will not be reported for this study. Instead, ADEs will be captured using the standard CDISC AE eCRF in conjunction with the Medical Device Deficiency eCRF. An ADE is defined as an AE for which the investigator classifies the relationship to Medical Device Deficiency for a non-serious adverse event as "Yes", where the start date of the AE occurs on the same date as the device deficiency.

Adverse events to identify ADEs will be coded using the standard Medical Dictionary for Regulatory Affairs (MedDRA dictionary), with the maximum severity of each AE determined by

the investigator (as mild, moderate or severe). A Standardised MedDRA Query (SMQ) will be used to identify all COVID-19 AEs.

An overview summary of ADEs, including counts and percentages of participants with any ADE and ADEs leading to discontinuation of the study inhaler (and therefore withdrawal from the study) will be produced. The summary tables will be displayed by SOC and PT.

The number and percentage of participants experiencing at least one ADE during the study, in which the medical device is used, will be summarised by each inhaler separately. Additionally, summaries of the number and percentage of participants with any ADEs by maximum severity will be produced. If an adverse event severity is missing, the severity is to be populated as "UNKNOWN".

The frequency and percentage of ADEs will be summarized and displayed in two ways:
1) in descending order by SOC and PT and 2) in descending order by PT only.

Common ADEs, defined as ≥3% (prior to rounding) in any inhaler group, will be reported. The summary table will be displayed by PT only.

A worst-case scenario approach will be taken to handle missing relatedness data, i.e. the summary table will include events with the relationship to study inhaler as "Yes" or missing. The summary table will be displayed by SOC and PT.

The number and percentage of participants experiencing at least one SAE during the study will be summarised.

The number and percentage of participants experiencing at least one SADE during the study, in which the medical device is used, will be summarised by each inhaler separately.

Listings will be presented separately for SAEs and SADEs. All SAEs, SAEs related to study treatment, fatal SAEs, fatal SAEs related to study treatment, all SADEs, fatal SADEs, and fatal SADEs will be produced. In addition, fatal and non-fatal SAEs, and, fatal and non-fatal SADEs will be reported separately.

A study treatment-related SAE is defined as an SAE for which the investigator classifies the relationship to study treatment (i.e. placebo) as "Yes". A worst-case scenario approach will be taken to handle missing data, i.e. the summary table will include events with the relationship to study treatment as "Yes" or missing. The summary tables will be displayed by SOC and PT.

An SADE is defined as an SAE for which the investigator classifies the relationship to Medical Device Deficiency for a serious adverse event as "Yes". A worst-case scenario approach will be taken to handle missing data, i.e. the summary table will include events with the relationship to study treatment as "Yes" or missing. The summary tables will be displayed by SOC and PT.

The incidence of AEs and SAEs (Fatal and Non-Fatal) of COVID-19, COVID-19 AEs leading to study inhaler discontinuation, COVID-19 AEs leading to study withdrawal, and COVID-19 AEs by maximum severity, will be obtained from the standard AE and SAE summaries.

4.4.2.1. Impact of COVID-19 Pandemic on Adverse Event Reporting

The number of participants with probable, suspected or confirmed COVID-19 infection will be reported. This display will also summarise the number of participants with a COVID-19 diagnosis test performed and the number of participants with positive, negative, or indeterminate results.

Additionally, a listing of COVID-19 assessments and symptoms for participants with COVID-19 AEs will be generated.

4.4.2.2. Cardiovascular Events and Deaths (All Causes)

Cardiovascular events and deaths (all causes) will be captured on targeted CV event eCRF pages for the following SAEs:

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

Separate patient profiles will be provided of participants for one or more of the above listed events.

4.5. Other Analyses

4.5.1. Subgroup analyses

No Subgroup analyses are planned for this study.

4.6. Interim Analyses

No interim analysis of data is planned for this study.

4.7. Changes to Protocol Defined Analyses

Changes from the originally planned statistical analysis specified in the protocol [(Dated: 05-JAN-2021)] are detailed in Table 3:

Table 3 Changes to Protocol Defined Analysis Plan

Protocol Defined Analysis	SAP Defined Analysis	Rationale for Changes
• Performance evaluable analysis set	• Modified intention-to-treat (mITT)	• The definition of the two analyses in the protocol and SAP are the same. The terminology has been updated in the SAP to "mITT" for the purpose of producing the programming outputs; more accurately aligned with current CDISC standards.

5. 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 (Lui, 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 J, 2016), (van der Palen J, 2018)] and with consideration given to observational studies in the literature [(Khassawneh BY, 2008), (Melani AS, 2011), (Arora P, 2014), (Chorão P, 2014), (Takaku Y, 2017), (Ocakli B, 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 J, 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 J, 2013). Moreover, both inhalers will contain placebo and participants may have up to a 30-minute break after demonstrating the first inhaler.

6. SUPPORTING DOCUMENTATION

6.1. Appendix 1 Abbreviations and Trademarks

6.1.1. List of Abbreviations

Abbreviation	Description
ADE	Adverse device effect
AE	Adverse Event
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
COVID-19	Coronavirus Disease-2019
CSR	Clinical Study Report
eCRF	Electronic Case Record Form
FAS	Full analysis set
GSK	GlaxoSmithKline
mITT	Modified Intention-to-Treat
OPS	Output and Programming Specification
SAP	Statistical Analysis Plan
SAE	Serious adverse event
SADE	Serious adverse device effect
VAS	Visual Analogue Scale

6.1.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
ELLIPTA

Trademarks not owned by the GlaxoSmithKline Group of Companies
SAS
BREEZHALER
WinNolin

7. 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. [Journal] // Respir Med. - 2014. - pp. 108 (7):992-998.

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

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

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. [Journal] // Respir Care . - 2008. - pp. 53 (3):324-328).

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

Mehta Cyrus R and Patel Nitin R Exact Logistic Regression : Theory and Examples [Journal]. - [s.l.] : Statisitcs in Medicine, 1995. - Vols. 14, 2143-2160.

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. [Journal] // Respir Med. - 2011. - pp. 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 [Journal] // Int J COPD. - 2018. - pp. 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 [Journal] // Respir Med. - 2017. - pp. 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. [Journal] // Int J Chron Obstruct Pulmon Dis.. - 2018. - pp. 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 COPD or asthma: comparison of ELLIPTA with other inhaler devices. [Journal] // NPJ Prim Care Respir Med. - 2016. - p. 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 [Journal] // Expert Opinion on Drug Delivery. - 2013. - pp. 10: 1171-1178.