TITLE PAGE

Protocol Title: An open-label study to evaluate correct use and ease of use of the ELLIPTA Dry Powder Inhaler (DPI) in pediatric patients currently receiving inhaled therapy for treatment of their asthma

Protocol Number: 206924

Short Title: An open-label study to evaluate correct use and ease of use of the ELLIPTA DPI in pediatric patients with asthma

Compound Number: GSK2285997

Sponsor Name and Legal Registered Address:

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PPD

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1. SYNOPSIS

Protocol Title: An open-label study to evaluate correct use and ease of use of the ELLIPTA Dry Powder Inhaler in pediatric patients currently receiving inhaled therapy for treatment of their asthma

Short Title: An open-label study to evaluate correct use and ease of use of the ELLIPTA Inhaler in pediatric patients with asthma

Rationale:

The ELLIPTA Dry Powder Inhaler (DPI) requires few steps, achieves consistent dosing and eliminates the hand-breath coordination required by metered dose inhalers (MDIs). While much research has assessed various features, including ease of use, correct use, critical errors and participant preference of the ELLIPTA DPI in an adult asthmatic population, there is very little information regarding these features in the pediatric population.

This study has been designed to assess the correct use of the ELLIPTA DPI in pediatric participants with asthma. It will also assess the ease of use of the ELLIPTA DPI, as evaluated by participants who have been deemed able to use the ELLIPTA DPI correctly.

Objectives and Endpoints:

- Stratum 1: 5 to 7 years old at V0 (inclusive)
- Stratum 2: 8 to 11 years old at V0 (inclusive)

Objectives	Endpoints
Primary	
• To determine the proportion of participants from each stratum who demonstrate correct use of the ELLIPTA DPI after the study period at V2.	• The percentage of participants from each stratum who demonstrate correct use of the ELLIPTA DPI after the study period at V2.
• To determine the proportion of participants from each stratum who rate the use of the ELLIPTA DPI as easy to use, from those who could demonstrate correct use of the ELLIPTA DPI after the study period at V2.	• The percentage of participants from each stratum who rate the ELLIPTA DPI as easy to use, from those who could demonstrate correct use of the ELLIPTA DPI after the study period at V2.
Secondary	
• To determine the proportion of participants from each stratum who demonstrate correct use of the ELLIPTA DPI after initial training from healthcare professional (HCP) at V1.	• The percentage of participants from each stratum who demonstrate correct use of the ELLIPTA DPI after initial training from HCP at V1.
• To determine the proportion of participants who demonstrate correct use of the ELLIPTA DPI after the study period at V2.	• The percentage of participants who demonstrate correct use of the ELLIPTA DPI after the study period at V2.
• To determine the proportion of participants	• The percentage of participants who rate the

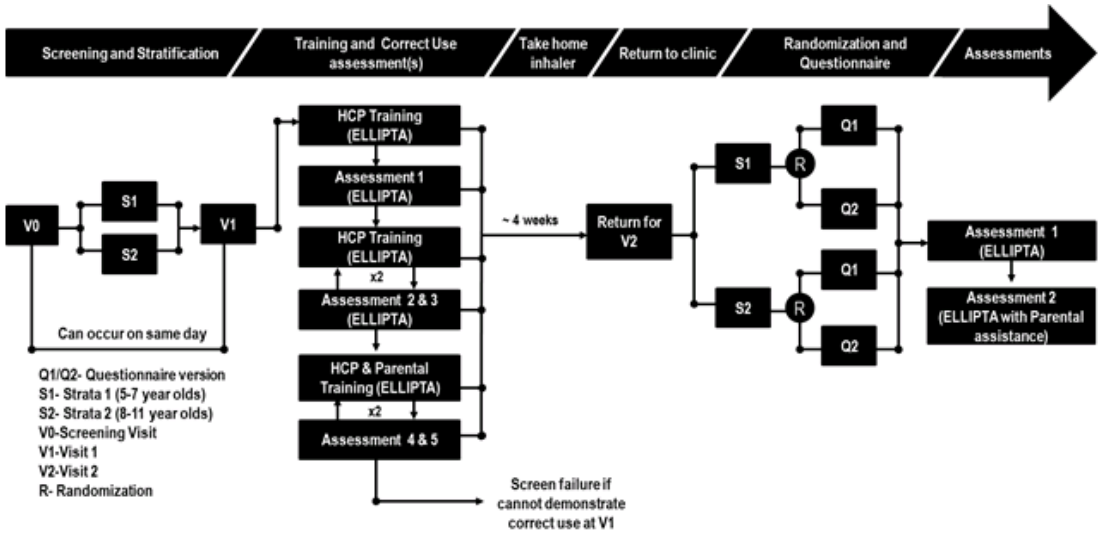
Objectives	Endpoints
who rate the use of the ELLIPTA DPI as easy to use, from those who could demonstrate correct use of the ELLIPTA DPI after the study period at V2.	ELLIPTA DPI as easy to use, from those who could demonstrate correct use of the ELLIPTA DPI after the study period at V2.
• To determine the proportion of participants who made at least one critical error during use of the ELLIPTA DPI after initial training from HCP at V1.	• The percentage of participants who made at least one critical error during use of the ELLIPTA DPI after initial training from HCP at V1.

Overall Design:

This is a multi-center, single arm, stratified, open-label, randomized (version of the ELLIPTA DPI ease of use questionnaire) placebo study. The study will involve up to 3 study visits. Participants will continue to use their prescribed asthma medications after meeting the eligibility criteria for the duration of the study. The study will consist of pediatric asthmatic patients and it will be stratified by age (Stratum 1; 5-7 years old inclusive and Stratum 2; 8-11 years old inclusive). Only participants who are naïve to the ELLIPTA DPI, have a documented history of symptoms consistent with a diagnosis of asthma and have been receiving inhaled therapy for treatment of their asthmatic symptoms for at least 3 months prior to V0 will be considered eligible.

V0 and V1 may take place on the same day. At V1, participants will be trained and demonstrate correct use of the ELLIPTA DPI. If successful, they will take the placebo ELLIPTA DPI home for the duration of the study period (28 ± 2 days) and take one dose daily. Upon return to the study clinic at V2, participants will complete the ease of use questionnaire to which they have been randomized and then demonstrate correct use of the ELLIPTA DPI prior to any re-training. Compliance with once daily usage of the ELLIPTA DPI during the study period will be recorded.

The protocol specific study requirements will be reviewed with each participant and their parent/guardian. Informed consent and the appropriate assent will be obtained from all who volunteer to take part in the study, prior to the initiation of the first study procedure.



Number of Participants:

Approximately 88 participants from Stratum 1 and 131 participants from Stratum 2 will need to be screened. Assuming a withdrawal rate during the study period of 3%, approximately 80 participants from strata 1 and 120 participants from strata 2 will complete the treatment period, return for V2 and be randomized to a version of ease of use questionnaire.

Treatment Groups and Duration:

The study population will be stratified by age (Stratum 1, 5 to 7 years old and Stratum 2, 8 to 11 years old). The study consists of up to 3 visits and a study period of 28 ± 2 days. Participants will be randomized to a version of the ease of use questionnaire in a 1:1 allocation by strata, as is defined below:

Randomization Group	Ease of Use Questionnaire Version
Stratum 1	A
	B
Stratum 2	A
	B

There is no active treatment provided during this study and participants will continue to take their own prescribed asthma medication for the duration of the study.

2. SCHEDULE OF ACTIVITIES (SOA)

The schedule of activities (SoA) in Table 1 details the timing of procedures / assessments to be performed in this study.

Any changes in the timing or addition of time points for any planned study assessments must be documented and approved by the relevant study team member and then archived in the sponsor and site study files, but will not constitute a protocol amendment. The institutional review boards (IRB)/ independent ethics committees (IEC) will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the informed consent form (ICF).

Table 1 Schedule of Activities

Procedure	Visit 0-Screening (up to 30 days before Day 1)	Treatment Period			Notes
		Visit 1 (can occur on same day as screening)	Early Withdrawal	Visit 2	
Day	-30	0		28 ± 2	All assessments concern study participants only, unless otherwise stated (parent/guardians).
Screening					
Informed consent and assent	X				Visit 1 must occur within 30 days of signing of providing informed consent. Must be signed before any study procedures. Assent must be provided.
Inclusion and exclusion criteria	X				All of the inclusion and none of the exclusion criteria must be met prior to inclusion at V0. This includes ability to demonstrate correct use of the ELLIPTA DPI after training.
Demography	X				Age, sex, race, ethnicity.
Physical Examination	X				Including height and weight,
Concomitant medications	X				Concomitant medications pertaining to the participant's diagnosis of asthma collected (minimum previous 3 months).
Past and current medical conditions	X				
Asthma History	X				Participant will have a medical history of symptoms consistent with a diagnosis of asthma.
Exacerbation History	X				Asthma exacerbation history for the previous year will be collected.
Randomization				X	Randomization refers to the version of the questionnaire only.
Safety					
AE review		←==========→			Collected from Visit 1 until the completion of the final assessment at Visit 2.
SAE review	←==========→				Collected from time of informed consent/assent until the completion of the final assessment at Visit 2.
Concomitant medications review	←==========→				Review any changes in concomitant medications.
Asthma exacerbations	←==========→				Asthma exacerbation information will be collected for the duration of the study (see Section 9.2.6)
Questionnaires and Assessments					

Procedure	Visit 0-Screening (up to 30 days before Day 1)	Treatment Period			Notes
		Visit 1 (can occur on same day as screening)	Early Withdrawal	Visit 2	
First training in correct use of ELLIPTA DPI by HCP		X			Initial training by HCP
Correct use of ELLIPTA DPI after first instruction by HCP		X			First demonstration of correct use of ELLIPTA DPI.
Second and third training in correct use of ELLIPTA DPI by HCP		X			Training only if necessary (participant made errors)
Correct use of ELLIPTA DPI after second and third instruction by HCP		X			Second and third demonstrations of correct use of ELLIPTA DPI
Fourth and fifth training in correct use of ELLIPTA DPI by HCP and parent/guardian		X			Training only if necessary (participant made errors)
Correct use of ELLIPTA DPI after fourth and fifth instruction by HCP and parent/guardian		X			Fourth and fifth demonstrations of correct use of ELLIPTA DPI. After which time they will be registered as a screen failure if correct use has not been demonstrated.
Ease of use Questionnaire completion				X	This is completed upon return to the site after the study period. This must occur before any other assessments at V2.
Compliance with ELLIPTA DPI			X	X	This will be taken from the dose counter.
Correct use of ELLIPTA DPI after treatment period				X	Demonstration of correct use of ELLIPTA DPI without any instruction at V2.
Correct use of ELLIPTA DPI with instruction from parent/guardian				X	Demonstration of correct use of ELLIPTA DPI with instruction from parent/guardian at V2. Only necessary if correct use is not demonstrated during first attempt.
Placebo ELLIPTA DPI					
Dispense Placebo ELLIPTA DPI(s)		X			Procedures for dispensation and return of clinical supplies will be described in detail in the Study Reference Manual (SRM). If a participant completes all study requirements, they will need 2 ELLIPTA DPIs. One will remain at site and the other will be used during the study period.
Return Placebo ELLIPTA DPI		X	X	X	

AE – Adverse Event, DPI - Dry Powder Inhaler, HCP - Healthcare Professional, SAE - Serious Adverse Events,

3. INTRODUCTION

3.1. Study Rationale

The ELLIPTA Dry Powder Inhaler (DPI) requires few steps, achieves consistent dosing and eliminates the hand-breath coordination required by metered dose inhalers (MDIs). While much research has assessed various features, including ease of use, correct use, critical errors (defined as an error that is likely to significantly inhibit delivery of the prescribed dose of medication to the patient) and patient preference of the ELLIPTA DPI in an adult asthmatic population, there is very little information regarding these features in the pediatric population [GlaxoSmithKline Document Number 2015N230821_00; GlaxoSmithKline Document Number 2017N314003_00; GlaxoSmithKline Document Number 2016N269989_01; Van der Palen, 2016a; Van der Palen, 2016b; Van der Palen, 2016c]. Previous studies in the pediatric population have shown that rates of correct use of inhalers is low, and even after instruction, patients still demonstrate poor inhalation technique when using a variety of Dry powder and Metered Dose Inhalers (MDI) [Kamps, 2000a; Kamps, 2002b]. Therefore, an inhaler that overcomes such barriers may be of high clinical relevance.

Accordingly, this study has been designed to assess the correct use of the ELLIPTA DPI in pediatric participants with asthma. It will also assess the ease of use of the ELLIPTA DPI, as evaluated by participants who have been deemed able to use the ELLIPTA DPI correctly. Recent work carried out by the GSK has helped guide the development of meaningful questionnaires for use within this study. The primary outcomes of this work illustrated that binary response options (easy and hard) were more meaningful in this population. Furthermore, it helped guide the method of delivery, in that, the 5-7 year old strata would need assistance when completing the questionnaire, unlike the 8-11 year old strata, who would be able to self-complete the questionnaire [NCT03315572, 2018].

3.2. Background

Asthma is a chronic inflammatory disease of the airways and lungs that results in hyperreactivity and clinically relevant episodes of wheezing. The global prevalence of asthma is on the rise. As of 2015, 358 million people globally suffer from asthma and it is one of the leading causes of disability in children between 5 and 11 years of age [GBD 2015, 2016]. It is most commonly treated with Inhaled Corticosteroids (ICS) alone or in combination with a long acting β_2 adrenergic agonist (LABA) [GINA, 2017].

Instances of problematic asthma cases in the pediatric population have been attributed to either; misdiagnosis, environmental factors and/or adherence to medication prescription [Bush, 2015]. The failure of a patient to adhere to their medication includes the inability to use their inhalation device correctly and subsequently receive their prescribed dose, the impact of which depends primarily upon the severity of the condition [Burgess, 2011]. Interventions to address issues related to adherence in pediatric populations have had limited success, with the most effective containing both educational and behavioral aspects [Morton, 2014].

Consequently, the ability of pediatric asthmatic patients to achieve and maintain correct use over time, which is defined as use of the inhaler in the manner described in the Instructions for Use (IFU) is becoming increasingly recognized.

The choice of inhalation device is an important decision when considering treatment for asthma in this age group. This has been illustrated in a recent study of 8-16 year-old asthmatic patients, where only 8% could use their MDI correctly, while 16% (Turbuhaler) and 22% (Diskus) were able to use their DPI correctly [Sleath, 2011]. Furthermore, inadequate technique reduces the effects of inhalation, thus a device that is easy to use and delivers drug to the lungs effectively is important.

In order to combat such educational and behavioral barriers, the ELLIPTA DPI has been designed to be simple for patients to use based on the number of steps required to use it correctly and the amount of time required to be trained in correct use. Previous studies in other populations have shown that the number of errors made while using the ELLIPTA DPI and the amount of time required to train users are reduced [Van der Palen, 2016a; Van der Palen, 2016b; Van der Palen, 2016c]. Therefore, the ELLIPTA DPI has the potential to address some of the limitations regarding the correct use of other inhalers in the pediatric asthmatic population [Kamps, 2002b].

Ultimately, the prescription and subsequent use of easy to use DPIs is paramount and could be of high clinical value for the treatment and management of asthma in this population. This study is designed to assess the correct use and ease of use of the ELLIPTA DPI by pediatric participants with asthma, a population yet to be studied for their use of the ELLIPTA DPI.

3.3. Benefit/Risk Assessment

This study involves use of placebo ELLIPTA DPI, which does not contain any active treatment. Participants will continue to take their own prescribed asthma medication and other concomitant medication for the duration of the study.

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

3.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP)		
Paradoxical bronchospasm, which may occur with an immediate increase in wheezing after inhalation.	As with other inhalation therapy, paradoxical bronchospasm may occur with an immediate increase in wheezing after dosing. From post-marketing data, paradoxical bronchospasm has been reported at a frequency of <1/10,000, including isolated reports [Nicklas, 1990].	This should be treated immediately with a fast and short acting inhaled bronchodilator. Investigators will be instructed to assess the subject's condition to determine their eligibility to continue in the study and the need for alternative therapy.
Allergic reaction due to hypersensitivity to placebo excipients.	The placebo inhalers contain the excipients lactose and lactose blended with magnesium stearate. There are known allergies to these ingredients.	Participants with a known hypersensitivity to any of these, or severe milk protein allergy that could contraindicate study participation are excluded from the study (Section 6). If an allergic reaction occurs, it should be treated immediately with a fast and short acting inhaled bronchodilator. Investigators will be instructed to assess the subject's condition to determine their eligibility to continue in the study and the need for alternative therapy.

3.3.2. Benefit Assessment

As this is a placebo only study, no direct benefit to the participant is expected as a result of taking part in the study. No active treatment will be provided during the study. All participants will continue to receive their own asthma therapy as prescribed for the duration of the study.

3.3.3. Overall Benefit:Risk Conclusion

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

4. OBJECTIVES AND ENDPOINTS

The study will evaluate different aspects of correct use and ease of use of the ELLIPTA DPI in pediatric patients with asthma. The population will be stratified into two different age groups and will be referred to as Stratum 1 and Stratum 2 throughout this protocol.

- Stratum 1: 5 to 7 years old at V0 (inclusive)
- Stratum 2: 8 to 11 years old at V0 (inclusive)

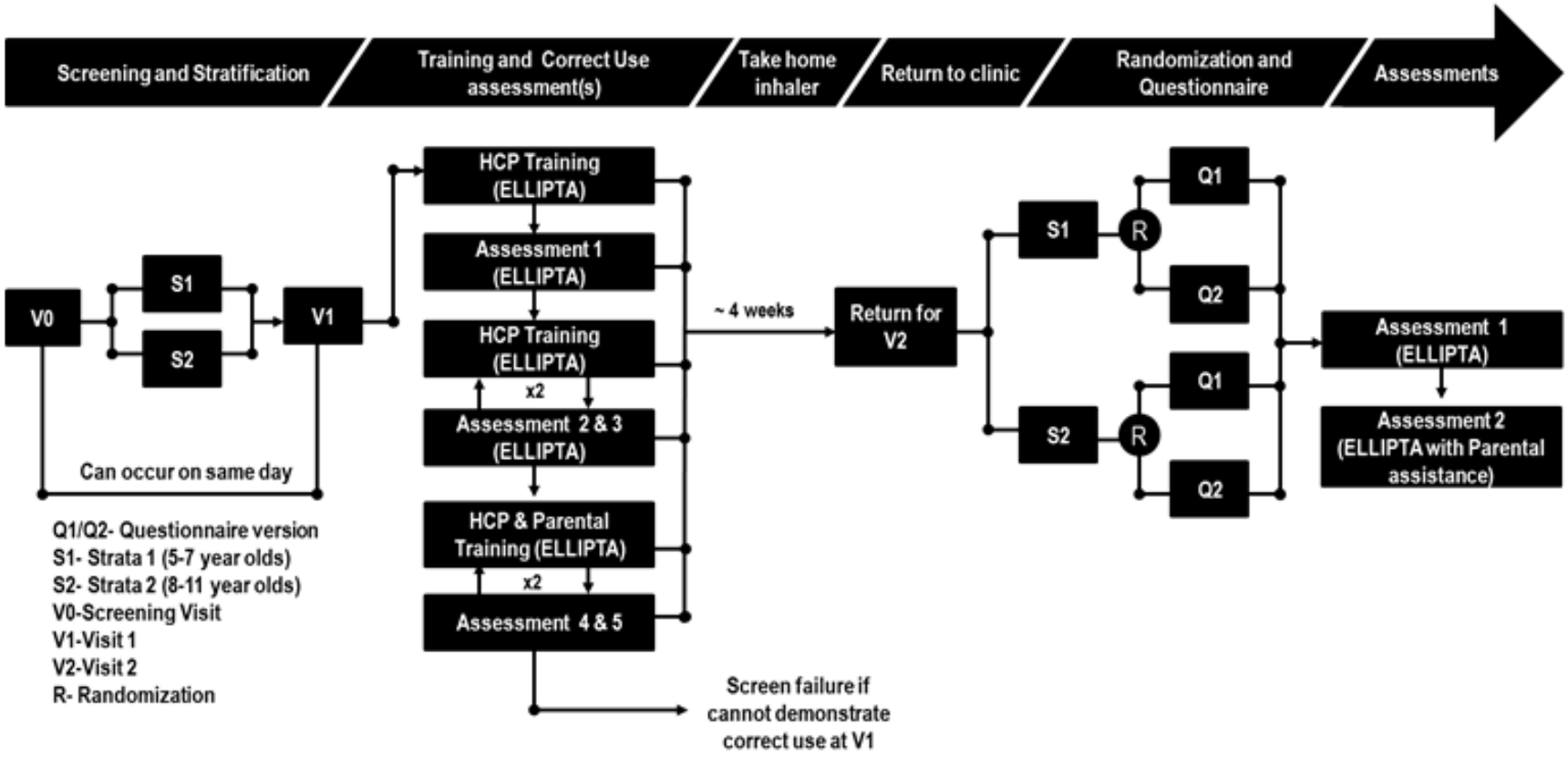
Objectives	Endpoints
Primary	
• To determine the proportion of participants from each stratum who demonstrate correct use of the ELLIPTA DPI after the study period at V2.	• The percentage of participants from each stratum who demonstrate correct use of the ELLIPTA DPI after the study period at V2.
• To determine the proportion of participants from each stratum who rate the use of the ELLIPTA DPI as easy to use, from those who could demonstrate correct use of the ELLIPTA DPI after the study period at V2.	• The percentage of participants from each stratum who rate the ELLIPTA DPI as easy to use, from those who could demonstrate correct use of the ELLIPTA DPI after the study period at V2.
Secondary	
• To determine the proportion of participants from each stratum who demonstrate correct use of the ELLIPTA DPI after initial training from HCP at V1.	• The percentage of participants from each stratum who demonstrate correct use of the ELLIPTA DPI after initial training from HCP at V1.
• To determine the proportion of participants who demonstrate correct use of the ELLIPTA DPI after the study period at V2.	• The percentage of participants who demonstrate correct use of the ELLIPTA DPI after the study period at V2.
• To determine the proportion of participants who rate the use of the ELLIPTA DPI as easy to use, from those who could demonstrate correct use of the ELLIPTA DPI after the study period at V2.	• The percentage of participants who rate the ELLIPTA DPI as easy to use, from those who could demonstrate correct use of the ELLIPTA DPI after the study period at V2.
• To determine the proportion of participants from each stratum who made at least one critical error during use of the ELLIPTA DPI after initial training from HCP at V1.	• The percentage of participants from each stratum who made at least one critical error during use of the ELLIPTA DPI after initial training from HCP at V1.

Objectives	Endpoints
Exploratory	
• To determine the proportion of participants from each stratum who rate the ability to tell how many puffs are left in the ELLIPTA DPI as easy after the study period at V2.	• The percentage of participants from each stratum who rate the ability to tell how many puffs are left in the ELLIPTA DPI as easy after the study period at V2.
• To determine the proportion of participant's parents/guardians who rate the ability to tell how many doses are remaining in the ELLIPTA DPI as easy or very easy after the study period at V2.	• The percentage of participant's parents/guardians who rate the ability to tell how many doses are remaining in the ELLIPTA DPI as easy or very easy after the study period at V2.
• To determine the proportion of participant's parents/guardians who would be 'likely' or 'very likely' to ask their doctor for the ELLIPTA DPI if the participants current daily inhaled medication(s) were available in the ELLIPTA DPI after the study period at V2.	• The percentage of participant's parents/guardians who would be likely or very likely to ask their doctor for the ELLIPTA DPI if the participants current daily inhaled medication(s) were available in the ELLIPTA DPI after the study period at V2.
• To determine the proportion of participants from each stratum who can demonstrate correct use after the study period at V2 with assistance from parents/guardians.	• The percentage of participants from each stratum who demonstrated correct use after the study period at V2 with assistance from parents/guardians.
• To determine the proportion of participants from each stratum who made at least one critical error during use of the ELLIPTA DPI after the study period at V2.	• The percentage of participants from each stratum who made at least one critical error during use of the ELLIPTA DPI after the study period at V2.
• To determine the proportion of participants who made at least one critical error during use of the ELLIPTA DPI after initial training from HCP at V1.	• The percentage of participants who made at least one critical error during use of the ELLIPTA DPI after initial training from HCP at V1.

5. STUDY DESIGN

5.1. Overall Design

Figure 1 Study Schematic



This is a multi-center, single arm, stratified, open-label, randomized (version of the ELLIPTA DPI ease of use questionnaire) placebo-only study. The study will involve up to 3 study visits. Participants will continue to use their prescribed asthma medications after meeting the eligibility criteria for the duration of the study. Further information regarding the assessments that will occur at each visit will be locate in the Study Reference Manual (SRM).

5.1.1. Visit 0

Visit 0 (V0) and Visit 1 (V1) can occur on the same day. Participants between 5 and 11 years old (inclusive) at V0, who are naive to the ELLIPTA DPI (with no previous treatment experience with any medication administered by the ELLIPTA DPI), have a documented history of symptoms consistent with a diagnosis of asthma and are currently receiving maintenance and/or rescue therapy for asthma treatment, will be considered eligible to participate in the study.

At V0, written informed consent will be obtained from eligible participant's parent/guardian and the respective assent, along with medical history, demography and current asthma therapy. Participants will also be stratified by age into one of two strata:

- Stratum 1: 5 to 7 years old at V0 (inclusive)
- Stratum 2: 8 to 11 years old at V0 (inclusive)

5.1.2. Visit 1

At V1, all participants will be trained in correct use of the ELLIPTA DPI by a Healthcare Professional (HCP) as would occur in general practice. Participants will then be asked to attempt to use the ELLIPTA DPI, without guidance from either the HCP or their parent/guardian. Should the study participant be unable to use the ELLIPTA DPI correctly, the HCP will be allowed to instruct the participant two more times. After each round of instruction, the participant will attempt to correctly use the ELLIPTA DPI. If the study participant is still unable to demonstrate correct use of the ELLIPTA DPI after all three instructions by the HCP, the parent/guardian of the participant will be able to assist in the instruction of correct use of the ELLIPTA DPI for another two attempts. It is therefore important that the parent/guardian is engaged with the HCP during delivery of the instructions on correct use. If the participant still cannot demonstrate correct use after all five attempts, they will be registered as a screen failure. All participants who can demonstrate correct use at any stage in this process will be informed of their correct use and will perform no further demonstrations at this visit.

Participants will then take a placebo ELLIPTA DPI home for the duration of the study period (28 (±2) days). Participants will be instructed to take one inhalation from the ELLIPTA DPI as would be prescribed (once daily) at approximately the same time every day. Participant's parent/guardian will need to make note of the date and time of each dose administered of the ELLIPTA DPI on the worksheet provided. This worksheet can also be used to make note of any adverse or serious adverse events (AEs/SAEs) that occur during the study period. Participant's parents/guardians must contact the investigative site if the participant experiences any clinical worsening of their asthma. Further information on this procedure is located in Section 9.1.1.

5.1.3. Visit 2

Participants will return to the site for V2 after the study period, and will be randomized (1:1 allocation) to determine the version of the ease of use questionnaire they will receive (Version A or Version B) located in Appendix 6. Prior to the correct use assessment, the participant will complete the version of the ease of use questionnaire according to their randomization allocation. The participant's parent/guardian will then complete a questionnaire to assess various features of the ELLIPTA DPI (Appendix 6) according to the same randomization allocation as their dependent.

After completion of the ELLIPTA questionnaire(s), the participant's ability to correctly use the ELLIPTA DPI will be assessed. At this visit during attempt 1, there will be no instruction, coaching, comment or direction given by the HCP or parent/guardian. Only one attempt to correctly use the inhaler will be conducted during this assessment. If the participant is unable to demonstrate correct use in their first attempt at this visit, they will have another attempt, in which, they will receive assistance from their parent/guardian.

At this visit, the number of doses administered by the participant during the study period will be noted and participants will be discharged from the study.

5.2. Number of Participants

Approximately 219 participants between 5 and 11 years old (inclusive) with a documented history of symptoms consistent with a diagnosis of asthma (88 participants from Stratum 1 and 131 participants from Stratum 2) will need to be screened to achieve 83 participants from stratum 1 and 124 participants from stratum 2 who meet the eligibility criteria at V1, assuming a 5% failure rate of being able to correctly use the ELLIPTA DPI at V1. Further participants may be screened to ensure that at least 83 participants from strata 1 and 124 participants from strata 2 enter the study period.

Assuming a withdrawal rate during the treatment period of 3%, approximately 80 participants from strata 1 and 120 participants from strata 2 will complete the treatment period, return for V2 and be randomized to a version of ease of use questionnaire. Based on the assumption that 80% of participants from both strata will be able to demonstrate correct use of the ELLIPTA DPI at V2. it is expected that 64 participants from stratum 1 and 96 participants from stratum 2 will be included in the analysis of the second primary endpoint regarding 'ease of use'.

5.3. Participant and Study Completion

A participant is considered to have completed the study if he/she has completed all phases of the study including the last scheduled procedure shown in the SoA (Section 2).

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

5.4. Scientific Rationale for Study Design

Participants are required to be naïve to (have no previous experience with) the ELLIPTA DPI in order to appropriately assess their ability to be trained in, demonstrate correct use and assess its ease of use.

Stratification by age of the participants involved in the study was chosen in order to appropriately account for the potential differences in cognitive ability with respect to the ease of use questionnaires. This enables analysis of these two strata separately for this study and allows for the variation in delivery of the questionnaires distributed. Previous questionnaires have been modified for suitability in this pediatric population. The development of these questionnaires and suggestions for their delivery has been informed by earlier work conducted by the Value Evidence Outcomes team with GSK [NCT03315572, 2018].

Inactive treatment was chosen as it avoids the potential bias related to the possible clinical improvement of the participant's attitudes and perceptions on the ease of use of the DPI an inactive treatment was chosen. Furthermore, adding a placebo ELLIPTA DPI to the participants existing asthma therapy avoids the need for wash-in/out periods and the need to discontinue current asthma medications for study visits.

The requirement for two study visits excluding screening is to assess the ability of the participant to be taught, retain that teaching/training and carry out a correct use demonstration. It will also determine if the ability of a pediatric participant to correctly use their inhaler diminishes or is lost over time after input from the participant's parent/guardian only. The time between visits of 4 weeks was chosen as this is deemed long enough to lose the ability to correctly use an inhaler and to accurately assess the ease of use of the ELLIPTA DPI. It also has been the time frame used in previous correct use studies in other populations [GlaxoSmithKline Document Number 2017N314003_00; GlaxoSmithKline Document Number 2016N269989_01]. Furthermore, this treatment period (approximately one month) resembles the timing of inhaler refill and potential education at a pharmacy or by a HCP.

5.5. Dose Justification

This is not applicable as this is a placebo-only study.

6. STUDY POPULATION

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

6.1. Inclusion Criteria

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

Age

1. Participants between 5 and 11 years old (inclusive), at the time of the V0.

Type of Participant and Disease Characteristics

2. Participants with a documented history of symptoms consistent with a diagnosis of asthma for at least 6 months prior to V0 (includes asthma diagnosis).

Sex

3. Males and premenarchial females.

Informed Consent

4. Written informed consent from at least one parent/guardian and the accompanying informed assent from the participant (where the participant is able to provide assent) prior to admission to the study.
    a. If applicable, the participant must be able and willing to give assent to take part in the study according to the local requirement. The study investigator is accountable for determining a child's capacity to assent to participation in a research study, taking into consideration any standards set by the responsible IEC/IRB.
5. Participant and their legal guardian understand and are willing, able, and likely to comply with study procedures and assessments.

Current Asthma Therapy

6. Participant must have been receiving asthma treatment (rescue or maintenance) for 3 months prior to entry onto the study.
7. Participant must have **never** been trained in correct use of, or used the ELLIPTA DPI previously.

Study Procedures

8. Participants must be able to demonstrate correct use of the ELLIPTA DPI after coaching/training at V1.
9. Participants must be able to converse and understand verbal instruction in English.

6.2. Exclusion Criteria

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

Medical Conditions

1. Concurrent diagnosis of other respiratory disorders including active tuberculosis, lung cancer, bronchiectasis, sarcoidosis, lung fibrosis, pulmonary hypertension, interstitial lung diseases, cystic fibrosis or other active pulmonary diseases.
2. Concurrent diagnosis of psychiatric or psychological or any other disorders that in the opinion of the investigator may affect the ability of the participant to comply with study procedures or requirements.

Asthma exacerbation history:

3. Has experienced an exacerbation which required oral/systemic corticosteroids in the three months prior to V0.
4. Has been hospitalized for an episode of asthma within three months of V0.
5. Has had an asthmatic episode requiring intubation, associated with hypercapnea, respiratory arrest or hypoxic seizures.

Contraindications:

6. Has exhibited symptoms of a recent acute respiratory tract infection within one week of V0.
7. History of hypersensitivity to any components of the study inhalers (e.g., lactose, magnesium stearate). In addition, participants with a history of severe milk protein allergy that, in the opinion of the study physician, contraindicates participation will also be excluded.
8. Historical or current evidence of clinically significant or rapidly progressing or unstable cardiovascular, neurological, renal, hepatic, immunological, endocrine (including diabetes or thyroid disease) or hematological abnormalities that are uncontrolled. Significant is defined as any disease that, in the opinion of the investigator, would put the safety of the participant at risk through participation, or which would affect the analysis if the disease/condition exacerbated during the study.

Diagnostic assessments and other criteria

9. Parent or Guardian with a history of psychiatric disease, intellectual deficiency, substance abuse or other condition (e.g. inability to read, comprehend or write) which may affect:

    - Validity of consent to participate in the study.
    - Adequate supervision of the participant during the study.
    - Compliance of participant with study medication and study procedures
    - Participant safety and well-being.

10. Participants who have received an investigational drug and/or medical device within 30 days of entry into this study (Screening), or within five drug half-lives of the investigational drug, whichever is longer.
11. 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.

6.3. Lifestyle Restrictions

There are no lifestyle restrictions.

6.3.1. Meals and Dietary Restrictions

There are no meals or dietary restrictions.

6.3.2. Activity

There are no restrictions on activity.

6.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but do not subsequently enter the 28-day treatment period. This includes any participant who is not able to demonstrate correct use of the ELLIPTA DPI at V1. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAEs.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once. Rescreened participants should be assigned a new participant number. Participants are not eligible for rescreening if they attended V1 and were instructed and/or assessed for their correct use of the ELLIPTA DPI in any way.

7. TREATMENTS

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

Participants will need 2 placebo ELLIPTA DPIs during the study. One of which will be used at the site for assessments and will remain at site during the study period. The other placebo ELLIPTA DPI will be taken home by the participant and will be used as directed for the duration of the study period.

7.1. Treatments Administered

Study Treatment Name:	**Placebo ELLIPTA DPI**
Dosage formulation:	Placebo DPI with two strips and 30 blisters per strip. First strip: lactose monohydrate Second strip: lactose monohydrate blended with magnesium stearate
Route of Administration	Oral Inhalation
Dosing instructions:	Once Daily
Packaging and Labelling	Placebo DPI will be provided in the appropriate container. Each container will be labelled as required per country requirement.
Manufacturer	GSK
Device	NA

7.2. Dose Modification

This is not applicable as this is a placebo only study and there will be no dose modification during this study.

7.3. Method of Treatment Assignment

Participants will be assigned to the ease of use questionnaire version (Appendix 6) they receive in accordance with the randomization schedule devised by clinical statistics. Participants will be randomized using an Interactive Web Response System (IWRS). The system will be used by the investigator or designee to register and randomize the participant. It will assign the participant to one of two questionnaire versions (Version A or Version B), see Appendix 6.

Eligible subjects will be randomized to receive 1 of the following 2 possible questionnaire versions (1:1 allocation) at V2. The variation between versions concerns the order of the response options provided to participants. This reduces the response bias caused by the ordering of the questionnaire responses (Appendix 6). Parents/guardians will receive the same ordering of responses as their dependent.

Randomization Group	Ease of Use Questionnaire Version
Stratum 1	A
	B
Stratum 2	A
	B

7.4. Blinding

This is an open-label study. The participants and the investigator will be able to recognize the study inhaler that the participant is receiving. The participant will be informed that the study inhalers contain no active treatment. However, the version of the ease of use questionnaire that will be answered by a participant and their legal guardian will be assigned using an IWRS. The site will use the IWRS prior to any assessments by the participant at V2. The site will record the randomization assignment on the applicable case report form, if required. Potential response bias will be reduced by randomizing the ease of use questionnaire answered by participants, which differ on the ordering of responses provided in each question.

7.5. Preparation/Handling/Storage/Accountability

- The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment. Details regarding transit and storage conditions for study treatments will be included in the SRM.
- Only participants enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
- The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (i.e. receipt, reconciliation, and final disposition records).
- Further guidance and information for the final disposition of unused study treatment are provided in the SRM.

- Under normal conditions of handling and administration, study treatment is not expected to pose significant safety risks to site staff.
- 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.

7.6. Treatment Compliance

When participants are dosed at the site, they will receive study treatment directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents. The dose of study treatment and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study treatment.

When participants self-administer study treatment at home, compliance with the ELLIPTA DPI dosing regimen will be assessed by recording the number of ELLIPTA DPI doses dispensed by each participant obtained by reading the dose counter upon return of the participant at V2. The participant's parent/guardian will also receive a worksheet to note the date and time of each dose administered during the study period.

This information must be maintained and reconciled with study treatment and compliance records. Compliance from the dose counter only will be entered will be recorded in the electronic case report form (eCRF).

7.7. Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrolment or receives during the study must be recorded along with:

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

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

7.8. Treatment after the End of the Study

There is no active treatment administered during this study. This is a placebo only study and participants will not receive any specific post-study treatments.

8. DISCONTINUATION CRITERIA

8.1. Discontinuation of Study Treatment

Participants will be considered to have completed the study upon completion of all study procedures at V2 (final clinic visit).

The definition of an early withdrawal from the study will be any participant who demonstrates correct use of the ELLIPTA DPI at V1, but is withdrawn or withdraws prior to completion of the V2 procedures.

A participant may voluntarily discontinue participation in the study at any time. The investigator may also, at his/her discretion; discontinue the participant from the study at any time. In addition, the investigator must make every effort to have the participant return to the clinic as soon as possible after discontinuation of study inhaler for an early withdrawal visit.

The participant will be withdrawn from the study if any of the following criteria apply:

- The participant experiences an asthma exacerbation (see Section 9.2.6) that in the opinion of the investigator may affect their ability to complete the requirements of the protocol.
- The participant begins using a medication that is delivered by the ELLIPTA DPI (excluding the study placebo ELLIPTA DPI).

After premature discontinuation from the study, the following evaluations and procedures should be completed at the early withdrawal visit and must be recorded in the eCRF as required.

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

8.1.1. Liver Chemistry Stopping Criteria

Not applicable as this is a placebo only study and there is not active treatment.

8.1.2. QTc Stopping Criteria

Not applicable as this is a placebo only study and there is not active treatment.

8.1.3. Temporary Discontinuation

Participants who withdraw from the study treatment will not be able to continue in the study.

8.2. Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioural, compliance or administrative reasons.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- Refer to the SoA (Section 2) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

8.3. Lost to Follow Up

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

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

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

9. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the SoA (Section 2). Protocol waivers or exemptions are not allowed. Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment. Adherence to the study design requirements, including those specified in the SoA (Section 2), 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 2).

9.1. Assessments

9.1.1. Screening and Critical Baseline Assessments

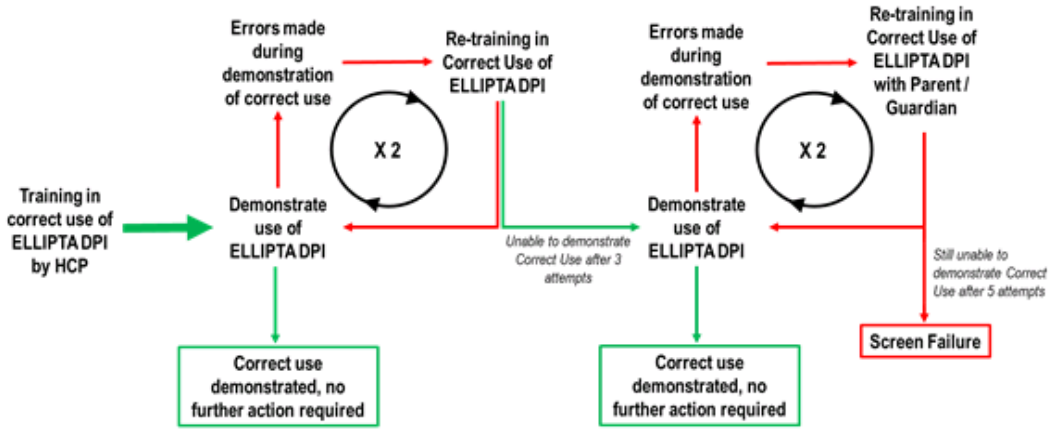
The following will be recorded in the eCRF at V1:

9.1.1.1. Visit 1

9.1.1.1.1. Training and correct use Assessments

During V1, participants will be trained in the correct use of the ELLIPTA DPI by the HCP. The course of events during the training and assessments that occur at V1 is shown in Figure 2 below. During training, parental/guardian involvement is important, as they will have to assist in the training of the participant if the participant is unable to demonstrate correct use after the first 3 attempts.

Figure 2 Training and assessments of correct use of ELLIPTA DPI at V1



9.1.2. V2 Assessments

After the 28-day treatment period, participants will return for V2. During this visit, the primary assessments occur. Detail regarding the order of assessments at V2 is provided in Figure 3.

The following will be recorded in the eCRF at V2:

9.1.2.1. Ease of use Questionnaire

Prior to any other assessments at V2, participants will answer the ease of use questionnaire. The exact wording that will be used in this questionnaire and further instructions for administration of these questionnaires is located in Appendix 6.

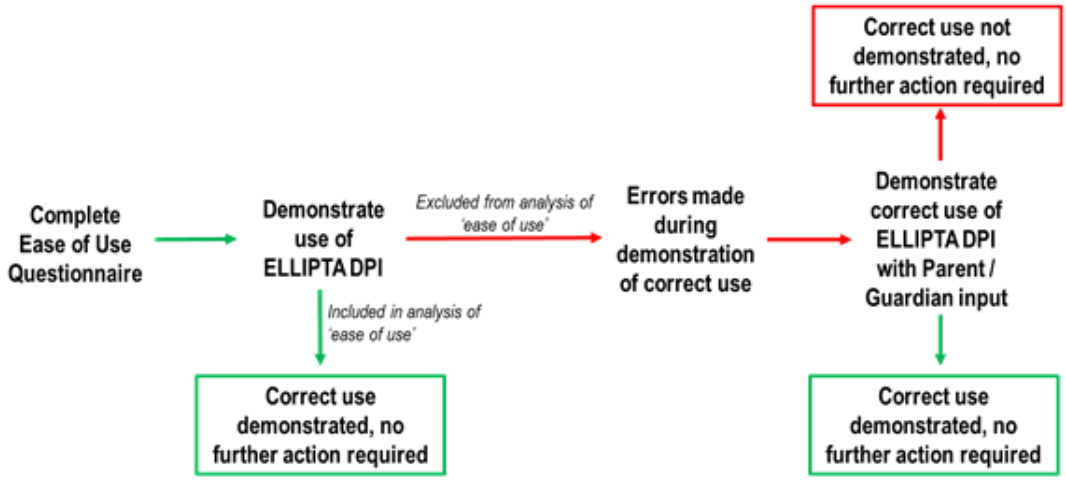
- For Stratum 1, the questionnaire will be administered by the interviewer. Responses will be provided according to the version to which the participant has been randomized.
- For Stratum 2, the questionnaire will be self-administered. Responses will be provided according to the version to which the participant has been randomized. If the participant is unable to self-administer the questionnaire, then they will be able to complete the questionnaire in the same manner as for stratum 1 (interviewer administered).
- Parents/Guardians will be assigned to the same version letter (A or B) of questionnaire to which their child/dependent was randomized.

9.1.2.2. Correct Use

At V2, participants will be assessed for their ability to demonstrate correct use of the ELLIPTA DPI. There will be no training in correct use prior to the assessment. There will also be no input from the participant's parent/guardian during the first attempt at V2.

If the participant is unable to demonstrate correct use at V2 after the initial attempt, the participant's parent/guardian will be asked to instruct the participant in how to use the device correctly before they have their second attempt.

Figure 3 Assessments regarding correct use and ease of use of the ELLIPTA DPI at V2



9.2. Adverse Events

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

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study treatment or the study, or that caused the participant to discontinue the study (see Section 8).

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

- All SAEs will be collected from the signing of the ICF until the time point specified in the SoA (Section 2).
- All AEs will be collected from the beginning of V1 until the timepoint specified in the SoA (Section 2).
- Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the eCRF not the AE section.
- All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.
- Investigators are not obligated to actively seek AEs or SAEs in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify the sponsor.

- The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

9.2.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AE and/or SAE. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrence. On the same worksheet that will be provided to note compliance (date and time) to their ELLIPTA DPI regimen, the participant's parent/guardian will be able to note any AEs and SAEs that occur during the study period.

9.2.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up (as defined in Section 8.3). Further information on follow-up procedures is given in Appendix 3.

9.2.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information, e.g. summary or listing of SAE) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

9.2.5. Death Events

For all deaths, whether or not they are considered SAEs, specific Death sections of the eCRF will be required to be completed. These sections include questions regarding cardiovascular (including sudden cardiac death) and non-cardiovascular death.

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

9.2.6. Asthma Exacerbation

An exacerbation is defined as deterioration of asthma requiring the use of systemic or oral corticosteroids (tablets, suspension, or injection) for at least 3 days or a hospitalization or emergency department visit due to asthma that required systemic corticosteroids.

Subjects who experience an asthma exacerbation during the treatment period may remain in the study and should continue to use their placebo ELLIPTA DPI if possible. Treatment of asthma exacerbations with short term antibiotics (less than or equal to 14 days) and systemic corticosteroids (less than or equal to 10 days) is permitted.

For worsening asthma symptoms/exacerbations requiring:

- Emergency treatment: the decision whether such a subject would continue in the study or be withdrawn would be determined per investigator discretion. The Study Medical Monitor would be available to discuss any related questions with the investigator.
- Hospitalization: such a subject should be withdrawn from the study

Asthma exacerbations should not be recorded as an AE, unless they meet the definition of a SAE and these SAEs will be recorded on the appropriate eCRF section and should be reported to GSK for all subjects. For the purposes of this study, asthma exacerbations will be collected and recorded on the asthma exacerbation log in the eCRF for all subjects. The time period for collection of asthma exacerbations on the asthma exacerbation log in the eCRF will begin from Visit 1 and will end when Visit 2/EW visit has been completed.

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

9.3. Treatment of Overdose

This study only contains placebo inhalers, with no active treatment. Therefore, management of an overdose does not apply.

9.4. Safety Assessments

There are no mandated safety assessments, other than monitoring for AEs and SAEs. This is described in detail in Section 9.2.

9.4.1. Physical Examinations

- A physical examination will include, at a minimum, assessments of the Cardiovascular, Respiratory, Gastrointestinal and Neurological systems. Height and weight will also be measured and recorded.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

9.4.2. Vital Signs

This is not applicable as it is a placebo only study.

9.4.3. Electrocardiograms

This is not applicable as it is a placebo only study.

9.4.4. Clinical Safety Laboratory Assessments

This is not applicable as it is a placebo only study.

9.4.5. Suicidal Risk Monitoring

This is not applicable as it is a placebo only study.

9.5. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

9.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study

9.7. Genetics

Genetics are not evaluated in this study.

9.8. Biomarkers

Biomarkers are not evaluated in this study.

9.9. Health Economics OR Medical Resource Utilization and Health Economics

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

10. STATISTICAL CONSIDERATIONS

10.1. Hypothesis

This is a descriptive, placebo only study and no formal inference is planned. The two primary objectives of the study are:

- To determine the proportion of participants from each stratum who demonstrate correct use of the ELLIPTA DPI after the study period at V2
- To determine the proportion of participants from each stratum who rate the use of the ELLIPTA DPI as easy to use, from those who could demonstrate correct use of the ELLIPTA DPI after the study period at V2.

10.2. Sample Size Determination

10.2.1. Sample Size Assumptions

The sample size calculation is based on the co-primary endpoints, the percentage of subjects who demonstrate correct use of the ELLIPTA DPI at V2, and the percentage of subjects who rate the use of the ELLIPTA DPI as easy, among those who demonstrate correct use of the inhaler at V2.

Approximately 219 subjects (i.e. 88 in stratum 1 and 131 in stratum 2) will be needed for screening in order to obtain 200 subjects (i.e. 80 in stratum 1 and 120 in stratum 2) with available data to be randomized to an "ease of use" questionnaire, in anticipation of a 5% V0/V1 screen failure rate and then a 3% drop-out in the 4-week interim period.

If the proportion of participants demonstrating correct use of the ELLIPTA DPI at V2 is 80% for both strata 1 and 2, a total sample size of 80 participants in stratum 1 and 120 participants in stratum 2 will produce a confidence interval (CI) equal to the sample proportion ± 9.28 and ± 7.51 percentage points. In addition, given the assumption that the proportion of participants demonstrating correct use and evaluating the ELLIPTA DPI at V2 as easy to use is 80% for both strata 1 and 2, a total sample size of 64 participants in stratum 1 and 96 participants in stratum 2 will produce a CI equal to the sample proportion ± 10.42 and ± 8.44 percentage points. The sample size software used to estimate the precision and following sensitivity analysis estimates is PASS version 12 [Hintze, 2013].

10.2.2. Sample Size Sensitivity

With an assumed sample size, the difference between the hypothesized and observed proportions of participants able to demonstrate correct use of the ELLIPTA DPI at V2 can affect the precision of the estimate. If it is hypothesized that the proportion of participants considered to be using the DPI correctly (observed proportion) is 80%, a sample size of 80 participants in stratum 1 could narrow the precision of the estimated proportion by as little as ± 5.47% if the observed proportion is 95%, or widen the precision to as large as ± 11.18% if the observed proportion is 60%. A sample size of 120 participants in stratum 2 could narrow the precision of the estimated proportion by as

little as ± 4.35% if the observed proportion is 95%, or widen the precision to as large as ± 9.09% if the observed proportion is 60%.

Also, the difference between the hypothesized and observed proportions of participants rating the ease of use of the ELLIPTA DPI at V2 as easy can also affect the precision of the estimate. If it is hypothesized that the proportion of participants who can correctly use the ELLIPTA DPI correctly is 80% and thus can rate the ELLIPTA DPI as easy to use (observed proportion), a sample size of 64 participants in stratum 1 could narrow the precision of the estimated proportion by as little as ± 6.21% if the observed proportion is 95%, or widen the precision to as large as ± 12.53% if the observed proportion is 60%. A sample size of 96 participants in stratum 2 could narrow the precision of the estimated proportion by as little as ± 4.93% if the observed proportion is 95%, or widen the precision to as large as ± 10.19% if the observed proportion is 60%.

10.3. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who sign the ICF
Intent-to-Treat (ITT)	The Intent-to-Treat (ITT) population is defined as all subjects who have been screened and received at least one dose of the study medication (placebo). This will constitute the primary population for all study population and safety displays, and for some secondary and exploratory efficacy endpoint displays.
Modified Intent-to-Treat (MITT)	The Modified Intent-to-Treat (MITT) population is defined as all subjects who have been screened, received at least one dose of the study medication (placebo) and were randomized to a questionnaire at V2. This will constitute the primary population for the primary and most secondary efficacy endpoint displays.

10.4. Statistical Analyses

Where possible, data from subjects who withdraw prematurely from the study treatment or the study will be included in any relevant analyses. Specific details for inclusion will be detailed in the Reporting and Analysis Plan (RAP).

10.4.1. Efficacy Analyses

Endpoint	Statistical Analysis Methods
Primary	The first primary analysis will calculate the proportion of subjects from each age stratum (5 to 7 years old (inclusive) and 8 to 11 years old (inclusive) who demonstrate correct use of the ELLIPTA DPI at V2. The proportion will be reported for both strata and calculated as those who demonstrate correct use at V2 / the number of participants whose use of the ELLIPTA DPI was evaluated at V2. This will be reported along with a 95% CI for the proportion calculated using the exact binomial distribution. The second primary analysis will calculate the proportion of subjects from each age stratum who rate the ELLIPTA DPI as 'easy to use', from those who demonstrated correct use of the ELLIPTA DPI at the end of the study period V2. The proportion will be reported for both strata and calculated as those who rate the ELLIPTA DPI as easy to use / those who demonstrate correct use of the ELLIPTA DPI at V2. This proportion will be presented along with a 95% CI calculated using the exact binomial distribution.
Secondary	The secondary endpoints will be reported in a similar fashion as the primary endpoints, with the proportion reported for each age stratum or collectively where necessary along with a 95% CI for the proportion calculated using the exact binomial distribution.
Exploratory	Will be described in the reporting and analysis plan

10.4.2. Safety Analyses

All safety analyses will be performed on the Safety Population.

Endpoint	Statistical Analysis Methods
Safety	Non-serious AEs, SAEs and AEs leading to study withdrawal will be collected. Safety endpoints will include: • Incidence and type of serious adverse events • Incidence and type of non-serious adverse events • Incidence and type of non-serious AEs leading to study withdrawal • Incidence of Asthma Exacerbations • Incidence of Pneumonia The incidence of any given adverse event is defined as the proportion of subjects who have experienced at least one such adverse event during the study period. The number and percentage of subjects with SAEs, non-serious AEs and AEs leading to study withdrawal will be summarized by preferred term.

10.4.3. Other Analyses

All other exploratory endpoints will be detailed in the RAP.

10.4.4. Interim Analyses

No interim analyses are planned for this study.

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12. APPENDICES

12.1. Appendix 1: Abbreviations and Trademarks

AE	Adverse Event
CFR	Code of Federal Regulation
CI	Confidence Interval
CIOMS	Council for International Organizations of Medical Sciences
CONSORT	Consolidated Standards of Reporting trials
CSR	Clinical Study Report
DPI	Dry Powder Inhaler
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EW	Early Withdrawal
GCP	Good Clinical Practice
HCP	Healthcare Professional
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements
ICS	Inhaled Corticosteroids
IEC	Independent Ethics Committees
IFU	Instructions for Use
IP	Investigational Product
IRB	Institutional Review Boards
ITT	Intent-to-Treat
IWRS	Interactive Web Response System
MDI	Metered Dose Inhaler
MITT	Modified Intent-to-Treat
LABA	Long Acting β_2-Agonist
MSDS	Material Safety Data Sheet
PIF	Peak inspiratory Flow
RAP	Reporting and Analysis Plan
SAE	Serious Adverse Events
SoA	Schedule of Activities
SRM	Study Reference Manual
SUSAR	Suspected Unexpected Serious Adverse Reactions

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
ELLIPTA

Trademarks not owned by the GlaxoSmithKline group of companies
None

12.2. Appendix 2: Study Governance Considerations

Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with:
    - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
    - Applicable International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) Guidelines
    - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (e.g. advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IEC/IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
    - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/ethics committee (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 Code of Federal Regulation (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.

- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study centre.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.
- Participants who are rescreened are required to sign a new ICF.
- Signed assent will be obtained where considered appropriate according to the subject's age and comprehension, as determined by the Investigator.

Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Committees Structure

Not Applicable

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 multi center studies only in their entirety and

not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Dissemination of Clinical Study Data

- Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.
- GSK will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate.
- GSK will provide the investigator with the randomization codes for their site only after completion of the full statistical analysis.
- The procedures and timing for public disclosure of the results summary and for development of a manuscript for publication will be in accordance with GSK Policy.
- A manuscript will be progressed for publication in the scientific literature if the results provide important scientific or medical knowledge.

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 eCRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 25 years from the issue of the final

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

Source Documents

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

Study and Site Closure

GSK or its designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of GSK. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines

Inadequate recruitment of participants by the investigator

Discontinuation of further study treatment development

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

Definition of AE

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

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

Events <u>NOT</u> Meeting the AE Definition
Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant’s condition. The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant’s condition.

Medical or surgical procedure (e.g. endoscopy, appendectomy): the condition that leads to the procedure is the AE.

Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of SAE

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

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

a. Results in death

b. Is life-threatening

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

c. Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AE. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred, or was necessary, the AE should be considered serious.

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

d. Results in persistent disability/incapacity

The term disability means a substantial disruption of a person's ability to conduct normal life functions.

This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

Medical or scientific judgment should be exercised in deciding whether SAE reporting is

appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Recording AE and SAE

AE and SAE Recording

When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g. hospital progress notes, laboratory, and diagnostics reports) related to the event.

The investigator will then record all relevant AE/SAE information in the eCRF.

It is **not** acceptable for the investigator to send photocopies of the participant's medical records to GSK in lieu of completion of the GSK /AE/SAE eCRF page.

There may be instances when copies of medical records for certain cases are requested by GSK. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to GSK.

The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.

Moderate: An event that causes sufficiently discomfort and interferes with normal everyday activities.

Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AE and SAE can be assessed as severe.

An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality
The investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE. A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. The investigator will use clinical judgment to determine the relationship. Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated. The investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment. For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality. There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to** GSK**.** The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment. The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE
The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by GSK to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide GSK with a copy of any post-mortem findings including histopathology. New or updated information will be recorded in the originally completed eCRF. The investigator will submit any updated SAE data to GSK within 24 hours of receipt of the information.

Reporting of SAE to GSK

SAE Reporting to GSK via Electronic Data Collection Tool
The primary mechanism for reporting SAE to GSK will be the electronic data collection

tool.

If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order 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 by telephone.

Contacts for SAE reporting can be found in the SRM.

12.4. Appendix 4: Country-specific requirements

N/A

12.5. Appendix 5: ELLIPTA DPI correct use and critical error checklist

12.5.1. Checklist

The Checklist for correct use of the ELLIPTA DPI, based on the steps identified in the IFU are included in the table below. This will be filled out by the HCP during the demonstration by the participant. Following removal of the inhaler from the packaging, an eligible study participant will be guided per the instructions in the (Schedule of Activities (SoA) (Section 2)) to demonstrate correct use of the ELLIPTA DPI. The steps outlined in these instructions require that actions be checked by an ELLIPTA trained HCP at both Visit 1 (up to 3 attempts with HCP and 2 further attempts with HCP and parent/guardian) and at Visit 2 (1 attempt with no training or instruction and then 1 attempt after instruction from parent/guardian).

The formatting or layout may change prior to use by the site. Furthermore, the IFU wording may alter depending the country involved in the study. However, the specific definition of correct use outlined in these checklists will not change.

Critical errors are indicated by the steps that are underlined in the checklists.

Protocol Identifier **206924**	**Subject Identifier** ☐☐☐☐☐☐	**ELLIPTA DPI correct use/critical error checklist** **Visit #**

Date of Assessment:	☐☐ DAY	☐☐☐ MONTH	☐☐ YEAR

IFU Step	IFU Wording (2017)	Correct use (Critical errors denoted by underlined steps)	YES	NO
1	**Open the cover of the inhaler** • Slide the cover down to expose the mouthpiece. You should hear a “click”. You do not need to shake this kind of inhaler. **Your inhaler is now ready to use** • If the counter does not count down as you hear the click, the inhaler will not deliver the medicine. Call your healthcare provider or pharmacist if this happens.	Participant slides the cover completely down to expose the mouthpiece until a “click” is heard.	☐	☐
		Participant **does not** shake the inhaler (Note: a “Yes” response indicates that the participant **did not** shake the inhaler after the click is heard)	☐	☐

IFU Step	IFU Wording (2017)	Correct use (Critical errors denoted by underlined steps)	YES	NO
2	**Breathe out** • While holding the inhaler away from your mouth, breathe out (exhale) fully. • • Do not breathe out into the mouthpiece.	Participant breathes out (exhales) while holding the inhaler away from their mouth.	☐	☐
		Participant **does not** breathe into the mouthpiece. (Note: a "Yes" response indicates that the participant **did not** breathe into the mouthpiece)	☐	☐
3	**Inhale your medicine** • Put the mouthpiece between your lips, and close your lips firmly around it. Your lips should fit over the curved shape of the mouthpiece • Take one long, steady, deep breath in through your mouth. **Do not** breathe in through your nose • Do not block the air vent with your fingers. • **Remove the inhaler from your mouth and hold your breath for about 3 to 4 seconds** (or as long as is comfortable for you).	Participant places mouthpiece between lips, and closes lips firmly around it.	☐	☐
		Participant takes one long steady deep breath in through their mouth.	☐	☐
		Participant **does not** block air vent with fingers. (Note: a "Yes" response indicates that the participant **did not** block the air vent with their fingers)	☐	☐
		Participant removes inhaler from his/her mouth and holds his/her breath.	☐	☐
4	**Breathe out slowly and gently.** • You may not taste or feel the medicine, even when you are using the inhaler correctly • **Do not** take another dose from the inhaler even if you do not feel or taste the medicine	Participant breathes out slowly and gently.	☐	☐
5	**Close the inhaler** • You can clean the mouthpiece if needed, using a dry tissue, before you close the cover. Routine cleaning is not required. • Slide the cover upwards as far as it will go to cover the mouthpiece.	Participant closes the inhaler completely.	☐	☐
6	**Rinse your mouth** • Rinse your mouth with water after you have used the inhaler and spit the water out. **Do not** swallow the water.			

12.6. Appendix 6: Ease of use Questionnaire(s)

Paper copies of the ease of use questions will be used by the administrator (Investigator or designee) to record participants' answers to the questions. The site will enter the answers into the electronic case report form (eCRF).

INSTRUCTIONS: The administrator (Investigator or designee) will complete the following questions related to the ELLIPTA inhalers used during this study.

Check only one response for the question asked.

Survey questions VERSION "A" **OR** "B" to be completed at Visit 2 as per randomization at Visit 2.

12.6.1. Ease of use Questionnaire (Participant Stratum 1, ages 5-7 years)

Instructions: "*I am going to ask you some questions about using this inhaler [interviewer has placebo ELLIPTA DPI]. The name of the inhaler is ELLIPTA. I will read the question and answers to you. Then I will ask you to choose the answer that matches what you thought about using the ELLIPTA at home. Do you have any questions for me?*"

12.6.1.1. Version A

1) Is it easy or hard to use the ELLIPTA inhaler?

   □ Easy
   □ Hard

2) Is it easy or hard is it to tell how many puffs are left in the ELLIPTA inhaler?

   □ Easy
   □ Hard

12.6.1.2. Version B

1) Is it hard or easy to use the ELLIPTA inhaler?

   □ Hard
   □ Easy

2) Is it hard or easy is it to tell how many puffs are left in the ELLIPTA inhaler?

   □ Hard
   □ Easy

12.6.2. Ease of use Questionnaire (Participant Stratum 2, ages 8-11 years)

Instructions: "I am going to give you a paper with three questions about the inhaler you used during the study *[interviewer has placebo ELLIPTA DPI]. The name of the inhaler is ELLIPTA. Read the questions and choose the answer that best matches what you*

thought about using the ELLIPTA at home. Do you have any questions?" [Pause and answer any questions from participant. If participant needs help in understanding the questions or responses, you can explain or define individual words but please take care not to influence his or her answer].

For participants that have difficulty completing the self-administered version, they may receive the questionnaire in the same manner as is provided for stratum 1.

12.6.2.1. Version A

1) Is it easy or hard to use the ELLIPTA inhaler?

   □ Easy
   □ Hard

2) Is it easy or hard is it to tell how many puffs are left in the ELLIPTA inhaler?

   □ Easy
   □ Hard

12.6.2.2. Version B

1) Is it hard or easy to use the ELLIPTA inhaler?

   □ Hard
   □ Easy

2) Is it hard or easy to tell how many puffs are left in the ELLIPTA inhaler?

   □ Hard
   □ Easy

12.6.3. Ease of use Questionnaire (Parent/Guardian)

Parents/Guardians will be assigned to the same version letter (A or B) to which their child/dependent was randomized.

12.6.3.1. Version A

1) How easy or difficult was it for you to tell how many doses were left in the ELLIPTA inhaler?

   □ Very Easy
   □ Easy
   □ Difficult
   □ Very Difficult

2) If your child's **current inhaled asthma medication** was available in the ELLIPTA inhaler, how likely would you be to request the ELLIPTA inhaler from your child's doctor?

□ Very Likely
□ Likely
□ Unlikely
□ Very Unlikely

12.6.3.2. Version B

1) How difficult or easy was it for you to tell how many doses were left in the ELLIPTA inhaler?

□ Very Difficult
□ Difficult
□ Easy
□ Very Easy

2) If your child's **current inhaled asthma medication** was available in the ELLIPTA inhaler, how likely would you be to request the ELLIPTA inhaler from your child's doctor?

□ Very Unlikely
□ Unlikely
□ Likely
□ Very Likely

12.7. Appendix 7: Protocol Amendment History

N/A