Division	:	Worldwide Development
Information Type	:	Reporting and Analysis Plan (RAP)

Title	:	Reporting and Analysis Plan for Study 206901: A randomized, open-label, cross-over, placebo inhaler study to evaluate the correct use of ELLIPTA™ dry powder inhaler (DPI) compared to DISKUS™ DPI used in combination with HandiHaler DPI in participants with Chronic Obstructive Pulmonary Disease (COPD)
Compound Number	:	GSK2834425 (GW685698 + GSK573719 + GW642444)
Effective Date	:	28-FEB-2018

Description :

- The purpose of this RAP is to describe the planned analyses and output to be included in the Clinical Study Report for Protocol 2016N305948_01. This RAP will be provided to the study team members to convey the content of the Statistical Analysis Complete (SAC) deliverable.

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TABLE OF CONTENTS

PAGE

1. INTRODUCTION

The purpose of this reporting and analysis plan (RAP) is to describe the analyses to be included in the Clinical Study Report for Protocol:

Revision Chronology:		
2016N305948_ 00	27 - FEB - 2017	Original
2016N305948_ 01	17 - MAY - 2017	Amendment 01 was created to make the following changes: to extend the time a participant must not have used the ELLIPTA, DISKUS, or HandiHaler inhalers prior to Visit 1, to delete one of the withdrawal criteria, to add an exclusion criteria for participants that are only taking a SABA, and to add some clarification to the overall study design. One additional endpoint was added to assess inhaler regimen preference based on the number of steps needed to take the medication.

2. SUMMARY OF KEY PROTOCOL INFORMATION

2.1. Changes to the Protocol Defined Statistical Analysis Plan

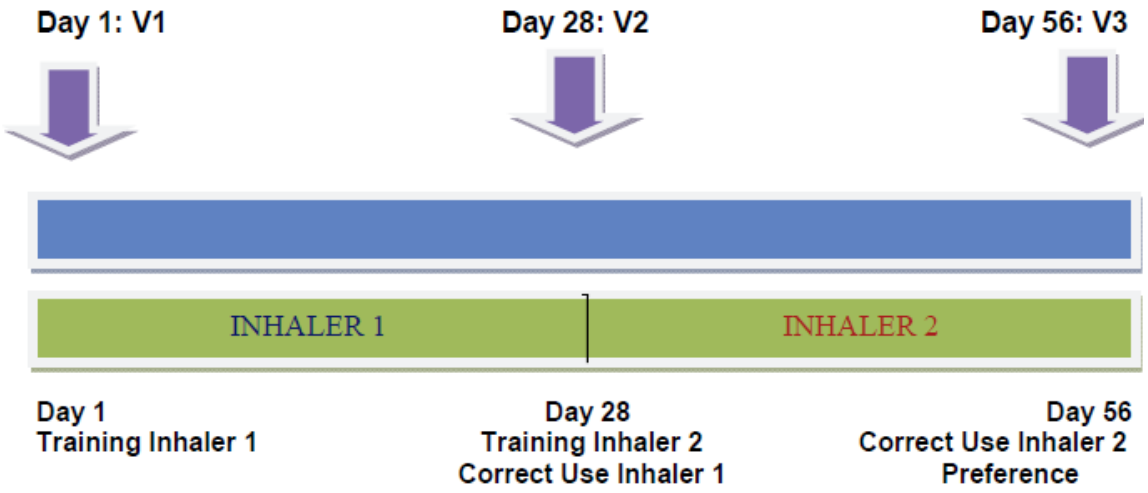
There were no changes or deviations to the originally planned statistical analysis specified in the protocol amendment 1 [(Dated: 17/MAY/2017)].

2.2. Study Objective(s) and Endpoint(s)

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

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

2.3. Study Design

Overview of Study Design and Key Features	
	
Design Features	The study will be conducted as a multi-centre, randomised, open-label, placebo-device, cross-over study, with a 2x2 complete block design. This study has 3 visits and will be completed in approximately 56 days. COPD diagnosed participants will attend the clinic for the screening visit (V0) and subsequent assessment visit (V1). These visits may occur on the same day. There is no active treatment and participants will continue to take their own prescribed COPD maintenance medication and rescue medications during the entire 56-day study period. The treatment groups are the following: • At Visit 1 (Day 1) half of the participants will be randomized to receive a placebo ELLIPTA (QD) inhaler for use during the first 28 day treatment period. The remaining half of the participants will receive a placebo DISKUS (BID) + placebo HandiHaler (QD) for use during the first 28 day treatment period. • At Visit 2 (Day 28) participants previously receiving the placebo DISKUS + placebo HandiHaler inhalers at Visit 1 will receive a placebo ELLIPTA (QD) inhaler for the second 28 day treatment period. Those participants initially receiving a placebo ELLIPTA inhaler at Visit 1 will receive a placebo DISKUS (BID) inhaler + a placebo HandiHaler (QD) inhaler for the second 28 day treatment period. • At Visit 3 (Day 56) after conducting their last correct inhaler use assessments, participants will answer either preference questionnaire 1 or preference questionnaire 2 depending on their randomization schedule.
Dosing	• Not applicable as this is a placebo study.

<table>
<tr><th colspan="2">Overview of Study Design and Key Features</th></tr>
<tr><td>Time & Events</td><td>• Refer to Appendix 2: Schedule of Activities</td></tr>
<tr><td>Treatment Assignment</td><td>
<table>
<tr><th>Sequence</th><th>Period 1</th><th>Period 2</th><th>Preference Questionnaire</th></tr>
<tr><td>A</td><td>ELLIPTA</td><td>DISKUS + HandiHaler</td><td>1</td></tr>
<tr><td>B</td><td>ELLIPTA</td><td>DISKUS + HandiHaler</td><td>2</td></tr>
<tr><td>C</td><td>DISKUS + HandiHaler</td><td>ELLIPTA</td><td>1</td></tr>
<tr><td>D</td><td>DISKUS + HandiHaler</td><td>ELLIPTA</td><td>2</td></tr>
</table>
</td></tr>
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2.4. Statistical Hypotheses / Statistical Analyses

The primary purpose of this study is to assess the number of errors made by COPD participants, for the ELLIPTA inhaler or DISKUS + HandiHaler inhalers combined after 28 days use. This is a superiority study.

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

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

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

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

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

3. PLANNED ANALYSES

3.1. Final Analyses

No interim analysis is planned.

The final planned primary analyses will be performed after the completion of the following sequential steps:

1. All subjects have completed the study as defined in the protocol.
2. All required database cleaning activities have been completed and final database release has been declared by Data Management.
3. All criteria for unblinding the randomisation codes have been met.
4. Randomisation codes schedule have been distributed according to RandAll NG procedures.
5. Database freeze has been declared by Data Management.

4. ANALYSIS POPULATIONS

Population	Definition / Criteria	Analyses Evaluated
All Subjects Enrolled (ASE)	• All participants who sign the ICF and for whom a record exists in the study database, including screen failures and any participant who was not screened but experienced an SAE between the date of informed consent and the planned date of the Screening visit.	• Study population • Subject disposition • Reason for withdrawal prior to randomisation • Inclusion, exclusion and randomisation criteria deviations
Intent-to-treat (ITT)	• All randomised participants, excluding those who were randomised in error, and did not have at least one error assessment at Visit 1. A participant who is recorded as a screen failure or run-in failure and also randomised will be considered to be randomised in error. Any other participant who receives a randomisation number will be considered to have been randomised. This population will be analysed according to the randomised sequence order and not the sequence order they actually followed.	• Study population • Efficacy
Safety	• This population will be the same as the Intent-to-Treat population.	• Safety

NOTES :

- Please refer to Appendix 10: List of Data Displays which details the population to be used for each displays being generated.

4.1. Protocol Deviations

Important protocol deviations (including deviations related to study inclusion/exclusion criteria, conduct of the trial, patient management or patient assessment) will be summarised and listed.

Protocol deviations will be tracked by the study team throughout the conduct of the study in accordance with the Protocol Deviation Management Plan Version 1 (07-Jul-2017) or later.

- Data will be reviewed prior to freezing and unblinding the database to ensure all important deviations are captured and categorised on the protocol deviations dataset.
- This dataset will be the basis for the summaries and listings of protocol deviations.

A separate summary and listing of all inclusion/exclusion criteria deviations will also be provided. This summary will be based on data as recorded on the inclusion/exclusion page of the eCRF.

5. CONSIDERATIONS FOR DATA ANALYSES AND DATA HANDLING CONVENTIONS

5.1. Study Treatment & Sub-group Display Descriptors

Treatment Group Descriptions			
RandAll NG		Data Displays for Reporting	
Code	Description	Description	Order [1]
A	ELLIPTA Inhaler	ELLIPTA	1
B	DISKUS Inhaler + HandiHaler Inhaler	DISKUS + HandiHaler	2
Q1	Preference Questionnaire 1	Questionnaire 1	3
Q2	Preference Questionnaire 2	Questionnaire 2	4

NOTES:

1. Order represents treatments being presented in TFL, as appropriate.

5.2. Multicentre Studies

In this single country study, enrolment will be presented by investigative site.

5.3. Examination of Covariates, Other Strata and Subgroups

5.3.1. Covariates and Other Strata

The list of covariates and other strata may be used in descriptive summaries and statistical analyses. Additional covariates and other strata of clinical interest may also be considered.

Category	Covariates and / or Subgroups
Number of prescribed maintenance inhalers	This will be included as a covariate in the model to examine whether additional background inhalers impact error rates. Number of prescribed maintenance inhalers will be fitted as a categorical variable.

5.3.2. Examination of Subgroups

No subgroup analysis is planned in this study.

5.4. Multiple Comparisons and Multiplicity

There is a single primary endpoint. There are no adjustments for multiplicity across the secondary endpoints.

5.5. Other Considerations for Data Analyses and Data Handling Conventions

Other considerations for data analyses and data handling conventions are outlined in the appendices:

Section	Component
10.3	Appendix 3: Assessment Windows
10.4	Appendix 4: Study Phases and Treatment Emergent Adverse Events
10.5	Appendix 5: Data Display Standards & Handling Conventions
10.6	Appendix 6: Derived and Transformed Data
10.7	Appendix 7: Reporting Standards for Missing Data
10.8	Appendix 8: Values of Potential Clinical Importance

6. STUDY POPULATION ANALYSES

6.1. Overview of Planned Study Population Analyses

The study population analyses will be based on the ITT population, unless specified to be on ASE population.

Study population analyses including analyses of subject's disposition, protocol deviations, demographic and baseline characteristics, prior and concomitant medications, and exposure and treatment compliance will be based on GSK Core Data Standards. Details of the planned displays are presented in Appendix 10: List of Data Displays.

6.2. Disposition

The study population summary will use the ASE population and show the number of subjects overall who were enrolled, the number of screen failures and the number with each reason for screen failure. It will also show the number of subjects who were randomised and who were in the ITT population.

For the ITT population reasons for withdrawal summary will show the number and percentage of subjects who completed the study, who withdrew prematurely from the study and who reported each primary and sub-reason for withdrawal.

6.3. Medical Conditions

The number and percentage of subjects reporting each current medical condition will be presented. This table will include a subheading of 'Cardiovascular Risk Factors,' which will summarise the information taken from the cardiac disorders page in the eCRF. All medical conditions must be summarised on this table regardless of frequency. This will be repeated for past medical conditions.

6.4. Concomitant Medications

Non-COPD medications will be summarised by Anatomical-Therapeutic-Chemical (ATC) level 1 and ingredient. COPD medications will be summarised by Respiratory Medication Class (RMC), and will be derived for each COPD concomitant medication. Multi-ingredient medications will be presented according to their combination ATC classification rather than the classifications of the ingredients.

COPD and non-COPD medications will be listed separately. A listing of the relationship between ATC Level 1, ingredient and verbatim text will be produced for non-COPD medications only.

7. EFFICACY ANALYSES

7.1. Primary Efficacy Analyses

7.1.1. Endpoint

Percentage of participants with zero errors after 28 days of use

7.1.2. Summary Measure

Odds Ratio: The odds of having zero errors on ELLIPTA after 28 days used compared to the odds of having zero errors on DISKUS + HandiHaler after 28 days use.

7.1.3. Population of Interest

The primary efficacy analyses will be based on the Intent-To-Treat population, unless otherwise specified.

7.1.4. Strategy for Intercurrent (Post-Randomization) Events

There are three intercurrent events identified which could impact upon the estimand of interest:

- The subject could withdraw from randomised study device sequence and therefore withdraw from the study
- The subject could change their standard COPD maintenance medication device to one delivered via ELLIPTA, DISKUS or HANDIHALER; these subjects should have been withdrawn from the study according to the protocol.
- The subject could attend the visit without the device/s they were randomised to, in which case correct use cannot be assessed as described in the protocol.

Rescue Medication use and change to maintenance COPD medication which is not delivered via ELLIPTA, DISKUS or HANDIHALER are not considered intercurrent events.

Subjects who withdrew in period 2 complete an error assessment at the early withdrawal visit, however no error assessments were made if they withdrew in period 1

Two estimands will be assessed:

- **Primary Estimand**: The treatment effect to be estimated is the principle strata of all subjects who stayed on their randomised study device sequence and did not change their standard COPD maintenance medication device to one delivered via ELLIPTA, DISKUS or HANDIHALER, throughout both 28 day treatment periods. In this analysis subjects with intercurrent events will have their data set to missing from the point of that event and so are not included in this analysis. Data from the early withdrawal visit will not be used.
- **Supplementary Estimand:** The treatment effect to be estimated will be the composite effect of initial randomized treatment. Error assessment from the early

withdrawal visit will be used for those who withdrew prematurely from the study in period 2. For those who withdrew without providing an assessment in period 2 it will be assumed that they made an error.

If subjects experience an intercurrent event in Period 1 then they should not have entered Period 2 and so their data in Period 2 will be set to missing for all estimands.

7.1.5. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 10: List of Data Displays and will be based on GSK data standards and statistical principles.

Unless otherwise specified, endpoints / variables defined in Section 7.1.1 will be summarised using descriptive statistics, graphically presented (where appropriate) and listed.

7.1.5.1. Statistical Methodology Specification

Endpoint
• Percentage of participants with zero errors after 28 days of use
Model Specification
• The primary endpoint of the percentage of participants with zero errors after 28 days of use, will be analysed using the Intent-to-treat population. • This endpoint will be analysed using conditional logistic regression with subject as fixed strata, and treatment option and period as fixed effects. • If there are low cell counts (<5) in the cross tabulation of subjects making errors on ELLITPA compared to DISKUS + HandiHaler or the model fails to converge with all cell counts >=5, then the exact conditional logistic regression with subject as fixed strata, and treatment option and period as fixed effects will be used instead.
Model Checking & Diagnostics
• None
Model Results Presentation
• The odds ratio, 95% CI and p-value will be presented for the comparison between treatment options. It will be based on a two-sided hypothesis testing approach of superiority.
Sensitivity and Supportive Analyses
• A sensitivity analysis will be performed using the Cochran-Mantel-Haenszel (CMH) test. The CMH test serves as a stratified approximation to the Mainland-Gart test, a variation of a one-sample chi-square test that accounts for study inhaler sequence (period). A subject who had an error with both devices or who had no errors with both devices does not provide any information about the superiority of either device. Only those subjects who had error(s) in one device and had no error in the other device are counted for in the Mainland-Gart test. • For the supplementary estimand a tipping point analysis will be performed to assess how robust the composite estimand is to missing data assumptions. To assess this the outcomes for subjects with missing error assessment in period 2 will be varied in the two treatment groups independently from imputing 0 subjects with an error to all subjects with an error.

7.2. Secondary Efficacy Analyses

7.2.1. Endpoint

1) Percentage of participants with zero critical errors after 28 days of use.
2) Number of errors by type for each inhaler after 28 days use
3) Number and change in errors per participant for each treatment group (V2 and V3) after 28 days use
4) Number and change in errors for each treatment group in participant with one or more errors after 28 days use

7.2.2. Summary Measure

1) Odds ratio
2) Summary statistics
3) Summary statistics
4) Summary statistics

7.2.3. Population of Interest

The secondary efficacy analyses will be based on the Intent-To-Treat population, unless otherwise specified.

7.2.4. Strategy for Intercurrent (Post-Randomization) Events

As these are secondary endpoints only the primary estimand will be assessed.

7.2.5. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 10: List of Data Displays, and will be based on GSK data standards and statistical principles.

Unless otherwise specified, endpoints / variables defined in Section 7.2.1 will be summarised using descriptive statistics, graphically presented (where appropriate) and listed.

The following secondary endpoints will be summarised only:

- Number of errors by type for each treatment group after 28 days of use.
- Number and change in errors per participant for each treatment group (V2 and V3) after 28 days of use.
- Number and change in errors for each inhaler in participants with one or more errors after 28 days of use.

7.2.5.1. Statistical Methodology Specification

Endpoint / Variables
• Percentage of participants with zero critical errors after 28 days of use
Model Specification
• See Section 7.1.5.1.
Model Checking & Diagnostics
• See Section 7.1.5.1.
Model Results Presentation
• See Section 7.1.5.1.
Sensitivity and Supportive Analyses
• See Section 7.1.5.1.

7.3. Exploratory Efficacy Analyses

7.3.1. Endpoint

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

7.3.2. Summary Measure

1) Odds ratio and p-value for interaction
2) Odds ratio
3) Summary statistics and p-value
4) Summary statistics and p-value
5) Summary statistics and p-value

7.3.3. Population of Interest

The secondary efficacy analyses will be based on the Intent-To-Treat population, unless otherwise specified.

7.3.4. Strategy for Intercurrent (Post-Randomization) Events

As these are exploratory endpoints only the primary estimand will be assessed.

7.3.5. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 10: List of Data Displays and will be based on GSK data standards and statistical principles.

Unless otherwise specified, endpoints / variables defined in Section 7.2.1 will be summarised using descriptive statistics, graphically presented (where appropriate) and listed.

7.3.5.1. Statistical Methodology Specification

Endpoint / Variables
• Comparison of correct inhaler use as defined by the percentage of participants with zero errors after 28 days of use, including the number of prescribed maintenance inhalers as a covariate.
Model Specification
• The primary endpoint of the percentage of participants with zero errors after 28 days of use, will be analysed using the Intent-to-treat population. • This endpoint will be analysed using conditional logistic regression with subject as fixed strata. Treatment option, number of COPD maintenance devices and period will be fixed effects. • Two models will be analysed. The first will contain the number of COPD maintenance devices and treatment option, whilst the second will include the interaction term between the number of COPD maintenance devices and treatment option. • If there are low cell counts (<5) in the cross tabulation of subjects making errors on ELLITPA compared to DISKUS + HandiHaler or the model fails to converge with all cell counts >=5, then the exact conditional logistic regression with subject as fixed strata, and treatment option and period as fixed effects will be used instead.
Model Checking & Diagnostics
• See Section 7.1.5.1.
Model Results Presentation
• See Section 7.1.5.1. In addition, for the interaction model the p-value for the interaction will also be produced.
Sensitivity and Supportive Analyses
• No sensitivity analysis will be performed.

Endpoint / Variables
• The comparison of participants making zero errors after reading the PIL (s) at the start of each treatment period
Model Specification
• See Section 7.1.5.1.
Model Checking & Diagnostics
• See Section 7.1.5.1.

Model Results Presentation
• See Section 7.1.5.1.
Sensitivity and Supportive Analyses
• No sensitivity analysis will be performed.

Endpoint / Variables
• Inhaler preference based on how easy it was to tell how many doses remain. • Inhaler dosing regimen preference. • Inhaler regimen preference based on the number of steps needed to take the medication.
Model Specification
• The endpoint of treatment preference will be analysed using the Intent-to-treat population. • This endpoint will be analysed using the Cochran-Mantel-Haelszel test.
Model Checking & Diagnostics
• None.
Model Results Presentation
• The percentage of preference for each specific attribute (i.e., preferring ELLIPTA inhaler, preferring DISKUS + HandiHaler, and no preference) will be summarised by inhaler use sequence. • Subject preference will also be analysed using a Cochran-Mantel-Haenszel test. The Cochran-Mantel-Haenszel test serves as a stratified approximation to Prescott's test, a variation of a one-sample chi-square test that accounts for study inhaler sequence and subjects who indicate no preference. P-values from this analysis will be presented in summary and analysis tables.
Sensitivity and Supportive Analyses
• No sensitivity analysis will be performed.

8. SAFETY ANALYSES

The safety analyses will be based on the Safety population, unless otherwise specified.

8.1. Adverse Events Analyses

Adverse events analyses including summaries of adverse events (AEs), Serious (SAEs) and other significant AEs will be based on GSK Core Data Standards. As this is a placebo only device study and no active drug is prescribed, summarises will be provided for all participants combined regardless of their randomised treatment sequence. The details of the planned displays are provided in Appendix 10: List of Data Displays.

A summary of the following AEs and SAEs will be provided:

- Any AE (pre treatment (SAE only)-, on- treatment or post-treatment)
- Any on-treatment drug related AE

- Any AE (pre-treatment or on-treatment) leading to permanent discontinuation of study treatment or withdrawal from study
- Any non-fatal SAE
- Any fatal SAE
- Any on-treatment non-fatal drug related SAE
- Any on-treatment fatal drug related SAE

AE incidence will be summarised overall using the primary System Organ Class (SOC) and preferred term. All listings of AEs/SAEs will identify whether each adverse event occurred pre-treatment, on treatment or after treatment.

8.2. Adverse Events of Special Interest Analyses

There are no adverse events of special interest in this study as this is a placebo only device study.

8.2.1. Cardiovascular Events

As for all non CV GSK studies, for subjects who report a cardiovascular event, individual patient profiles will be produced for one or more of the following categories:

- Myocardial infarction/unstable angina
- Congestive heart failure
- Arrhythmias
- Valvulopathy
- Pulmonary hypertension
- Cerebrovascular events/stroke and transient ischemic attack
- Peripheral arterial thrombosis
- Deep Venous Thrombosis
- Revascularization

8.2.2. Pregnancies

Any pregnancies reported during the study will be summarised in case narratives. Any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE or SAE and included in summaries and listings of AEs/SAEs.

9. REFERENCES

GlaxoSmithKline Document Number 2016N305948_01, Protocol: A randomized, open-label, cross-over, placebo inhaler study to evaluate the correct use of ELLIPTA™ dry powder inhaler (DPI) compared to DISKUS™ DPI used in combination with HandiHaler DPI in participants with Chronic Obstructive Pulmonary Disease (COPD), 17 May 2017

Prescott, RS. The comparison of success rates in cross-over trials in the presence of an order effect. *Appl Stat*. 1981; 30:9-15.

Senn, Stephen. Cross-over Trials in Clinical Research, 2nd ed. Chichester: John Wiley & Sons, Ltd, 2002. pp 128-131, 202-203.

10. APPENDICES

10.1. Appendix 1: Protocol Deviation Management and Definitions for Per Protocol Population

The full list of protocol deviations collected on the eCRF is in the Protocol Deviation Management Plan (PDMP). Please refer to this document for current guidance.

There is no per protocol population in this study.

10.2. Appendix 2: Schedule of Activities

10.2.1. Protocol Defined Schedule of Events

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

Procedures	Visit 0 Screening (Can occur on same day as V1)	Visit 1 Randomization (Can occur on the same day as V0)	Visit 2 Assessment/ Cross-over	Visit 3 Last Visit/ End of Study
Worksheets and medication				
Dispense study inhaler(s)		**X**	**X**	
Collect study inhaler(s)			**X**	**X**
Dispense Medical Problems/Medications Taken Worksheet [7]		**X**	**X**	
Collect and review Medical Problems/Medications Taken Worksheet [7]			**X**	**X**

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

10.3. Appendix 3: Assessment Windows

10.3.1. Definitions of Assessment Windows for Analyses

Analysis Set / Domain	Parameter (if applicable)	Target	Analysis Window		Analysis Timepoint
			Beginning Timepoint	Ending Timepoint	
Efficacy	All	Day 28	Day 26	Day 30	Visit 2
		Day 56	Day 54	Day 58	Visit 3

As per the PDMP all assessments will be included in the analysis even if they are considered out of window.

10.4. Appendix 4: Study Phases and Treatment Emergent Adverse Events

10.4.1. Study Phases

Assessments and events will be classified according to the time of occurrence relative to Visit 1 (Study Day 1):

Study Phase	Definition
Pre-Treatment	Date < Study Treatment Start Date
On-Treatment	Study Treatment Start Date ≤ Date ≤ Study Treatment Stop Date +1
Post-Treatment	Date > Study Treatment Stop Date 1+1

10.4.2. Study Phases for Concomitant Medication

Treatment phases for summaries of COPD and non-COPD concomitant medications will be defined as follows:

Definition	Treatment Phase		
	Pre-Treatment	On-Treatment	Post-Treatment
Subject did not take study treatment (e.g, screening failures) and conmed stop date > date of Screening or variable that asks if conmed is on-going (refer hereafter as goingmed) is “yes”	Y		
(Conmed start date<treatment start date or variable that asks if medication taken prior to study is ”yes”(refer hereafter as priormed)) and date of Screening < conmed stop date <treatment start date	Y		
(Conmed start date<treatment start date or priormed is yes) and treatment start date≤conmed stop date≤treatment stop date	Y	Y	
(Conmed start date<treatment start date or priormed is yes) and (conmed stop date>treatment stop date or goingmed is “yes”)	Y	Y	Y
(Treatment start date≤conmed start date<treatment stop date and treatment start date≤conmed stop date≤treatment stop date) or (Treatment start date=conmed start date=conmed stop date=treatment stop date)		Y	
([Treatment start date≤conmed start date<treatment stop date] or [Treatment start date=conmed start date=treatment stop date]) and(conmed stop date>treatment stop date or		Y	Y

Definition	Treatment Phase		
	Pre-Treatment	On-Treatment	Post-Treatment
goingmed is Yes)			
Conmed start≥treatment stop date and treatment start date ≠ treatment stop date			Y

NOTES:

- A concomitant medication will be classed in every period of the study in which it was taken (e.g., run-in, on-treatment or post-treatment).
- See Section 10.7.2.1 for handling of partial dates.
- If the study treatment stop date is missing, it will be imputed as described in Section 10.6.1.
- Medications that stopped prior to Screening will not be assigned a treatment phase and will not be summarized.

10.4.3. Treatment Emergent Flag for Adverse Events

Flag	Definition
Treatment Emergent	• As this study only administers placebo in both treatment periods, all AEs will be combined regardless of which device was used in each cross-over period to give the overall AEs associated with placebo. • If AE onset date is on or after Visit 1 start date & on or before Visit 3 stop date. • Visit 1 Date ≤ AE Start Date ≤ Visit 3 Date + 1 days

NOTES:

- If the study treatment stop date is missing, then the AE will be considered to be On-Treatment.

10.5. Appendix 5: Data Display Standards & Handling Conventions

10.5.1. Reporting Process

Software	
• The currently supported versions of SAS software will be used. • The currently supported versions of TSCG software will be used.	
Reporting Area	
HARP Server	: uk1salx00175
HARP Area	/arenv/arprod/gsk2834425/mid206901/final_01
Analysis Datasets	
• Analysis datasets will be created according to Legacy GSK A&R dataset.	
Generation of RTF Files	
• RTF files will be generated for use in writing the CSR.	

10.5.2. Reporting Standards

General	

• The current GSK Integrated Data Standards Library (IDSL) will be applied for reporting, unless otherwise stated (IDSL Standards Location: https://spope.gsk.com/sites/IDSLLibrary/SitePages/Home.aspx):
  • 4.03 to 4.23: General Principles
  • 5.01 to 5.08: Principles Related to Data Listings
  • 6.01 to 6.11: Principles Related to Summary Tables
  • 7.01 to 7.13: Principles Related to Graphics
• Do not include subject level listings in the main body of the GSK Clinical Study Report. All subject level listings should be located in the modular appendices as ICH or non-ICH listings	

Formats	
• GSK IDSL Statistical Principles (5.03 & 6.06.3) for decimal places (DP's) will be adopted for reporting of data based on the raw data collected, unless otherwise stated. • Numeric data will be reported at the precision collected on the eCRF.	
Unscheduled Visits	
• Unscheduled visits will not be included in summary tables and/or figures. • All unscheduled visits will be included in listings.	
Descriptive Summary Statistics	
Continuous Data	Refer to IDSL Statistical Principle 6.06.1
Categorical Data	N, n, frequency, %
Graphical Displays	
• Refer to IDSL Statistical Principals 7.01 to 7.13.	

10.6. Appendix 6: Derived and Transformed Data

10.6.1. Study Population

Treatment Compliance
• Treatment compliance will be calculated for each inhaler separately based on the following formula: **Treatment Compliance = Number of Actual Doses / (Planned Treatment Duration in Days * Frequency)** • Frequency is 2 for BID and 1 for QD. Treatment compliance could be greater than 100% if there are events of overdose.

10.6.2. Efficacy

10.6.2.1. Critical and Overall Errors

Critical and Overall errors

If a subject answered 'No' to any of the following it is considered a critical error for the ELLIPTA device:

- Subject slides the cover completely down to expose the mouthpiece until a "click" is heard.
- Subject **does not** shake the inhaler after the click is heard upon opening cover. (Note: a "Yes" response indicates that the subject did not shake the inhaler after the click is heard.)
- Subject **does not** breathe out (exhale) into the mouthpiece. (Note: a "Yes" response indicates that the subject did not breathe into the mouthpiece.)
- Subject places mouthpiece between lips, and closes lips firmly around it.
- Subject takes one long steady deep breath in through their mouth.

If a subject answered 'No' to any of the following it is considered a critical error for the DISKUS device:

- Subject opened cover
- Subject slid the lever away from the mouthpiece as far as it would go until it clicked. Note: If the subject presses the lever more than once or slides the lever back to its starting position, this box should be checked No.
- Subject did not tilt or shake the device after dose preparation Note: A Yes response means the subject **did not** tilt or shake the inhaler after preparing the dose
- Subject did not exhale into the mouthpiece
- Subject placed the mouthpiece between his/her lips

If a subject answered 'No' to any of the following it is considered a critical error for the HandiHaler device:

- Subject opened the mouthpiece by pulling the mouthpiece ridge up and away from the base so the center chamber is showing
- Subject appropriately only opened 1 capsule from the blister card
- Subject placed the capsule in the center chamber of the inhaler
- Subject closed the mouthpiece against the gray base, a click was heard, and the dust cap was left open

Critical and Overall errors

- Subject pressed the green piercing button **once** and released the button (Note: if subject pressed the piercing button more than once, check 'No')
- Subject **did not** shake the inhaler after piercing the capsule (Note: A 'Yes" response means the subject did not shake the inhaler)
- Subject **does not** breathe out (exhale) into the mouthpiece. (Note: a "Yes" response indicates that the subject did not breathe into the mouthpiece.)
- Subject closed his/her lips tightly around the mouthpiece
- Subject heard or felt the capsule vibrate (rattle) Note: The HCP may need to ask the subject if they heard or felt the capsule vibrate (rattle)

For CMH sensitivity analysis:

An ordinal variable (error) will be derived to indicate where a participant had any error, or any critical error whilst demonstrating correct device use. If the subject has an overall/critical error the error=Y whilst if they did not have an overall/critical error then error=N. The variables errty/errtycd will be used to determine whether the variable error is referring to a critical or overall error.

An ordinal variable (err_ord) will be derived to indicate the responses of critical error based on comparing responses for the device sequences used. This variable will be used in the sensitivity analysis for critical error data.

If the sequence of inhaler use is ELLIPTA inhaler in the 1st period and DISKUS + HandiHaler inhalers in the 2nd period, then for critical error in relation to sequence:

- error_ord = -1, if subject had critical error in the 1st period but NOT in the 2nd period
- error_ord = 1, if subject had critical error in the 2nd period but NOT in the 1st period
- error_ord = 0, if subject had critical errors in BOTH periods or had NO critical errors in BOTH periods

If the sequence of inhaler use is DISKUS + HandiHaler inhalers in the 1st period and ELLIPTA inhaler in the 2nd period, then for each preference question:

- error_ord = -1, if subject had critical error in the 1st period but NOT in the 2nd period
- error_ord = 1, if subject had critical error in the 2nd period but NOT in the 1st period
- error_ord = 0, if subject had critical errors in BOTH periods or had NO critical errors in BOTH periods

The above method also applies to overall errors.

Note: Only error_ord = -1 or 1 will be used within the analysis. The coding of error_ord = 0 is only to ensure that this data can be excluded.

10.6.2.2. Responses to Preference Questions

Preference Questions
An ordinal variable (pref_ord) will be derived to indicate the responses to preference based on the sequence of inhaler use. This variable will be used in the statistical analysis for preference data. If the sequence of inhaler use is ELLIPTA in the 1st period and DISKUS + HandiHaler in the 2nd period, then for each preference question: • pref_ord = -1, if subject prefer ELLIPTA • pref_ord = 1, if subject prefer DISKUS + HandiHaler • pref_ord = 0, if subject has no preference If the sequence of inhaler use is DISKUS + HandiHaler in 1st period and ELLIPTA in 2nd period, then for each preference question: • pref_ord = 1, if subject prefer ELLIPTA • pref_ord = -1, if subject prefer DISKUS + HandiHaler • pref_ord = 0, if subject has no preference

10.6.2.3. Number of maintenance COPD

Number of maintenance COPD inhalers
The covariate of number of maintenance COPD inhalers will be calculated using the CONMED page in the eCRF. To calculate this all inhaled medications will be counted if: • They were delivered by a device for ≥ 4 weeks prior to randomisation (as per inclusion criteria in the protocol) • The subject was still using the device at the time of randomisation • The reason for medication is 'COPD' • The frequency is not 'PRN' as this is used to denote rescue medications These devices will then be summed in order to find the total number of COPD maintenance inhalers per subject..

10.7. Appendix 7: Reporting Standards for Missing Data

10.7.1. Premature Withdrawals

Element	Reporting Detail
General	• For reporting purposes, subject study completion will be defined as completion of all two randomised periods (both devices and questionnaire) on the day of study visit. • Withdrawn subjects will be defined as those who used at least one device once but did not complete all assessments. • Withdrawn subjects will not be replaced in the study. • All available data from subjects who were withdrawn from the study will be listed and all available planned data will be included in summary tables and figures, unless otherwise specified.

10.7.2. Handling of Missing Data

Element	Reporting Detail
General	• Missing data occurs when any requested data is not provided, leading to blank fields on the collection instrument : ○ These data will be indicated by the use of a “blank” in subject listing displays. Unless all data for a specific visit are missing in which case the data is excluded from the table. ○ Answers such as “Not applicable” and “Not evaluable” are not considered to be missing data and should be displayed as such. ○ As subjects need to be assessed for errors on both devices, if they only complete one period (one device) they have their missing data imputed as described in Section 10.7.2.2. Subjects who complete both devices, but do not answer the preference questionnaire will be included in the primary analysis as completed without any imputations.
Outliers	• Whilst outliers are not anticipated within this study any subjects excluded from the summaries and/or statistical analyses will be documented along with the reason for exclusion in the clinical study report.

10.7.2.1. Handling of Missing and Partial Dates

Element	Reporting Detail
General	• Partial dates will be displayed as captured in subject listing displays.
Concomitant Medications/ Medical History	• Partial dates for any concomitant medications recorded in the CRF will be imputed using the following convention: ○ If the partial date is a start date, a '01' will be used for the day and 'Jan' will be used for the month ○ If the partial date is a stop date, a '28/29/30/31' will be used for the day (dependent on the month and year) and 'Dec' will be used for the month. • The recorded partial date will be displayed in listings.

10.7.2.2. Handling of Missing Data for Statistical Analysis

Element	Reporting Detail
Correct Use and Questionnaire	• If part or all of a correct use assessment is missing then the whole assessment will be considered missing. For example if a subject has data for DISKUS but not HandiHaler then this will be considered missing data for the 'DISKUS + HandiHaler' assessment. The only exception will be when they had an error on the device that they did complete in which case the assessment will be set to an error. • All missing data will be handled according to estimand of interest as described within the main body of the RAP

10.8. Appendix 8: Values of Potential Clinical Importance

As this is a placebo only device study there are no values of potential clinical importance.

10.9. Appendix 9: Abbreviations & Trade Marks

10.9.1. Abbreviations

Abbreviation	Description
A&R	Analysis and Reporting
AE	Adverse Event
CI	Confidence Interval
CSR	Clinical Study Report
DOB	Date of Birth
DP	Decimal Places
eCRF	Electronic Case Record Form
GSK	GlaxoSmithKline
ICH	International Conference on Harmonisation
IDSL	Integrated Data Standards Library
ITT	Intent-To-Treat
PDMP	Protocol Deviation Management Plan
QC	Quality Control
RAMOS	Randomization & Medication Ordering System
RAP	Reporting & Analysis Plan
SAC	Statistical Analysis Complete
SOP	Standard Operation Procedure
TFL	Tables, Figures & Listings

10.9.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
DISKUS
ELLIPTA

Trademarks not owned by the GlaxoSmithKline Group of Companies
HandiHaler
SAS

10.10. Appendix 10: List of Data Displays

10.10.1. Data Display Numbering

The following numbering will be applied for RAP generated displays:

Section	Tables	Figures
Study Population	1.1 to 1.n	1.1 to 1.n
Efficacy	2.1 to 2.n	2.1 to 2.n
Safety	3.1 to 3.n	3.1 to 3.n
Section	**Listings**	
ICH Listings	1 to x	
Other Listings	y to z	

10.10.2. Mock Example Shell Referencing

Non IDSL specifications will be referenced as indicated and if required example mock-up displays provided in Appendix 11: Example Mock Shells for Data Displays.

Section	Figure	Table	Listing
Study Population	POP_Fn	POP_Tn	POP_Ln
Efficacy	EFF_Fn	EFF_Tn	EFF_Ln
Safety	SAFE_Fn	SAFE_Tn	SAFE_Ln

NOTES:

- Non-Standard displays are indicated in the 'IDSL / Example Shell' or 'Programming Notes' column as '[Non-Standard] + Reference.'

10.10.3. Deliverables

Delivery [Priority] [1]	Description
SAC [1]	Final Statistical Analysis Complete

NOTES:

1. Indicates priority (i.e. order) in which displays will be generated for the reporting effort

10.10.4. Study Population Tables

Study Population Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliver-able**
Subject Disposition and Demography					
1.1.	ASE	IDSL_SP01	Summary of Subject Populations	Total column only	SAC
1.2.	ASE	IDSL_ES6	Summary of Screening Status and Reasons for Screen Failures		SAC
1.3.	ASE	IDSL_DM1	Summary of Age Ranges		SAC
1.4.	ITT	IDSL_SP02	Summary of Attendance at Each Clinic Visit	Total column only	SAC
1.5.	ITT	IDSL_SD1	Summary of Treatment Status and Reasons for Discontinuation of Study Treatment		SAC
1.6.	ITT	IDSL_ES1	Summary of End of Study Record		SAC
1.7.	ITT	IDSL_DM2	Summary of Demographic Characteristics		SAC
1.8.	ITT	IDSL_NS1	Summary of Number of Subjects by Centre		SAC
1.9.	ITT	IDSL_DM5	Summary of Race and Racial Combinations		SAC
1.10.	ITT	IDSL_DM6	Summary of Race and Racial Combination Details		SAC
1.11.	ITT	IDSL_TC1	Summary of Study Compliance	Show compliance on all three devices separately	SAC
Protocol Deviations					
1.12.	ITT	IDSL_SP04	Summary of Important Protocol Deviations		SAC
1.13.	ITT	IDSL_IE1	Summary of Inclusion/ Exclusion/ Randomisation Criteria Deviations for Intent-to-treat	Include both high level and lower level categories	SAC

Study Population Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliver-able**
Medical Condition & Concomitant Medications					
1.14.	ITT	IDSL_MH4	Summary of Current Medical Conditions		SAC
1.15.	ITT	IDSL_MH4	Summary of Past Medical Conditions		SAC
1.16.	ITT	IDSL_SP07	Summary of Family History of Cardiovascular Risk Factors		SAC
1.17.	ITT	IDSL_SP08	Summary of COPD History and COPD Exacerbation History at Screening		SAC
1.18.	ITT	IDSL_SP10	Summary of Smoking Status		SAC
1.19.	ITT	IDSL_SP11	Summary of COPD Medications		SAC
1.20.	ITT	IDSL_CM1	Summary of Non-COPD Medications		SAC

10.10.5. Efficacy Tables

Overall Summary of Errors					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliver-able**
2.01	ITT	EFF_T01	Summary of Errors on ELLIPTA		SAC
2.02	ITT	EFF_T01	Summary of Errors on DISKUS + HandiHaler	Page by DISKUS + HandiHaler Errors, DISKUS Errors and HandiHaler Errors	SAC
2.03	ITT	EFF_T06	Summary of Overall Errors		SAC
2.04	ITT	EFF_T06	Summary of Overall Errors by Age	Use age categories: 40-64, 65-74 and ≥75.	SAC
2.05	ITT	EFF_T06	Summary of Critical Errors		SAC
Primary Efficacy Tables					
Percentage of Overall Errors					
2.06	ITT	EFF_T04	Analysis of Percentage of Participants making Zero Errors after 28 days use (Primary Estimand: Principle Strata)		SAC
2.07	ITT	EFF_T04	Analysis of Percentage of Participants making Zero Errors after 28 days use (Supplementary Estimand: Composite)		SAC
2.08	ITT	EFF_T09	Tipping Point Analysis of Participants making Zero Errors after 28 days use (Supplementary Estimand: Composite)		SAC
2.09	ITT	EFF_T07	Sensitivity Analysis of Percentage of Participants making Zero Errors after 28 days use (Primary Estimand: Principle Strata)		SAC

Overall Summary of Errors					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliver-able**
2.10	ITT	EFF_T07	Sensitivity Analysis of Percentage of Participants making Zero Errors after 28 days use (Supplementary Estimand: Composite)		SAC
Secondary Efficacy Tables					
Percentage of Critical Errors					
2.11	ITT	EFF_T04	Analysis of Percentage of Participants making Zero Critical Errors after 28 days use (Primary Estimand: Principle Strata)		SAC
Number of Overall Errors					
2.12	ITT	EFF_T01	Summary of Number of Errors by Type for each Inhaler after 28 Days of Use	Replace 'Early withdrawal' column with 'Difference (ELLIPTA minus DISKUS + HandiHaler)	SAC
2.13	ITT	EFF_T08	Summary of Number and Change in Errors per Participant for each Treatment Group (V2 and V3) after 28 Days of Use		SAC
2.14	ITT	EFF_T08	Summary of Number and Change in Errors for each Treatment Group in Participants with One or more Errors after 28 Days of Use		SAC
Exploratory Efficacy Tables					
Preference Attributes					
2.15	ITT	EFF_T04	Analysis of Percentage of Participants with Zero Errors after 28 Days of Use, including the Number of Prescribed Maintenance Inhalers as a Covariate.		SAC
2.16	ITT	EFF_T04	Analysis of Percentage of Participants with Zero	Include an additional row for	SAC

Overall Summary of Errors					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliver-able**
			Errors after 28 Days of Use, including the Number of Prescribed Maintenance Inhalers as a Covariate (Interaction Model).	the p-value of the interaction between number of prescribed maintenance Inhalers and treatment option.	
2.17	ITT	EFF_T04	Analysis of Participants making Zero Errors after Reading the PIL (s) at the Start of Each Treatment Period.		SAC
2.18	ITT	EFF_T03	Summary and Analysis of Treatment Preference		SAC
2.19	ITT	EFF_T03	Summary of Treatment Preference by Age	This is a summary table only so do not include any analysis. Use age categories: 40-64, 65-74 and ≥75	SAC

10.10.6. Safety Tables

No.	Population	IDSL / TST ID / Example Shell	Title	Programming Notes	Deliver-able
Adverse Events					
3.01	ITT	IDSL_AE1	Summary of Adverse Events		SAC
3.02	ITT	IDSL_AE1	Summary of On-Treatment Adverse Events		SAC
3.03	ITT	IDSL_AE1	Summary of Post-Treatment Adverse Events		SAC
3.04	ITT	IDSL_AE1	Most Common Non-Serious Drug Related Adverse Events	> 3 %	SAC
3.05	ITT	IDSL_AE1	Summary of Serious Adverse Events		SAC
3.06	ITT	IDSL_AE1	Summary of Serious Drug Related Events		SAC
3.07	ITT	IDSL_AE1	Most Common Serious Drug Related Adverse Events	> 3 %	SAC
3.08	ITT	IDSL_AE1	Summary of Fatal Adverse Events		SAC
3.09	ITT	IDSL_AE1	Summary of Non-Fatal Serious Adverse Events		SAC
3.10	ITT	IDSL_AE1	On-treatment AEs leading to Discontinuation of Study Treatment or Withdrawal from the Study		SAC
3.11	ITT	SAFE_T01	Summary of On-Treatment Moderate/Severe COPD Exacerbations		SAC
3.12	ITT	SAFE_T01	Summary of Post-Treatment COPD Moderate/Severe Exacerbations		SAC
3.13	ITT	IDSL_AE1	Summary of Serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences)		SAC

10.10.7. Efficacy Figures

Primary Efficacy Analysis					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
2.1	ITT	EFF_F01	Percentage of Participants with Zero Errors and Zero Critical Errors by Treatment Group		SAC

10.10.8. ICH Listings

ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Study Population: Subject Disposition and Demography					
01	ASE	IDSL_ES7	Listing of Screen Failures		SAC
02	ITT	IDSL_ES2	Listing of Reasons for Study Withdrawal		SAC
Study Population: Protocol Deviations					
03	ITT	IDSL_SP01	Listing of Important Protocol Deviations		SAC
04	ASE	IDSL_IE3	Listing of Inclusion/ Exclusion/ Randomisation Criteria Deviations		SAC
Study Population: Treatment					
05	ITT	IDSL_TA1	Listing of Randomised and Actual Treatment Sequence		SAC
Study Population: Demography					
06	ITT	IDSL_DM2	Listing of Demographic Characteristics	Include BMI as the optional	SAC

ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
				measurement. In addition, include a country column as the first sort variable.	
07	ITT	IDSL_DM9	Listing of Race	Include a country column as the first sort variable.	SAC
Safety: Adverse Events					
08	ASE	IDSL_AE7	Listing of Subject Numbers for Individual Adverse Events		SAC
09	ASE	IDSL_AE8	Listing of All Adverse Events	ICH E9	SAC
10	ASE	IDSL_AE8	Listing of All Serious Adverse Events	ICH E9	SAC
11	ASE	IDSL_AE14	Listing of Reasons for Considering as a Serious Adverse Event	ICH E9	SAC
12	ASE	IDSL_AE8	Listing of Non-Serious Adverse Events Leading to Withdrawal from Study / Permanent Discontinuation of Study Treatment	ICH E9	SAC
13	ASE	IDSL_AE8	Listing of Serious Adverse Events Leading to Withdrawal from Study / Permanent Discontinuation of Study Treatment	ICH E9	SAC
Efficacy: Primary Endpoint					
14	ITT	EFF_L01	Listing of Subject Errors		SAC

10.10.9. Non ICH Listings

Non-ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Study Population: Subject Disposition					
15	ITT	IDSL_POP4	Listing of Subjects by Country and Centres		SAC
Study Population: Protocol Deviations					
16	ITT	IDSL_TA1	Listing of Treatment Sequence Misallocations		SAC
Study Population: Medical Conditions & Concomitant Medications					
17	ITT	IDSL_MH2	Listing of Medical Conditions		SAC
18	ITT	IDSL_SP05	Listing of Family History of Cardiovascular Risk Factors		SAC
19	ITT	IDSL_SP06	Listing of COPD History and COPD Exacerbation History		SAC
20	ITT	IDSL_SP07	Listing of Smoking History and Smoking Status		SAC
21	ITT	IDSL_CM2	Listing of COPD Medications		SAC
22	ITT	IDSL_CM2	Listing of Non-COPD Medications		SAC
23	ITT	IDSL_CM6	Relationship between ATC Level 1, Ingredient and Verbatim Text		SAC
Study Population: Devices					
24	ITT	IDSL_SP08	Listing of Naivety to Inhaler Devices		SAC
Efficacy: Secondary Efficacy Analysis					
25	ITT	EFF_L03	Listing of Preference Questionnaire		SAC
Safety					
26	ITT	IDSL_S3	Listing of COPD Exacerbations		SAC

Non-ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
27	ITT	IDSL_VS4	Listing of Myocardial infarction/unstable angina		SAC
28	ITT	IDSL_S06	Listing of Congestive heart failure		SAC
29	ITT	IDSL_VS4	Listing of Arrhythmias		SAC
30	ITT	IDSL_S06	Listing of Valvulopathy		SAC
31	ITT	IDSL_VS4	Listing of Pulmonary hypertension		SAC
32	ITT	IDSL_S06	Listing of Cerebrovascular events/stroke and transient ischemic attack		SAC
33	ITT	IDSL_S06	Listing of Peripheral arterial thromboembolism		SAC
34	ITT	IDSL_VS4	Listing of Deep venous thrombosis/pulmonary embolism		SAC
35	ITT	IDSL_S06	Listing of Revascularisation		SAC
36	ITT	IDSL_VS4	Listing of All cause deaths		SAC
37	ITT	IDSL_PREG1a	Listing of All subjects who became pregnant during the study		SAC

10.11. Appendix 11: Example Mock Shells for Data Displays

Example : EFF_T01
Protocol : 206901
Population : Intent to Treat

Table X.X
Summary of errors on ELLIPTA

Inhaler errors test	After Reading Leaflet (Day 1) (N=XXX)	After 28 days use (N=XXX)	At early withdrawal visit (N=XXX)
Number of Subjects with Errors	XXX (XX%)	XXX (XX%)	XXX (XX%)
Number of Subjects with Critical Errors	XXX (XX%)	XXX (XX%)	XXX (XX%)
Total Number of Errors	XXX	XXX	XXX
Total Number of Critical Errors	XXX	XXX	XXX
Failed to open cover [1]	XXX (XX%)	XXX (XX%)	XXX (XX%)
Shook the device upside down after dose preparation [1]	XXX (XX%)	XXX (XX%)	XXX (XX%)
Inhalation manoeuvre: long, steady, deep	XXX (XX%)	XXX (XX%)	XXX (XX%)
Blocked air inlet during inhalation manoeuvre	XXX (XX%)	XXX (XX%)	XXX (XX%)
No exhalation before an inhalation	XXX (XX%)	XXX (XX%)	XXX (XX%)
Exhaled directly into mouthpiece [1]	XXX (XX%)	XXX (XX%)	XXX (XX%)
No seal by the lips round the mouthpiece during the inhalation [1]	XXX (XX%)	XXX (XX%)	XXX (XX%)
Did not hold breath	XXX (XX%)	XXX (XX%)	XXX (XX%)
Did not close the device	XXX (XX%)	XXX (XX%)	XXX (XX%)

[1] Indicates a Critical Error.
Note: Percentages for number of subjects are calculated from the total number of subjects who used the device(s), percentage of type of errors are calculated based on the number of subjects with errors.
Programming notes: Percentages for rows 1 and 2 are calculate from the total number of subjects in the ITT population shown in the heading, the remaining percentages are calculated based on the total number of subjects who had errors. For DISKUS + HandiHaler the first page should only contain the first four rows which will the overall summary of number of subjects with errors/critical errors and total number of errors/critical errors. The remaining two pages will be a replicate of the shell above but for two devices separately.

Example : EFF_T02
Protocol : 206901
Population : Intent to Treat

Table X.X
Summary and Analysis of Treatment Preference

	Total (N=XXX)	P-Value
Inhaler preference based on how easy it was to tell how many doses remain.		
n	XXX	X.XXX
ELLIPTA	XXX (XX%)	
DISKUS + HandiHaler	XXX (XX%)	
No Preference	XXX (XX%)	
Inhaler dosing regimen preference.		
n	XXX	X.XXX
ELLIPTA	XXX (XX%)	
DISKUS + HandiHaler	XXX (XX%)	
No Preference	XXX (XX%)	
Inhaler regimen preference based on the number of steps needed to take the medication.		
n	XXX	X.XXX
ELLIPTA	XXX (XX%)	
DISKUS + HandiHaler	XXX (XX%)	
No Preference	XXX (XX%)	

Note: The p-value is from the Cochran-Mantel-Haenszel Test.
Programming notes: %'s calculated out of the small n for each question.

Example : EFF_T04
Protocol : 206901
Population : Intent to Treat

Table X.X
Analysis of Percentage of Participants making Zero Errors after 28 days use

	ELLIPTA (N=XXX)	DISKUS + HandiHaler (N=XXX)
Zero Errors	XXX (XX%)	XXX (XX%)
At Least one Error	XXX (XX%)	XXX (XX%)
ELLIPTA vs DISKUS + HandiHaler		
Odds Ratio	X.XX	
95% CI	(X.XX, X.XX)	
p-value	X.XXX	

Note: Odds ratio, 95% CI and p-value obtained from a conditional logistic regression model. Subject is included in the model as fixed strata, treatment option and period included as fixed effects.

Example : EFF_T06
Protocol : 206901
Population : Intent to Treat

Table X.X
Summary of Overall Errors

	Total (N=XXX)
Zero Errors on ELLIPTA	XXX (XX%)
At least one Error on ELLIPTA	XXX (XX%)
Zero Errors on DISKUS + HandiHaler	XXX (XX%)
At least one Error on DISKUS + HandiHaler	XXX (XX%)
Zero Errors on ELLIPTA or DISKUS + HandiHaler	XXX (XX%)
At least one Error on ELLIPTA and DISKUS + HandiHaler	XXX (XX%)
Number of subjects with discordant results [1]	XXX (XX%)
At least one Error on ELLIPTA and Zero Errors on DISKUS + HandiHaler [2]	XXX (XX%)
At least one Error on DISKUS + HandiHaler and Zero Errors on ELLIPTA [2]	XXX (XX%)

[1] Defined as an error in one device and not the other.
[2] Percentage is out of the number of subjects with discordant results.

Example : EFF_T07
Protocol : 206901
Population : Intent to Treat

Table X.X
Sensitivity Analysis of Percentage of Subjects making Zero Errors

	Result
Overall Errors	
Number of subjects with discordant results [1]	XXX
Number of subjects with an error on ELLIPTA	XXX (XX%)
Number of subjects with an error on DISKUS + HandiHaler	XXX (XX%)
p-Value [2]	
Critical Errors	
Number of subjects with discordant results [1]	XXX
Number of subjects with a critical error on ELLIPTA	XXX (XX%)
Number of subjects with a critical error on DISKUS + HandiHaler	XXX (XX%)
p-Value [2]	X.XXX

[1] Defined as an error in one device and not the other.
[2] Analysis performed using the Cochran-Mantel-Haenszel test
Note: Subjects are only included in the analysis if they have discordant data.

Example : EFF_T08
Protocol : 206901
Population : Intent to Treat

Table X.XX
Summary of Number and Change in Errors per Participant in Each Treatment Group

Treatment Group: ELLIPTA

Inhaler errors test		After Reading Leaflet (Day 1) (N=XXX)	After 28 days use (N=XXX)	Difference (Day 28 – Day 1) (N=XXX)
Overall Errors	n	XXX	XXX	XXX
	Minimum	XXX	XXX	XXX
	Medium	XXX	XXX	XXX
	Maximum	XXX	XXX	XXX
Critical Errors	n	XXX	XXX	XXX
	Minimum	XXX	XXX	XXX
	Medium	XXX	XXX	XXX
	Maximum	XXX	XXX	XXX

Note: n is the number of subjects making at least one overall/critical error

Programming notes: Page by ELLIPTA and DISKUS + HandiHaler.

Example : EFF_T09
Protocol : 206901
Population : Intent to Treat

Table X.XX
Tipping Point Analysis of Participants making Zero Errors after 28 days use
(Supplementary Estimand: Composite)

Number of Subjects with Errors on DISKUS + HandiHaler (N=XX)	Number of Subjects with Errors on ELLIPTA (N=XX)				
	0	1	2	3	4
0	x.xx	x.xx	x.xx	x.xx	x.xx
1	x.xx	x.xx	x.xx	x.xx	x.xx
2	x.xx	x.xx	x.xx	x.xx	x.xx
3	x.xx	x.xx	x.xx	x.xx	x.xx
4	x.xx	x.xx	x.xx	x.xx	x.xx

Note: N is the total amount of missing data for each treatment option.
Values in the table are p-values obtained from a conditional logistic regression model. Subject is included in the model as fixed strata, treatment option and period included as fixed effects.

Programming notes: If this doesn't fit into one table then use symbols to identify where p < 0.05 or p >= 0.05 and add a footnote to explain.

Example : SAFE_T01
Protocol : 206901
Population : Intent to Treat

Summary of On-Treatment COPD Exacerbations

	Overall (N=XXX) n (%)
Number of subjects an COPD exacerbation	XXX (XX%)
Total number of COPD exacerbations per subject	
n	XXX
0	XXX (XX%)
1	XXX (XX%)
2	XXX (XX%)
>=3	XXX (XX%)

[1] Percentages calculated using the total number of moderate/severe COPD exacerbations as the denominator.
[2] More than one treatment may be selected for a given exacerbation.
Note: Moderate exacerbations are defined as exacerbations that required treatment with systemic corticosteroids and/or antibiotics (not involving hospitalisation). Severe exacerbations are defined as exacerbations that required hospitalisation.

	Overall (N=XXX) n (%)
Total number of COPD exacerbations	XXX
Total number of exacerbations	XXX
Total number of exacerbations leading to withdrawal	XXX
Treatment [1][2]	
Took oral/systemic corticosteroids	XXX (XX%)
Took antibiotics	XXX (XX%)
Visited emergency room	XXX (XX%)
Hospitalised	XXX (XX%)
Intubated	XXX (XX%)
Outcome [1]	
Resolved	XXX (XX%)
Fatal	XXX (XX%)
Not resolved	XXX (XX%)

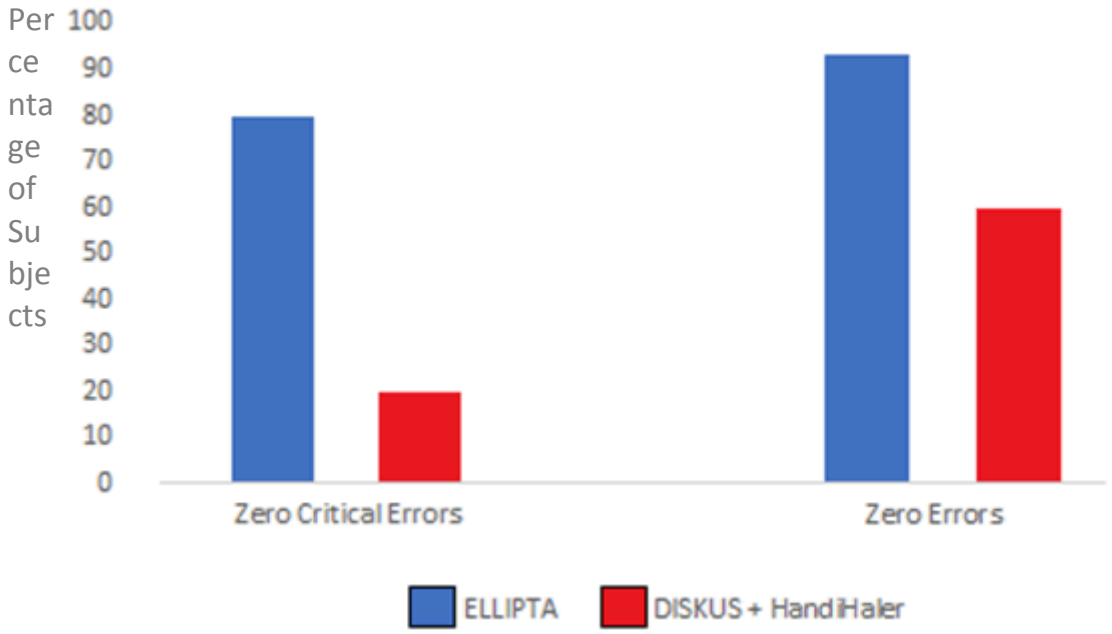
[1] Percentages calculated using the total number of COPD exacerbations as the denominator.
[2] More than one treatment may be selected for a given exacerbation.
Note: Moderate exacerbations are defined as exacerbations that required treatment with systemic corticosteroids and/or antibiotics (not involving hospitalisation). Severe exacerbations are defined as exacerbations that required hospitalisation.

	Overall (N=xxx)
Duration of moderate/severe COPD exacerbation (days)	
n	xxx
Mean	xx.x
SD	xx.xx
Median	x.x
Min.	xx
Max.	xx

[1] Percentages calculated using the total number of moderate/severe COPD exacerbations as the denominator.
[2] More than one treatment may be selected for a given exacerbation.
Note: Moderate exacerbations are defined as exacerbations that required treatment with systemic corticosteroids and/or antibiotics (not involving hospitalisation). Severe exacerbations are defined as exacerbations that required hospitalisation.

Example : EFF_F01
Protocol : 206901
Population : Intent to Treat

Figure X.X
Percentage of Participants with Zero Errors and Zero Critical Errors by Treatment Group



Example : EFF_L01
Protocol : 206901
Population : Intent to Treat

Listing X.X
Listing of Subject Errors by Assessment

Sub-study 1: ELLIPTA vs DISKUS + HandiHaler

Subject ID	Period	Treatment	Assessment	Total Errors	Device	Type of Error
XXXX	1	ELLIPTA	After reading the PIL	2	ELLIPTA	Exhaled directly into mouthpiece Failed to open cover
			After 28 days use	1	ELLIPTA	Did not hold breath
	2	DISKUS + HandiHaler	Reading the PIL	3	DISKUS	Failed to open cover Lever is not pushed back
					HandiHaler	Did not hold breath
			After 28 days use	2	DISKUS	Failed to open cover
					HandiHaler	Did not hold breath [1]

...

[1] Indicates a Critical Error.

Example : EFF_L02
Protocol : 206901
Population : Intent to Treat

Listing X.X
Listing of Preference Questionnaire

Sub-study 1: ELLIPTA vs DISKUS + HandiHaler

Subject ID	Treatment Sequence	Question 1	Question 2	Question 3
XXXX	ELLITA/DISKUS + HandiHaler/Q1	ELLIPTA	ELLIPTA	ELLIPTA
XXXX	DISKUS + HandiHaler/ELLIPTA/Q2	DISKUS + HandiHaler	DISKUS + HandiHaler	ELLIPTA
XXXX	ELLITA/DISKUS + HandiHaler/Q2	No Preference	No Preference	No Preference

...

Note: Q1 = Questionnaire 1, Q2 = Questionnaire 2
Question 1 = Inhaler preference based on how easy it was to tell how many doses remain.
Question 2 = Inhaler dosing regimen preference
Question 3 = Inhaler regimen preference based on the number of steps needed to take the medication